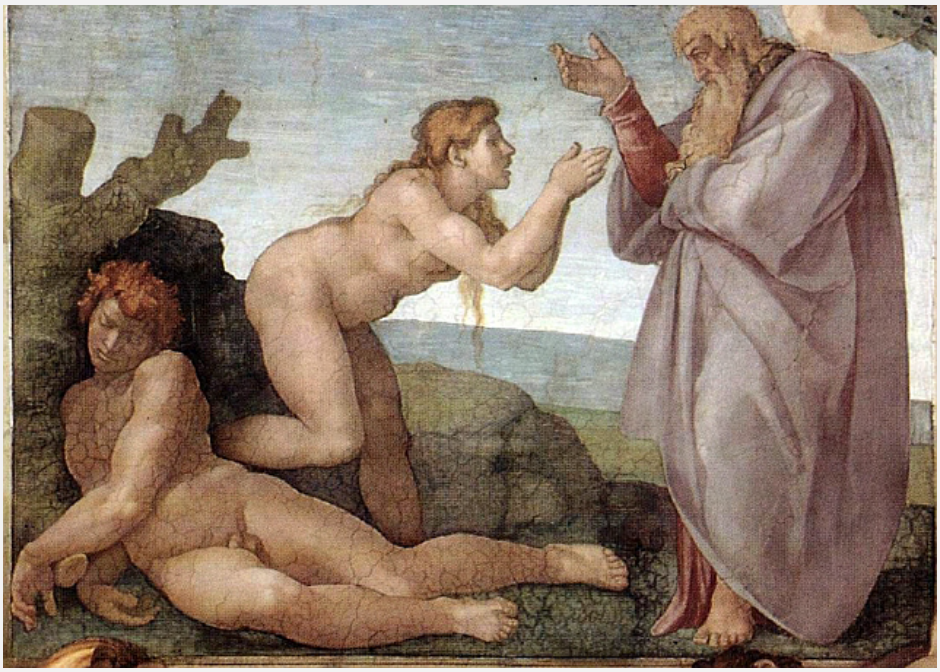
Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman



Michelangelo (1475-1564): Center of the ceiling: Creation of Eve [before restoration], Vatican, Sistine Chapel ©1990. Photo Scala, Florence

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Progress in Osteoporosis is a quarterly review journal that provides a summary of the most important literature published in the field of osteoporosis in the preceding 3-4 months.

Managing Editor: Fina Liu

International Osteoporosis Foundation

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When, in disgrace with fortune and men's eyes,
I all alone beweep my outcast state
And trouble deaf heaven with my bootless cries
And look upon myself and curse my fate,
Wishing me like to one more rich in hope,
Featur'd like him, like him with friends possess'd,
Desiring this man's art and that man's scope,
With what I most enjoy contented least;
Yet in these thoughts myself almost despising,
Haply I think on thee, and then my state,
Like to the lark at break of day arising
From sullen earth, sings hymns at heaven's gate;
For thy sweet love remember'd such wealth brings
That then I scorn to change my state with kings.

Sonnet XXIX
William Shakespeare


E. Lau


M. Lechanteur


R. Lederman


B. Masri

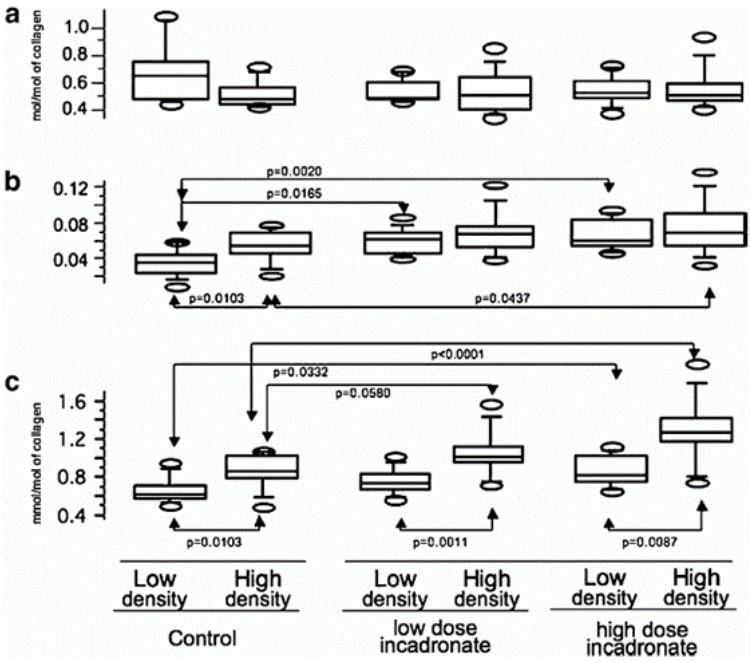

P.D. Miller


H. Orimo

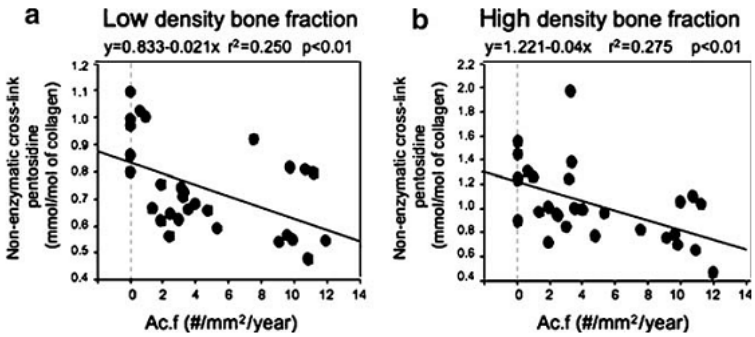
Overview

Treatment

Saito et al treated 29 one-year-old beagles (15 males, 14 females) with incadronate at doses of 0.3 or 0.6 mg/kg/day orally for 3 years. A cortex of a rib was fractionated into low and high density portions. Calcium, phosphorus, and pentosidine contents and the ratio of mature to immature crosslinks increased with incadronate in a dose-dependent manner, but the total amount of enzymatic crosslinks was unchanged. The pentosidine content correlated inversely with cortical activation frequency. Long term suppression of bone remodelling by bisphosphonate increases degree of mineralization, collagen maturity, and nonenzymatic crosslinking. **Osteoporos Int 2008;19:1343-54**



The total enzymatic crosslink contents (a), the ratio of total mature to immature enzymatic crosslinks (b), and the content of Pen (c) in low and high density bone fractions from dog rib cortex. Low and high density bone are composed of less mineralized and highly mineralized bone, respectively. Total enzymatic crosslink content is estimated by the sum of immature (DHLNL, HLNL, and LNL) and mature (Pyr and Dpyr) crosslinks. The ratio of total mature to immature crosslinks is estimated as the ratio of the sum of mature (Pyr and Dpyr) to the sum of immature (DHLNL, HLNL, and LNL) crosslinks. Data are depicted as box-and whisker-plots showing medians, 25th and 75th quartiles, and complete data range. Low dose incadronate group (0.3 mg/kg/day), high dose incadronate group (0.6 mg/kg/day). Reproduced from Osteoporos Int 2008;19:1343-54 with permission from Springer.



Linear regression analyses of the relations between activation frequency (Ac.f) and the nonenzymatic crosslink, pentosidine, in low (a) and high (b) density bone fractions from dog rib cortex. Low and high density bone are composed of less mineralized and highly mineralized bone, respectively. Ac.f is associated with increased pentosidine contents in both low density bone ($r=-0.559$, $p<0.01$) and high density bone ($r=-0.507$, $p<0.01$). Reproduced from Osteoporos Int 2008;19:1343-54 with permission from Springer.

Sunyecz et al report women ≥45 years of age and who filled a new bisphosphonate prescription during years 2000-2002. In 32,944 women who filled a new prescription for daily or weekly alendronate (n=26,581) or risedronate (n=6,363), at 3 years, 37% were compliant and 21% were persistent. Unadjusted total mean healthcare costs were lower for the compliant vs. noncompliant and persistent vs. nonpersistent cohorts. Total healthcare costs were reduced by 8.9% for persistent patients (p<0.001) and 3.5% for compliant patients (p=0.014). Persistence decreased the likelihood of inpatient admission by 47%. **Osteoporos Int 2008;19:1421-9**

Iwamoto et al report 49 female rats, 3 months of age, were randomized into five groups according to control, glucorticoid (GC), GC+vitamin K_2, risedronate, or vitamin K_2+risedronate. At the end of the 8 weeks, GC decreased percent cortical bone area and increased percent marrow area as a result of decreased periosteal bone formation, and increased endocortical bone erosion, and increased cortical porosity. Vitamin K_2 prevented a reduction in periosteal bone formation but did not affect percent cortical bone and marrow areas. Risedronate prevented a reduction in periosteal bone formation and an increase in endocortical bone erosion, resulting in prevention of alterations in percent cortical bone and marrow areas. Both increased osteocyte density and lacunar occupancy and prevented a GC-induced increase in cortical porosity. Vitamin K_2 and risedronate had additive effects on osteocyte density and lacunar occupancy and a synergistic effect on cortical porosity. **Calcif Tissue Int 2008;83:121-8**

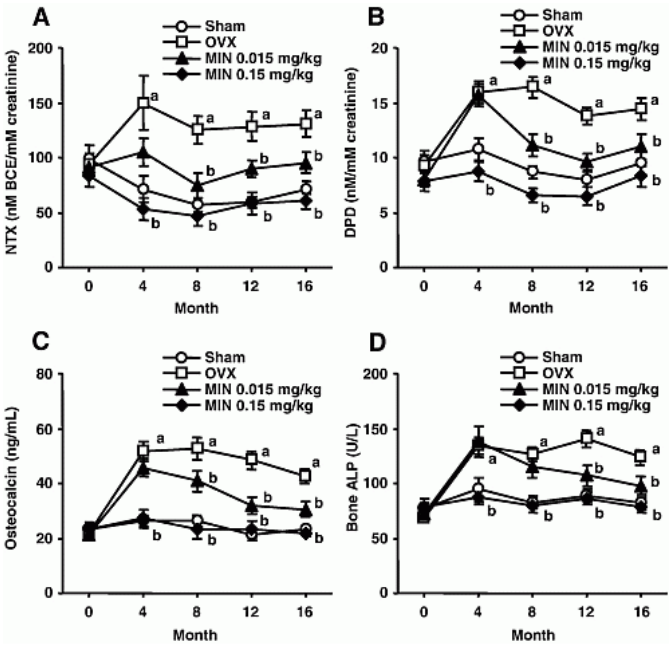
Syed et al reanalysed bone biopsies from a randomized, placebo controlled trial involving 56 postmenopausal osteoporotic women (mean age, 64 years) treated with placebo (n=27) or transdermal estradiol (E) (0.1 mg/d, n=29) for one year. Adipocyte volume/tissue volume (AV/TV) and adipocyte number increased by about 20% in the placebo but was unchanged or decreased in the E group. E also prevented increases in mean adipocyte size over one year. **Osteoporos Int 2008;19:1323-30**

Strontium ranelate in ovariectomized rats (25 or 150 mg/kg/day) for 90 days did not increase bone formation on trabecular or periosteal bone surfaces, and failed to inhibit bone resorption of trabecular bone regardless of Ca intake. There were no improvements in bone mass, volume or strength with either dose of strontium ranelate given normal Ca. **Osteoporos Int 2008;19:1331-41**

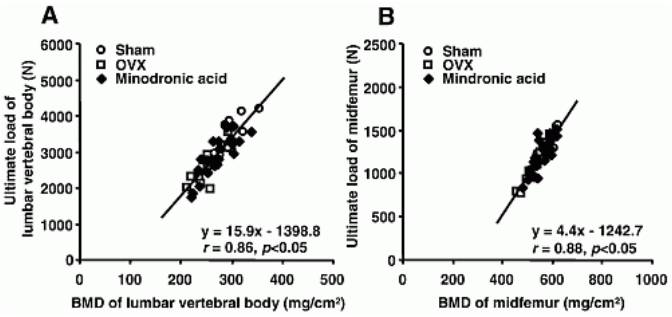
Whyte et al report that prolonged bisphosphonate in children produced bone fragility. A 12-year-old boy developed osteopetrosis (OPT) receiving pamidronate. Now 17 years of age, he had further fractures of a metacarpal, an osteosclerotic distal radius, and a dense diaphyseal ulna "chalkstick" break that remained incompletely healed after 2 years. Modelling disturbances of OPT persisted. Metaphyseal osteosclerosis had remodelled imperfectly. Newer metaphyseal bone was osteopenic, with thin cortices and a paucity of trabeculae. Femoral necks had become short and wide. A "bone-within-

bone" configuration was present. In vertebrae, endplates were thin, and trabecular osteopenia was present. BMD Z-scores assessed by DXA had decreased into the normal range. **J Bone Miner Res 2008;23:1698-707**

Mori et al studied female cynomolgus ovariectomized monkeys and given minodronic acid which inhibited bone turnover markers and the decrease in lumbar vertebral BMD. Ultimate load on lumbar vertebral bodies and femoral neck of the OVX-control animals were reduced compared to the sham. Minodronic acid prevented and perhaps reversed some of these reductions in strength and maintained trabecular architecture. **Bone 2008;43:840-8**



Effect of minodronic acid (MIN) on biochemical markers of bone turnover. (A) Urinary NTX. (B) Urinary DPD. (C) Serum osteocalcin. (D) Serum Bone ALP. Data are presented as mean±SE (n=11-12). [a]Significantly different from sham; P<0.05. [b]Significantly different from OVX-control; P<0.05. Reproduced from Bone, 43:840-8, Copyright (2008), with permission from Elsevier.



Effect of minodronic acid (MIN) on BMD measured by DXA. (A) Lumbar vertebra (L3-L5). (B) Proximal femur. Data are presented as mean percentages of baseline and SE (n=11-12). [a]Significantly different from sham; P<0.05. [b]Significantly different from OVX-control; P<0.05. Reproduced from Bone, 43:840-8, Copyright (2008), with permission from Elsevier.

Gallagher et al identified 44,531 patients prescribed alendronate or risedronate; 58.3% continued bisphosphonate for >1 year and 23.6% for >5 years. The risk of hip/femur fracture (RR, 0.78; 95% CI 0.64-0.94) and osteoporotic fracture (RR, 0.85; 95% CI 0.76-0.94) were lower with current than past bisphosphonate use. The largest reduction in hip/femur and osteoporotic fracture risk was observed in patients treated for at least 6 months and no reduction in those treated for <6 months. Increased risks were found in patients with low compliance. Use of bisphosphonates was associated with fracture risk reductions after 6-12 months of treatment, but only 58% of the patients were treated for at least one year. **J Bone Miner Res 2008;23:1569-75**

DeMichele et al report that in a case-control study of women age 50-79 years diagnosed with endometrial cancer, of 547 cases and 1,410 controls, 3.3% cases had taken raloxifene and 6.2% had taken tamoxifen. Among controls, 6.6% had taken raloxifene and 2.4% had taken tamoxifen. The adjusted odds of endometrial cancer among raloxifene users was 50% that of nonusers (OR=0.50, 0.29-0.85); whereas tamoxifen users had three times the odds of developing endometrial cancer compared with raloxifene users (OR=3.0, 1.3-6.9). Endometrial tumors in raloxifene users had a more favorable histologic profile and were predominantly stage I and low grade. **J Clin Oncol 2008;26:4151-9**

Hershman et al report that zoledronic acid (4 mg intravenously every 3 months) given for one year in 101 premenopausal women prevented the decline in BMD associated with chemotherapy. Bone loss in the placebo arm was associated with decline in LS BMD at both 6 (2.4%) and 12 (4.1%) months. Similarly, total hip BMD declined by 0.8% at 6 months and 2.6% at 12 months. **J Clin Oncol 2008 [Epub ahead of print]**

Ellis et al report that women with hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy were randomly assigned to placebo (n=125) or subcutaneous denosumab 60 mg (n=127) every 6 months. At 12 and 24 months, spine BMD increased by 5.5% and 7.6%, respectively, in the denosumab group versus placebo. Increases were observed at one month and were not influenced by duration of aromatase inhibitor therapy. Increases in BMD were also observed at the cortical sites. Bone turnover markers decreased with denosumab. **J Clin Oncol 2008 [Epub ahead of print]**

Curtis et al studied 9,063 older women compliant with bisphosphonates ≥2 years. Hip fracture incidence in women who discontinued bisphosphonates versus those who did not was 8.43 versus 4.67 per 1000 person-years (p=0.016). The adjusted hazard ratio of hip fracture per 90 days following discontinuation was 1.2 (1.1-1.3). For women with higher compliance at 2 years (MPR ≥80%) or compliant for 3 years, there were no significant differences in risk associated with discontinuation. The rate

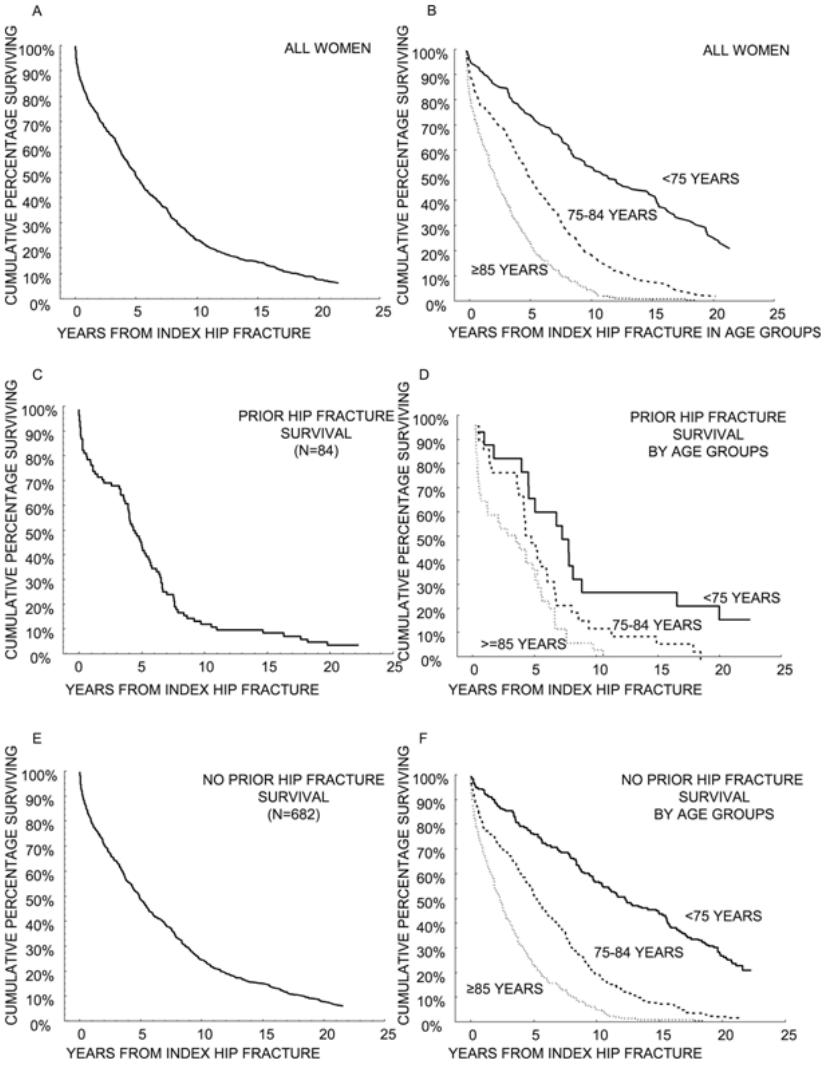
of hip fracture was increased among women compliant with bisphosphonate therapy for 2 years who subsequently discontinued, suggesting that discontinuation is not advisable. **Osteoporos Int 2008;19:1613-2**

Ayukawa et al report simvastatin injected into a rat bony defect for 3 days from surgery demonstrated larger new bone area. The number of tartrate-resistant acid phosphatase-positive multinucleated cells was less than in the control and the expressions of both alkaline phosphatase and BMP2 mRNA increased. The expression of cathepsin K was suppressed. The expression of RANKL was depressed. At day 10, there were no differences among the groups in either histomorphometric or reverse transcription polymerase chain reaction analyses. New bone area increased under the influence of simvastatin; however, the effect did not continue when the administration was terminated. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008 [Epub ahead of print]**

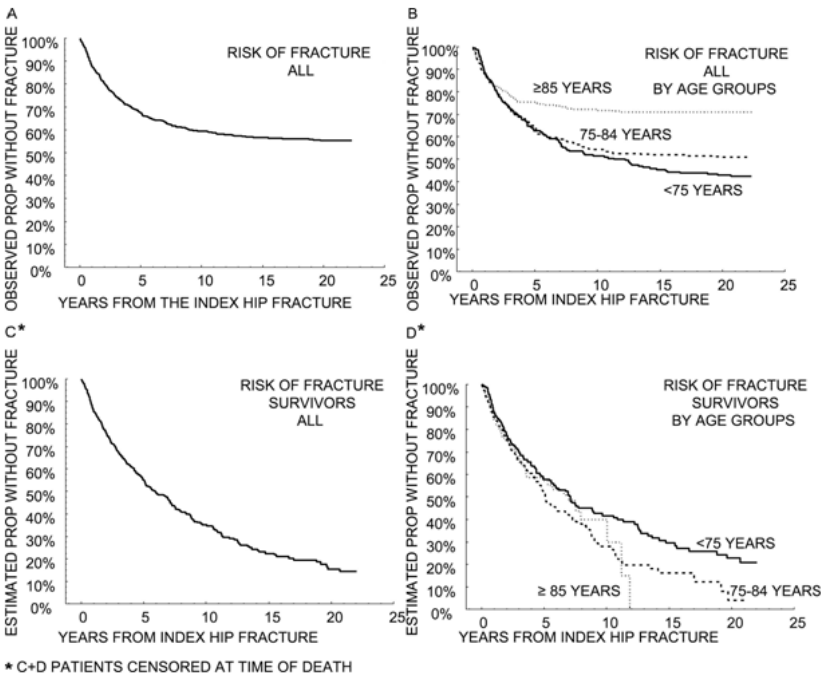
Wu et al induced osteonecrosis by low dose lipopolysaccharide and subsequent pulsed high dose methylprednisolone. Rabbits in the treated group were subjected to subcutaneous injections of G-CSF at a dose of 100 μg/kg and SCF 25 μg/kg per day for 5 days. All rabbits displayed increased osteocalcin protein expression in response to G-CSF/SCF. MRI scans showed a reactive interface between the necrotic and reparative zones after G-CSF/SCF. Quantitative analysis showed new vessel formation. The histologic and histomorphometric analysis revealed that the new bone volume was higher in the G-SCF/SCF group than in the control group at 4 weeks. **J Rheumatol 2008 [Epub ahead of print]**

Morbidity / Mortality

It may appear too late to treat the elderly, certainly a view held by the very low use of drug therapy in this group, and the virtual lack of therapy given after hip fractures. This is not right and **von Friesendorff et al** demonstrate why. This instructive study shows that of women suffering a hip fracture during 1984-1985 in Malmo (n=766), mortality after one year was 7%, 21%, and 33% for <75, 75-84, and ≥85 years of age, respectively, and 95% of those ≥85 years old were dead at 10 years. 768 fractures occurred in 342 women (45%; mean, 2.3 fractures/woman; range, 1-11 fractures/woman). Of the fracture occasions, 15% occurred within the first year, 27% within the second year, and 73% within 5 years. The residual lifetime fracture risk was 45%, with a mortality-adjusted increase to 86%. The 10-year fracture risk was 40%; with a mortality-adjusted increased to 65%. Almost half of all women with a hip fracture suffer a new fracture. The message is clear – treat these patients after they sustain a fracture. **J Bone Miner Res 2008;23:1832-41**



Survival with Kaplan-Meier analysis during 22-yr follow-up. (A) The entire group (n=766). The 5-yr survival in the entire group was 48%, and survival at end of follow-up only 6%. (B) The entire group of women divided in three age groups. The 50% survival was 2 yr in the oldest age group (≥85 yr of age at time of index hip fracture), 5 yr in the middle group (75-84 yr), and 11 yr in the youngest group (<75 yr). (C) All women with a prior hip fracture (n=84; 11%) and (D) women with a prior hip fracture divided in the three age groups. (E) All women without a prior hip fracture (n=682). The mean age in women with prior hip fracture was higher (p=0.01). (F) Women without a prior hip fracture divided in three age groups. Reproduced from J Bone Miner Res 2008;23:1832-41 with permission of the American Society of Bone and Mineral Research.

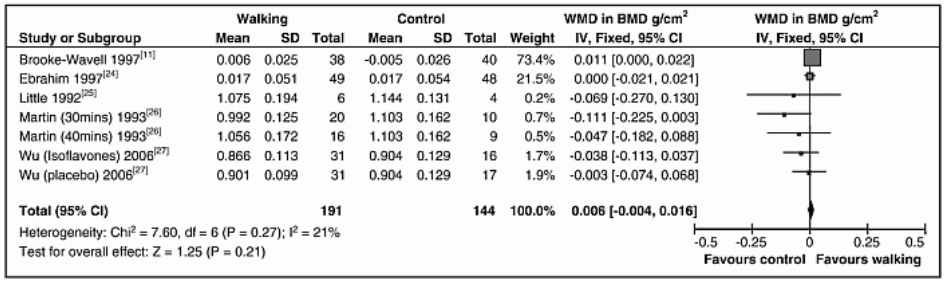


The observed risk of new fracture after the index hip fracture (A) in the entire group and (B) by age groups. At 10 yr, 40% had suffered a new fracture, and the risk for new fracture were similar in all age groups within 2 yr, whereafter the two younger age groups continue to follow for another 5 yr. The estimated risk of new fracture after the index hip fracture supposed all women would still be alive at end of study (C) in the entire group and (D) by age groups. The estimated risk of fracture was 65% after 10 yr in the entire group. By age groups, the estimated risk of fracture was similar within the first 4 yr. Reproduced from J Bone Miner Res 2008;23:1832-41 with permission of the American Society of Bone and Mineral Research.

Exercise

Martyn-St James et al report a meta-analysis showing regular walking has no effect on preservation of BMD at the spine in postmenopausal women, whilst significant positive effects at femoral neck were found. While meta-analyses may be regarded by some as the highest level of evidence, the authors make the point that the work is very difficult to interpret in any way given the diverse methodological and reporting discrepancies in the published trials. **Bone 2008;43:521-31**

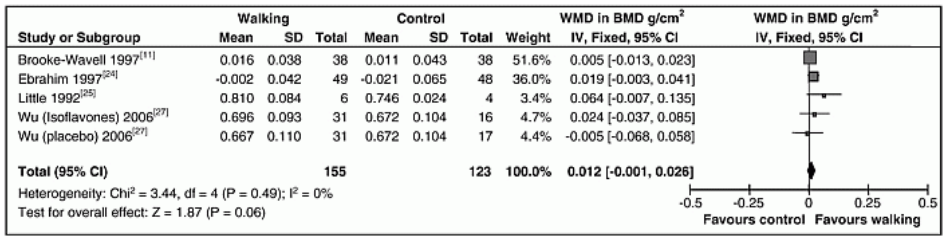
Sample et al report adaptation is neuronally regulated. Load induced responses in the left and right ulnas and humeri were determined after loading of the right ulna in male Sprague Dawley rats. Neuronal block by perineural anesthesia of the brachial plexus during loading prevented loading induces adaptive responses by bone formation. **J Bone Miner Res 2008;23:1372-81**



Study or Subgroup	Walking Mean	Walking SD	Walking Total	Control Mean	Control SD	Control Total	Weight	WMD in BMD g/cm² IV, Fixed, 95% CI
Brooke-Wavell 1997[11]	0.006	0.025	38	-0.005	0.026	40	73.4%	0.011 [0.000, 0.022]
Ebrahim 1997[24]	0.017	0.051	49	0.017	0.054	48	21.5%	0.000 [-0.021, 0.021]
Little 1992[25]	1.075	0.194	6	1.144	0.131	4	0.2%	-0.069 [-0.270, 0.130]
Martin (30mins) 1993[26]	0.992	0.125	20	1.103	0.162	10	0.7%	-0.111 [-0.225, 0.003]
Martin (40mins) 1993[26]	1.056	0.172	16	1.103	0.162	9	0.5%	-0.047 [-0.182, 0.088]
Wu (Isoflavones) 2006[27]	0.866	0.113	31	0.904	0.129	16	1.7%	-0.038 [-0.113, 0.037]
Wu (placebo) 2006[27]	0.901	0.099	31	0.904	0.129	17	1.9%	-0.003 [-0.074, 0.068]
Total (95% CI)			**191**			**144**	**100.0%**	**0.006 [-0.004, 0.016]**

Heterogeneity: Chi² = 7.60, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 1.25 (P = 0.21)

Forest plot for RCT effects of walking on lumbar spine bone mineral density. Reproduced from Bone, 43:521-31, Copyright (2008), with permission from Elsevier.



Study or Subgroup	Walking Mean	Walking SD	Walking Total	Control Mean	Control SD	Control Total	Weight	WMD in BMD g/cm² IV, Fixed, 95% CI
Brooke-Wavell 1997[11]	0.016	0.038	38	0.011	0.043	38	51.6%	0.005 [-0.013, 0.023]
Ebrahim 1997[24]	-0.002	0.042	49	-0.021	0.065	48	36.0%	0.019 [-0.003, 0.041]
Little 1992[25]	0.810	0.084	6	0.746	0.024	4	3.4%	0.064 [-0.007, 0.135]
Wu (Isoflavones) 2006[27]	0.696	0.093	31	0.672	0.104	16	4.7%	0.024 [-0.037, 0.085]
Wu (placebo) 2006[27]	0.667	0.110	31	0.672	0.104	17	4.4%	-0.005 [-0.068, 0.058]
Total (95% CI)			**155**			**123**	**100.0%**	**0.012 [-0.001, 0.026]**

Heterogeneity: Chi² = 3.44, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

Forest plot for RCT effects of walking on femoral neck bone mineral density. Reproduced from Bone, 43:521-31, Copyright (2008), with permission from Elsevier.

Biomechanics

van Lenthe et al report beam theory underestimates tissue modulus. Femoral geometry and size had strong effects on beam theory-derived tissue moduli. Owing to their relatively thin cortex, underestimation was higher for B6 than C3H. Underestimation was dependent on support width in a strain-specific manner. **Bone 2008;43:717-23**

Lochmuller et al mechanically tested the right forearm and left distal radius of 130 human specimens to failure with the hand, elbow, ligaments, and tendons intact. BMD of the distal radius correlated (r=0.82) with failure loads. Microstructural parameters showed correlation coefficients with the failure loads of ~0.55 and did not add to DXA in predicting failure loads. **Calcif Tissue Int 2008;83:293-9**

Arlot et al report microdamage in cancellous bone from human lumbar (L2) vertebral bodies obtained from 23 donors 54-93 years

of age related to 3D microarchitecture, as assessed by high-resolution microCT. There were no sex differences although women had a higher microcrack density (Cr.Dn) than men. Cr.Dn increased with age (r=0.65) and correlated with BV/TV (r=–0.55) trabecular number (Tb.N; r=–0.56), structure model index (SMI; r=0.59), and trabecular separation (Tb.Sp; r=0.59). SMI was the best predictor of microdamage, explaining 35% of the variance in Cr.Dn and 20% of the variance in diffuse damage accumulation. Microcrack length was greater in the highest versus lowest tertiles of SMI. **J Bone Miner Res 2008;23:1613-8**

Men

Mellstrom et al studied 2639 men with a mean age 75 for 3.3 years. Fracture incidence was 20.9/1000 person-years. Estradiol levels per SD decrease conferred a hazard of 1.34 (1.22-1.49), free estradiol (fE2 1.41, 1.28-1.55), testosterone (T 1.27, 1.16-1.39), and free testosterone (fT 1.32, 1.21-1.44) were all inversely, while SHBG (HR per SD increase, 1.41, 1.22-1.63) was directly related to fracture risk. fE2 and SHBG, but not fT, were associated with fracture risk. fE2 was inversely associated with clinical vertebral fractures (1.57, 1.36-1.80), nonvertebral osteoporosis fractures (1.42, 1.23-1.65), and hip fractures (1.44, 1.18-1.76). The inverse relation between serum E2 and fracture risk was nonlinear with a strong relation <16 pg/ml for E2 and 0.3 pg/ml for fE2. **J Bone Miner Res 2008;23:1552-60**

To begin at the beginning:
It is spring, moonless night in the small town, starless
and bible-black, the cobblestreets silent and the
hunched, courters'-and-rabbits' wood limping
invisible down to the sloeblack, slow, black, crowblack,
fishingboat-bobbing sea. The houses are blind as
moles (though moles see fine to-night in the snouting,
velvet dingles) or blind as Captain Cat there in
the muffled middle by the pump and the town clock,
the shops in mourning, the Welfare Hall in widows'
weeds. And all the people of the lulled and
dumbfound town are sleeping now.

From *Under Milk Wood*
Dylan Thomas

Note from the Editor

The purpose of *Progress in Osteoporosis* is to provide the reader with a summary of the most important literature published in the preceding three to four months in the field of osteoporosis. Most reviews and original research are cited. In addition, summaries and figures are provided for readers who may not have easy access to all the specialist literature. The summaries are based on the contents of abstracts, which have been abbreviated to concisely convey the main theme. The contents of the abstracts and figures should be used only as a means of directing the reader to the original literature and should not be quoted verbatim or cited as a reference. The opinions expressed in the Overview are my own and do not necessarily reflect those of the International Osteoporosis Foundation.

Ego Seeman

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 1, 2008

Epidemiology

10.1.1 Fracture mechanisms and fracture pattern in men and women aged 50 years and older: A study of a 12-year population-based injury register, Umea, Sweden

Bergstrom U, Bjornstig U, Stenlund H, Jonsson H, Svensson O

Osteoporos Int 2008;19:1267-73

This population-based register (1993-2004) comprises a total of 113,668 injuries (29,189 fractures). Patients ≥50 years contributed to 13,279 fractures. Low-energy trauma (fall <1 m) caused 53% of all fractures ≥50 years and older. In those over 75 low-energy trauma caused >80%. The seasonal variation of fractures was maximally 25%. With increasing age, proximal fractures became more common, in both upper and lower extremities. Proximal locations predominate in older age groups.

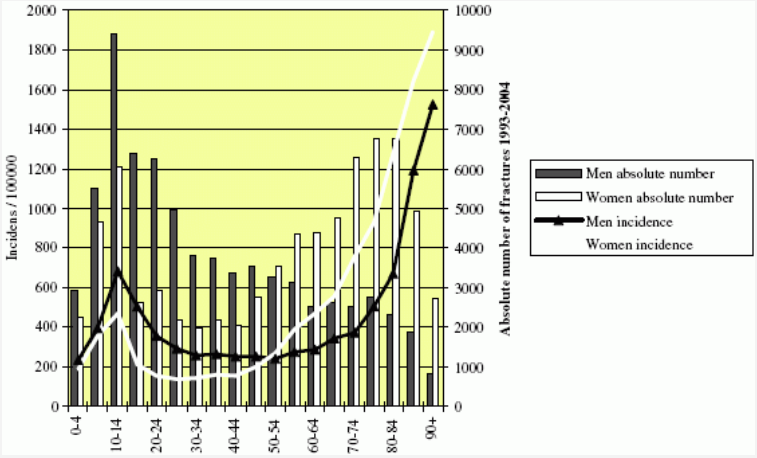


Fig. 10.1.1a Absolute numbers and incidence of fractures 1993-2004. Reproduced from Osteoporos Int 2008;19:1267-73 with permission from Springer.

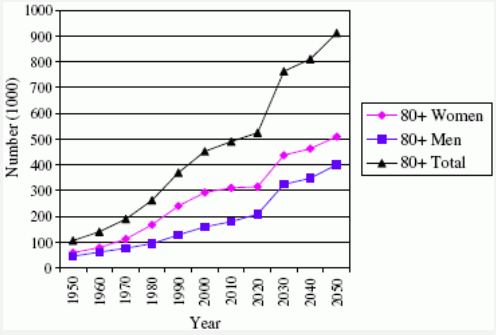


Fig. 10.1.1b Changes in the older population in Sweden 1950-2050. Reproduced from Osteoporos Int 2008;19:1267-73 with permission from Springer.

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Morbidity/Mortality

10.1.2 Long-term survival and fracture risk after hip fracture: A 22-year follow-up in women
von Friesendorff M, Besjakov J, Akesson K
J Bone Miner Res 2008;23:1832-41

All women suffering a hip fracture during 1984-1985 in Malmo, Sweden, were identified (n=766) and followed up to 22 yr or death. Mean age was 79.6 yr (range, 31.6-99.4 yr), with 42% between 75 and 85 yr of age. Overall 22-yr survival was 6%: 79% at 1, 48% at 5, and 33% at 10 yr. One-year mortality was 7%, 21%, and 33% for <75, 75-84, and ≥85 yr of age, respectively, and 95% of those ≥85 yr were dead at 10 yr. Prior hip fracture did not affect age-adjusted mortality (OR, 1.05). 768 fractures were registered at 715 occasions in 342 women (45%; mean, 2.3 fractures/woman; range, 1-11 fractures/woman). Of the fracture occasions, 15% occurred within the 1st, 27% within 2nd, and 73% within 5 yr. The residual lifetime fracture risk was 45%, with a mortality-adjusted increase to 86%. The 10-yr fracture risk was 40%; with a mortality-adjusted increased to 65%. Almost half of all women with a hip fracture suffer a new fracture.

10.1.3 Prevalent vertebral fractures in black women and white women
Cauley JA, Palermo L, Vogt M, Ensrud KE, Ewing S, Hochberg M, Nevitt MC, Black DM
J Bone Miner Res 2008;23:1458-67

In 7860 white and 472 black women ≥65 yr of age enrolled in the Study of Osteoporotic Fractures the prevalence of vertebral fractures was 10.6% in black and 19.1% in white women. In age-adjusted logistic regression models, a 1 SD decrease in femoral neck BMD was associated with 47% increased odds of fracture in black women (OR=1.47; 95% CI 1.12-1.94) and 80% increased odds in white women (OR=1.80; 95% CI 1.68-1.94; interaction p=0.14). The overall lower odds of fracture among black women was independent of femoral neck BMD and other risk factors (OR=0.51; 95% CI 0.37-0.72). However, the prevalence of vertebral fractures increased with increasing number of risk factors in both groups.

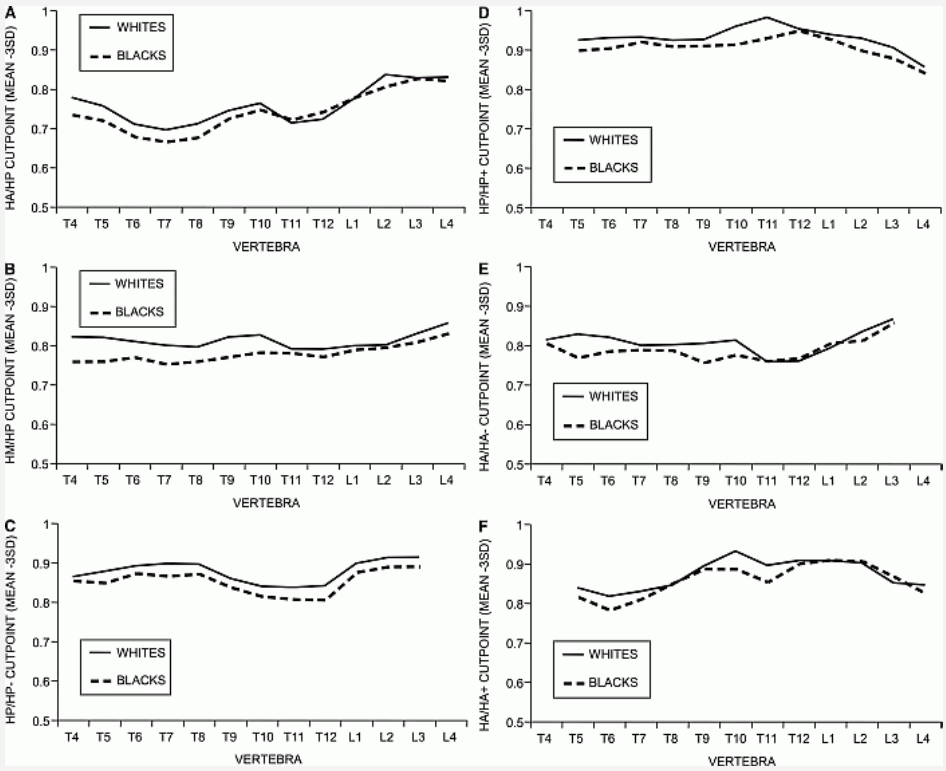

Fig. 10.1.3 Mean normative vertebral height ratios for white and black women by vertebral level: (A) Ha/Hp; (B) Hm/Hp; (C) Hp/Hp −; (D) Hp/Hp+; (E) Ha/Ha−; and (F) Ha/Ha+. Reproduced from J Bone Miner Res 2008;23:1458-67 with permission of the American Society of Bone and Mineral Research.

10.1.4 Harnessing stakeholder perspectives to improve the care of osteoporosis after a fracture
Feldstein AC, Schneider J, Smith DH, Vollmer WM, Rix M, Glauber H, Boardman DL, Herson M
Osteoporos Int 2008;19:1527-40

10.1.5 Severity of depression risk predicts health outcomes and recovery following surgery for hip-fractured elders
Shyu YI, Chen MC, Cheng HS, Deng HC, Liang J, Wu CC, Tsai WC
Osteoporos Int 2008;19:1541-7

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Genetics

10.1.6 Genetic variation in candidate osteoporosis genes, bone mineral density, and fracture risk: The Study of Osteoporotic Fractures
Tranah GJ, Taylor BC, Lui LY, Zmuda JM, Cauley JA, Ensrud KE, Hillier TA, Hochberg MC, Li J, Rhees BK, Erlich HA, Sternlicht MD, Peltz G, Cummings SR
Calcif Tissue Int 2008;83:155-66

Genotyping of 31 polymorphisms from 18 candidate osteoporosis genes was performed in 6752 women. In follow-up of 14.5 years, a total of 849 hip, 658 vertebral, and 2496 nonhip/nonvertebral fractures occurred. Women carrying the ALOX15_G48924T T/T genotype had a higher rate of hip fracture (hazard ratio [HR]=1.33; 95% CI 1.00-1.77) compared with the G/G genotype. Compared with those carrying the PRL_T228C T/T genotype, women with either the C/C (HR=0.80; 95% CI 0.67-0.95) or C/T (HR=0.81; 95% CI =0.68-0.97) genotype had a lower rate of nonvertebral/nonhip fractures. Women carrying the BMP2_A125611G G/G genotype had a higher rate of vertebral fracture (odds ratio [OR]=1.51; 95% CI 1.03-2.23) compared with the A/A genotype. Women with the ESR1_C1335G G/G genotype had a higher rate of vertebral fracture (OR=1.64; 95% CI 1.07-2.50) compared with the C/C genotype. Compared with those with the MMP2_C595T C/C genotype, women with the C/T (OR=0.79; 95% CI 0.65-0.96) or T/T (OR=0.44; 95% CI 0.27-0.72) genotype had a lower rate of vertebral fracture.

10.1.7 Impact of genetics on low bone mass in adults
Sigurdsson G, Halldorsson BV, Styrkarsdottir U, Kristjansson K, Stefansson K
J Bone Miner Res 2008;23:1584-90

440 Icelandic families with 869 first-degree relatives of both sexes. Index cases (male or female) had BMD in the lumbar spine or hip >1.5 SD less than sex-matched controls. Heritability was 0.61-0.66. Relative risk among first-degree relatives was 2.28, and the yield of screening was as high as 36%. The genetic deficit in BMD was present before 35 yr and equalled bone loss during 8-30 yr after menopause.

10.1.8 A Bivariate Whole Genome Linkage Study Identified Genomic Regions Influencing Both BMD and Bone Structure
Liu XG, Liu YJ, Liu J, Pei Y, Xiong DH, Shen H, Deng HY, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Deng HW
J Bone Miner Res 2008;23:1806-14

10.1.9 Identification of a linkage disequilibrium block in chromosome 1q associated with BMD in premenopausal white women
Ichikawa S, Koller DL, Curry LR, Lai D, Xuei X, Pugh EW, Tsai YY, Doheny KF, Edenberg HJ, Hui SL, Foroud T, Peacock M, Econs MJ
J Bone Miner Res 2008;23:1680-8

10.1.10 A missense t(brachyury) mutation contributes to vertebral malformations
Ghebranious N, Blank RD, Raggio CL, Staubli J, McPherson E, Ivacic L, Rasmussen K, Jacobsen FS, Faciszewski T, Burmester JK, Pauli RM, Boachie-Adjei O, Glurich I, Giampietro PF
J Bone Miner Res 2008;23:1576-83

10.1.11 Quantitative trait loci for BMD in an SM/J by NZB/BINJ intercross population and identification of Trps1 as a probable candidate gene
Ishimori N, Stylianou IM, Korstanje R, Marion MA, Li R, Donahue LR, Rosen CJ, Beamer WG, Paigen B, Churchill GA
J Bone Miner Res 2008;23:1529-37

10.1.12 Osteoporosis-pseudoglioma syndrome: Description of 9 new cases and beneficial response to bisphosphonates
Streeten EA, McBride D, Puffenberger E, Hoffman ME, Pollin TI, Donnelly P, Sack P, Morton H
Bone 2008;43:584-90

10.1.13 Polymorphisms in the estrogen receptor genes are associated with hip fractures in Chinese
Wang JT, Guo Y, Yang TL, Xu XH, Dong SS, Li M, Li TQ, Chen Y, Deng HW
Bone 2008;43:910-4

10.1.14 Interactions of interleukin-6 gene polymorphisms with calcium intake and physical activity on bone mass in pre-menarche Chinese girls
Li X, He GP, Zhang B, Chen YM, Su YX
Osteoporos Int 2008;19:1629-37

10.1.15 Autosome-wide linkage analysis of hip structural phenotypes in the Old Order Amish
Streeten EA, Beck TJ, O'Connell JR, Rampersand E, McBride DJ, Takala SL, Pollin TI, Uusi-Rasi K, Mitchell BD, Shuldiner AR
Bone 2008;43:607-12

10.1.16 Linkage screen for BMD phenotypes in male and female COP and DA rat strains
Koller DL, Liu L, Alam I, Sun Q, Econs MJ, Foroud T, Turner CH
J Bone Miner Res 2008;23:1382-8

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Measurement of Bone Mass

10.1.17 Effect of total hip bone area on osteoporosis diagnosis and fractures
Leslie WD, Tsang JF, Lix LM
J Bone Miner Res 2008;23:1468-76

Total hip bone area affected osteoporosis diagnosis with much higher rates in Q1 (14.4%) than Q4 (8.9%). However, incident fracture rates were constant across all area quartiles, and prevalent fractures were fewer in smaller area quartiles ($p<0.001$ for trend). Age was a potential confounder that correlated positively with area ($r=0.12$, $p<0.0001$). When age was not included in a Cox regression model, Q1 seemed to have a lower rate of incident osteoporotic fractures (HR=0.80, 95% CI 0.66-0.98, reference Q4) and hip fractures (HR=0.63, 95% CI 0.43-0.94) for a given level of BMD. In age-adjusted regression models, total hip BMD was strongly predictive of incident osteoporotic fractures (HR per SD =1.83, 95% CI 1.68-1.99) and hip fractures (HR per SD =2.80, 95% CI 2.33-3.35), but there was no independent effect of bone area (categorical or continuous). Nested matched subgroup analysis and ROC analysis confirmed that bone area had no appreciable effect on incident fractures.

10.1.18 Optimal decision criterion for detecting change in bone mineral density during serial monitoring: A Bayesian approach
Sadatsafavi M, Moayyeri A, Wang L, Leslie WD
Osteoporos Int 2008;19:1589-96

10.1.19 Heteroscedastic regression analysis of factors affecting BMD monitoring
Sadatsafavi M, Moayyeri A, Wang L, Leslie WD
J Bone Miner Res 2008;23:1842-9

10.1.20 Improved precision with Hologic Apex software
Fan B, Lewiecki EM, Sherman M, Lu Y, Miller PD, Genant HK, Shepherd JA
Osteoporos Int 2008;19:1597-602

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Bone Material

10.1.21 The role of mineralization and organic matrix in the microhardness of bone tissue from controls and osteoporotic patients

Boivin G, Bala Y, Doublier A, Farlay D, Ste-Marie LG, Meunier PJ, Delmas PD

Bone 2008;43:532-8

The purpose of this study was to analyze the relationship between the microhardness, the degree of mineralization of bone (DMB) and the organic matrix, measured in BSUs from human iliac bone biopsies. Iliac bone samples from controls and osteoporotic patients. Assessed on the whole bone sample, microhardness and DMB were lower (-10% and -7%, respectively) in osteoporotic patients versus controls ($p<0.001$). When measured separately at the BSU level, there were positive correlations between microhardness and DMB in controls ($r^2=0.36$, $p<0.0001$) and osteoporotic patients ($r^2=0.43$, $p<0.0001$). Mineralization is an important determinant of the microhardness, but did not explain all of its variance. To highlight the role of the organic matrix in bone quality, microhardness of both osteoid and adjacent calcified matrix were measured in iliac samples from subjects with osteomalacia. Microhardness of organic matrix is 3-fold lower than the microhardness of calcified tissue. In human calcanei, microhardness correlated with DMB ($r^2=0.33$, $p=0.02$) and apparent Young's modulus ($r^2=0.26$, $p=0.03$). Bone microhardness is linked to Young's modulus of bone and is strongly correlated to mineralization, but the organic matrix accounts for about one third of its variance.

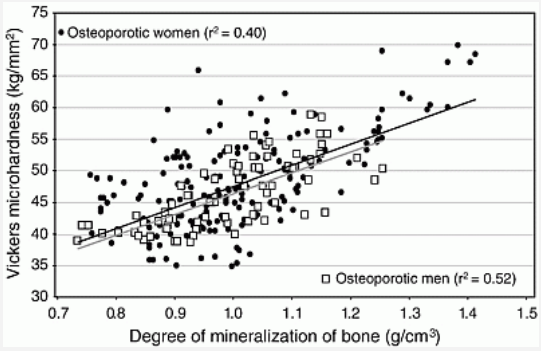

Fig. 10.1.21a Measured separately in 185 BSUs fromosteoporotic women(black dot, y=33.31x+14.87) and 80 BSUs from osteoporotic men (open square, y=32.71x+14.33), Vickers microhardness was significantly (p<0.0001) correlated with the degree of mineralization of bone. Reproduced from Bone, 43:532-8, Copyright (2008), with permission from Elsevier.

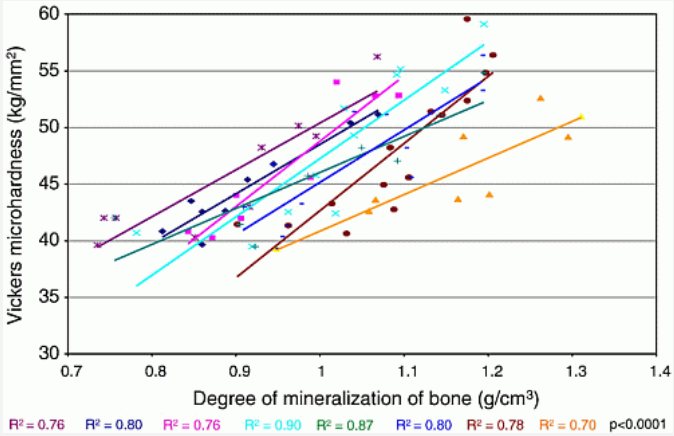

Fig. 10.1.21b In 8 osteoporotic men, there are significant correlations between the Vickers microhardness and the degree of mineralization of bone within subjects, but large between subjects variability (from $r^2=0.80$ to 0.76, the regressions equations are the following: y=0.018x +0.072, y=0.019x+0.058, y=0.014x+0.304, y=0.013x+0.349, y=0.022x−0.046, y=0.014x+0.366, y=0.012x+0.510, y=0.022x+0.133). Similar observations (not shown) were obtained in osteoporotic women. Reproduced from Bone, 43:532-8, Copyright (2008), with permission from Elsevier.

10.1.22 Quantitative assessment of bone tissue mineralization with polychromatic micro-computed tomography

Burghardt AJ, Kazakia GJ, Laib A, Majumdar S

Calcif Tissue Int 2008;83:129-38

The full length of a commercial density phantom was imaged by microCT, and mean calibration parameters were determined for a volume of interest at 10 random positions along the longitudinal axis. Phantom heterogeneity was associated with <0.5% root mean square error. The coefficient of variation for five repeat measurements was generally <0.25% across all energies and phantom densities. Bone mineral content was strongly correlated to ash weight ($R^2=1.00$ for both specimen groups and both threshold methods). Ash density was well correlated for the trabecular bone specimens ($R^2>0.80$). In cortical bone specimens, the correlation was ($R^2=0.67$) when a global threshold was applied compared to the local threshold method ($R^2=0.78$).

10.1.23 A comparison of the physical and chemical differences between cancellous and cortical bovine bone mineral at two ages
Kuhn LT, Grynpas MD, Rey CC, Wu Y, Ackerman JL, Glimcher MJ
Calcif Tissue Int 2008;83:146-54

Bovine mineral crystals from young (1-3 months) and old (4-5 years) postnatal bovine animals were analyzed. Spectra obtained from XRD, FTIR, and ^{31}P NMR all confirmed that the mineral was calcium phosphate in the form of carbonated apatite; however, a crystal maturation process was evident between the young and old and between cancellous and cortical mineral crystals. Larger increases of crystal size and Ca/P ratio for the cortical vs. cancellous bone of 1-3 month than the 4-5 year animals. The Ca/($P+CO_3$) remained nearly constant within a given bone type and in both bone types at 4-5 years. The carbonate and phosphate

FTIR band ratios revealed a decrease of labile ions with age and in cortical, relative to cancellous, bone. Overall, the same aging or maturation trends were observed for young vs. old and cancellous vs. cortical. The major differences between the cancellous and cortical mineral crystals must be ascribed to differences in average age of the crystals.

10.1.24 Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs
Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K
Osteoporos Int 2008;19:1343-54

29 one-year-old beagles (15 males, 14 females) were given vehicle or incadronate at doses of 0.3 or 0.6 mg/kg/day orally for three years. A cortex of a rib was fractionated into low and high density portions. Calcium, phosphorus, and pentosidine contents and the ratio of mature to immature crosslinks increased with incadronate in a dose-dependent manner, but the total amount of enzymatic crosslinks was unchanged. The pentosidine content correlated inversely with cortical activation frequency ($p<0.01$). Long-term suppression of bone remodeling by bisphosphonate increases degree of mineralization, collagen maturity, and nonenzymatic crosslinking.

10.1.25 Differences in matrix composition between calvaria and long bone in mice suggest differences in biomechanical properties and resorption: Special emphasis on collagen
van den Bos T, Speijer D, Bank RA, Bromme D, Everts V
Bone 2008;43:459-68

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Bone Structure

10.1.26 High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures
Vico L, Zouch M, Amirouche A, Frere D, Laroche N, Koller B, Laib A, Thomas T, Alexandre C
J Bone Miner Res 2008;23:1741-50

Postmenopausal women (C, controls, n=54; WF, wrist, n=50; HF, hip, n=62 recent fractured patients) were analyzed using principal component analysis (PCA) extracting factors that best represent bone variables. Two factors (>80% of the entire variability) are extracted by PCA: at the radius, the first is a combination of trabecular parameters and the second of cortical parameters. At the tibia, the reverse was found. Femoral neck aBMD is decreased in WF (8.6%) and in HF (18%) groups. WF showed a 20% reduction in radius trabecular vBMD and number. Radius cortical vBMD and thickness decrease by 6% and 14%, respectively. At the tibia, only the cortical compartment is affected, with a 20% reduction in bone area, thickness, and section modulus and 6% reduction in vBMD. HF showed same radius trabecular alterations than WF, but radius cortical parameters are more severely affected than WF with reduced bone area (25%), thickness (28.5%), and vBMD (11%). At the tibia, trabecular vBMD and number decrease by 26% and 17.5%, respectively. Tibia cortical bone area, thickness, and section modulus showed a >30% decrease, whereas vBMD reduction reached 13%. Geometry parameters at the tibia displayed the greatest differences between healthy and fractured patients and between wrist and hip fractures.

10.1.27 Signs of irreversible architectural changes occur early in the development of experimental osteoporosis as assessed by in vivo micro-CT
Campbell GM, Buie HR, Boyd SK
Osteoporos Int 2008;19:1409-19

The proximal tibiae of OVX (N=10) and sham (N=10) operated mature female Wistar rats were micro-CT scanned every two weeks from week 0 to week 12, excluding week 10. All of the measured architectural parameters changed over the study in the OVX group, including irreversible changes reflected by connectivity density after two weeks. Osteocalcin was elevated in the OVX group. Moderate changes in the mechanical properties of the femora midshaft and vertebrae were observed.

10.1.28 Interindividual and intraspecimen variability of 3-D bone microarchitectural parameters in iliac crest biopsies imaged by conventional micro-computed tomography
Chappard C, Marchadier A, Benhamou L
J Bone Miner Metab 2008;26:506-13

To assess the interindividual variability (inter-indVar) and the intrasample variability (intra-sampVar) of iliac crest biopsies, we used a Bordier needle trephine in 35 postmenopausal female cadavers (mean age, 74.4±10.4 years). Images were performed with a desktop microCT with a voxel size of 10.77 µm. We BV/TV, Tb.N, and PoV/TV were negatively correlated with age and Tb.Sp* and SMI were positively correlated. The mean difference of absolute individual variations in percentage with the middle area used as a reference, comparatively to external and internal areas, ranged from 6.6% (Tb.Sp*) to 27.8% (BV/TV), except Tb.Pf, which showed large variability. There was no difference between external and internal areas, with a tendency for lower values of BV/TV, Tb.Th*, and Tb.N in the middle of the iliac crest and higher values of Tb.Sp* and BS/BV. The evaluation of bone microarchitecture of iliac crest samples on microCT images is reliable.

10.1.29 Measurement of trabecular bone microstructure does not improve prediction of mechanical failure loads at the distal radius compared with bone mass alone
Lochmuller EM, Kristin J, Matsuura M, Kuhn V, Hudelmaier M, Link TM, Eckstein F
Calcif Tissue Int 2008;83:293-9

The right forearm and left distal radius of 130 human specimens were examined. The specimens were mechanically tested to failure in a fall configuration, with the hand, elbow, ligaments, and tendons intact. Cylindrical bone samples from the metaphysis of the contralateral distal radius were obtained adjacent to the subchondral bone plate and scanned with microCT. When analyzing the total sample, BMD of the distal radius displayed a correlation of r=0.82 with mechanical failure loads. After excluding 21 specimens with no obvious radiological sign of fracture after the test, the correlation increased to r=0.85. When only including 79 specimens with loco typico fractures, the correlation was r=0.82. The microstructural parameters showed correlation coefficients with the failure loads of ≤0.55 and did not add significant information to DXA in predicting failure loads in multiple regression models.

10.1.30 Cortical and trabecular bone distribution in the femoral neck in osteoporosis and osteoarthritis
Blain H, Chavassieux P, Portero-Muzy N, Bonnel F, Canovas F, Chammas M, Maury P, Delmas PD
Bone 2008;43:862-8

The authors compared the distribution of bone in the ultradistal femoral neck in 21 postmenopausal women with OA (mean age: 66 yrs) and 20 postmenopausal women with an hip fracture (OP) (mean age: 79.5 yrs). Compared to OA, cortical thickness was decreased in OP but was the highest in the inferior part in both groups. Cortical porosity was 13.48±1.02 and 8.4±1.07% in OA and OP, respectively. Compared to OA, the trabecular bone volume was decreased by 50% in OP with a diminution of the trabecular number and thickness. OP group was characterized by a poor connectivity evaluated by the decreased number of nodes ($p<0.0001$), higher trabecular bone pattern factor ($p<0.0001$) and greater marrow star volume ($p<0.0001$). The connectivity was the lowest in the inferior quadrant in OP but not in OA. Cortical thinning, the loss of the trabecular bone mass and connectivity play a role in the skeletal fragility associated with hip fracture. The spatial distribution of the trabeculae differs between OP and OA whereas cortical thinning is similar.

10.1.31 Regional variations of vertebral trabecular bone microstructure with age and gender
Chen H, Shoumura S, Emura S, Bunai Y
Osteoporos Int 2008;19:1473-83

56 fourth lumbar vertebral bodies from 28 women and men (57-98 years of age) cadaver donors. The subjects were chosen to give an even age and gender distribution. Both women and men were divided into three age groups, 62-, 77- and 92-year-old groups. Reduced bone volume (BV/TV), trabecular number (Tb.N) and connectivity density (Conn.D), and increased structure model index (SMI) were found between ages 62 and 77 years, and between ages 77 and 92 years. As compared with women, men had higher Tb.N in the 77-year-old group and higher Conn.D in the 62- and 77-year-old groups. The central and anterosuperior regions had lower BV/TV and Conn.D than their corresponding posteroinferior region. Increased resorbing surfaces, perforated or disconnected trabeculae and microcallus formations were found with age. Vertebral trabeculae are microstructurally heterogeneous. Decreases in BV/TV and Conn.D with age are similar in women and men.

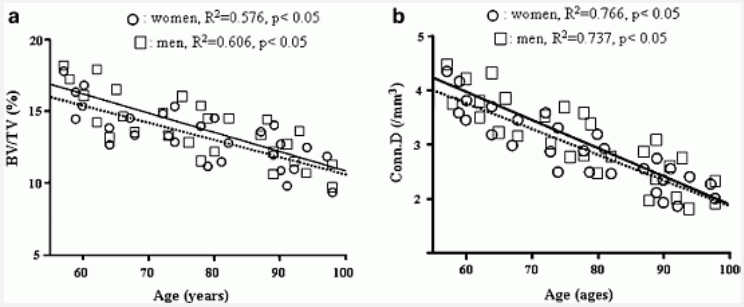

Fig. 10.1.31 Linear relationships between BV/TV and age (a), between Conn.D and age (b). BV/TV and Conn.D decreased significantly with age for both women and men. Reproduced from Osteoporos Int 2008;19:1473-83 with permission from Springer.

10.1.32 Age-and region-dependent changes in three-dimensional microstructural properties of proximal femoral trabeculae
Cui WQ, Won YY, Baek MH, Lee DH, Chung YS, Hur JH, Ma YZ
Osteoporos Int 2008;19:1579-87

162 trabecular bone cores from six regions of 27 femora of male cadaver donors were scanned using microCT. Age-related changes in trabecular microstructure varied from different regions of the proximal femur. There was a decrease in bone volume fraction and an almost identical decrease in trabecular thickness associated with aging at any region. Regional analysis demonstrated a significant difference in BV/TV, Tb.Th, Tb.Sp, Tb.N and DOA between superior and inferior neck, as well as a significant difference in BV/TV, Tb.Sp, Tb.N, SMI and DOA between superior and inferior trochanter. Age-related changes in bone loss and trabecular microstructure within the male proximal femur are not uniform in this cadaveric population.

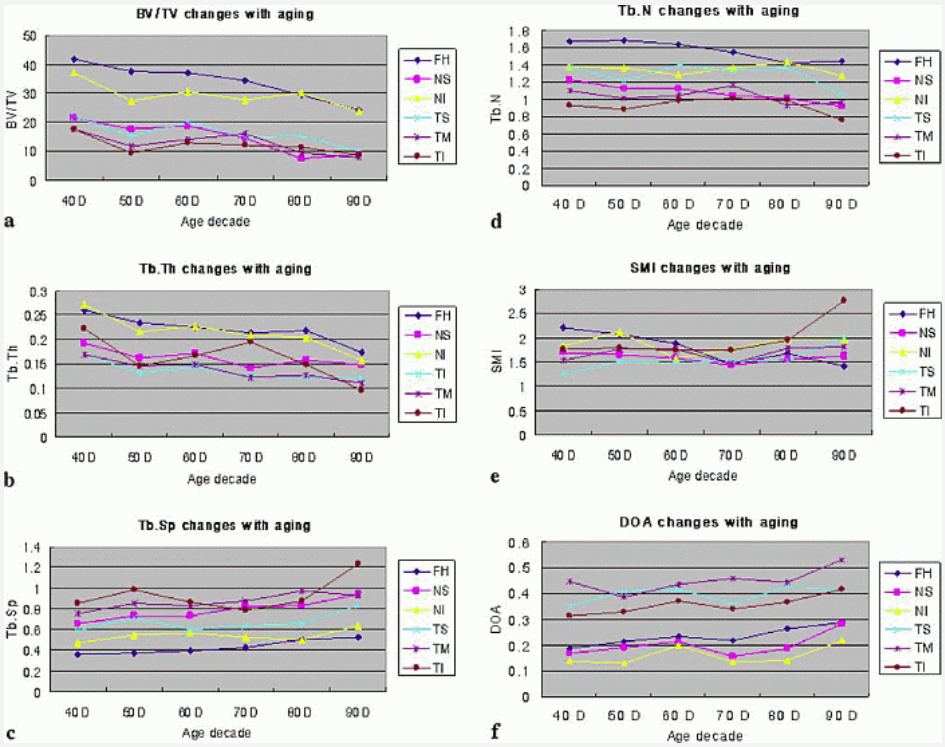

Fig. 10.1.32 (a) Age-related decrease in BV/TV showed a proximate linear fashion in all regions at different baseline, except for NI. The trend was for NI to retain the relative high volume of trabecular bone after 50 years of age. (b) Similar to BV/TV, Tb. Th decreased significantly with age in all regions, except for NS region. (c) BV/TV and Tb.Th decreased with increasing age, while the trend for Tb.Sp was toward to increase in all regions. (d) Only in FH and NS regions Tb.N significantly decreased with age, while the trend for NI and TI was toward to increase. (e) With increasing age, SMI significantly increased in three regions of the trochanter. (f) The trend for DOA was toward to increase with aging in all regions.

10.1.33 Three-dimensional microstructure of the bone in a hamster model of senile osteoporosis
Chen H, Zhou X, Washimi Y, Shoumura S
Bone 2008;43:494-500

Using microCT, in the proximal tibia and distal femur, trabecular bone volume (BV/TV), trabecular number (Tb.N), trabecular

thickness (Tb.Th) and BMD increased to a maximum at 6 or 12 months and then declined progressively from 12 to 24 months of age. Trabecular separation (Tb.Sp), trabecular bone pattern factor (TBPf) and structure model index increased with age. As compared with male hamsters, BV/TV and Tb.N were significantly lower in females at 18 and 24 months of age. Age-related decrease of trabecular BV/TV in the vertebral body was less than that of the femoral and tibial metaphyses. In the mid-femoral diaphysis, cortical bone area remained constant from 3 to 24 months of age. Cortical thickness decreased from 12 to 24 months and cortical BMD declined significantly from 18 to 24 months of age.

10.1.34 Differential effects of bone structural and material properties on bone competence in C57BL/6 and C3H/He inbred strains of mice
Voide R, van Lenthe GH, Muller R
Calcif Tissue Int 2008;83:61-9

A low bone mass phenotype, C57BL/6 (B6), and a high bone mass phenotype, C3H/He (C3H) were studied with femora of 12- and 16-week-old B6 and 12- and 16-week-old C3H inbred strains tested under axial loading of the femoral head. B6 femora became stiffer, stronger, and tougher at 12-16 weeks, while bone brittleness stayed constant. C3H bone stiffness increased, but strength remained constant, work to failure decreased, and bone became more brittle. These age effects indicated that B6 did not reach peak bone properties at 16 weeks of age and C3H did reach maximal skeletal biomechanical properties before 16 weeks of age. Our investigations showed that 83% of the strength of the femoral neck in the B6 strain was explained by cortical thickness at this location; in contrast, in C3H none of the mechanical properties of the femoral neck was explained by bone structural parameters. The relative contributions of bone structural and material properties on bone strength are different in B6 and C3H.

10.1.35 Effects of long-term immobilisation on cortical bone mass after traumatic amputation of the phalanges estimated by digital X-ray radiogrammetry
Schafer ML, Pfeil A, Renz DM, Lehmann G, Schmidt M, Hansch A, Hein G, Wolf G, Kaiser WA, Bottcher J
Osteoporos Int 2008;19:1291-9

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Histomorphology

10.1.36 Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease stages 3-5
Lehmann G, Ott U, Kaemmerer D, Schuetze J, Wolf G
Clin Nephrol 2008;70:296-305

Progress in
OSTEOPOROSIS
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editor E. Seeman

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Biomechanics

10.1.37 Microarchitecture influences microdamage accumulation in human vertebral trabecular bone
Arlot ME, Burt-Pichat B, Roux JP, Vashishth D, Bouxsein ML, Delmas PD
J Bone Miner Res 2008;23:1613-8

Microdamage in cancellous bone from human lumbar (L2) vertebral bodies obtained from 23 donors 54-93 yr of age (8 men and 15 women) was measured using histologic techniques of sequential labeling with chelating agents and was related to 3D microarchitecture, as assessed by high-resolution microCT. There were no significant differences between sexes, although women tended to have a higher microcrack density (Cr.Dn) than men. Cr.Dn increased with age (r=0.65, p<0.001) and correlated with BV/TV; r=–0.55; p<0.01, trabecular number (Tb.N; r=–0.56 p=0.008), structure model index (SMI; r=0.59; p=0.005), and trabecular separation (Tb.Sp; r=0.59; p<0.009). SMI was the best predictor of microdamage, explaining 35% of the variance in Cr.Dn and 20% of the variance in diffuse damage accumulation. In addition, microcrack length was significantly greater in the highest versus lowest tertiles of SMI. In conclusion, in human vertebral cancellous bone, microdamage increases with age and is associated with low BV/TV and a rod-like trabecular architecture.

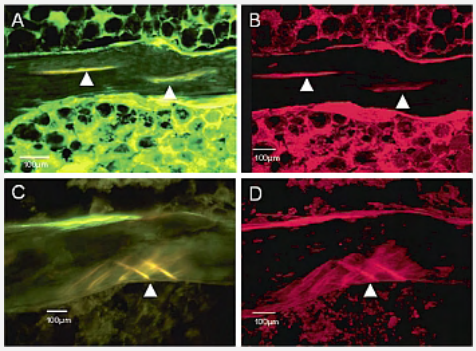

Fig. 10.1.37a Representative micrographs of a linear microcrack (A and B) and diffuse damage (C and D) under brightfield (A and C) and laser scanning confocal (B and D) microscopy. Reproduced from J Bone Miner Res 2008;23:1613-8 with permission of the American Society of Bone and Mineral Research.

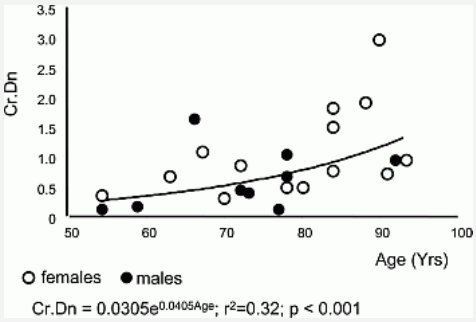

Fig. 10.1.37b Variation of linear microcrack density as a function of donor age in human vertebral cancellous bone. Reproduced from J Bone Miner Res 2008;23:1613-8 with permission of the American Society of Bone and Mineral Research.

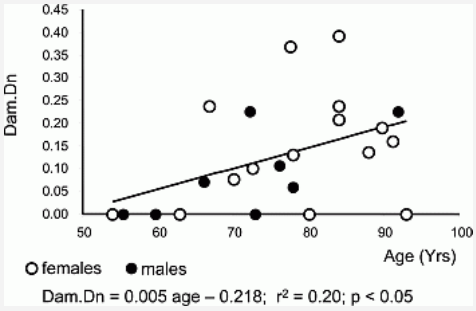

Fig. 10.1.37c Variation of diffuse damage density as a function of donor age in human vertebral cancellous bone. Reproduced from J Bone Miner Res 2008;23:1613-8 with permission of the American Society of Bone and Mineral Research.

10.1.38 Relating osteon diameter to strain
van Oers RF, Ruimerman R, van Rietbergen B, Hilbers PA, Huiskes R
Bone 2008;43:476-82

Osteon diameter is smaller in regions that experience larger strains. Strain-induced osteocyte signals inhibit osteoclastic bone resorption. This mechanism was shown to produce load-aligned osteons in computer simulations. It also predicts smaller

osteon diameter for higher loads. Additionally, osteon development with two cutting cones may occur, one moving up and one moving down the loading axis. A steep gradient in strain magnitude can result in an osteonal tunnel with continuous resorption along the less strained side, which corresponds to 'drifting osteons' reported in literature.

10.1.39 In vivo linear microcracks of human femoral cortical bone remain parallel to osteons during aging
Wasserman N, Brydges B, Searles S, Akkus O
Bone 2008;43:856-61

Longitudinal cross sections were taken at the mid-diaphysis of femurs from 13 male donors (23-85 years old) after staining with basic fuchsin. The mean crack density was 0.1118±0.0417 mm^{-2} in the longitudinal plane and increased with age. The median crack length along the longitudinal plane did not change with age. The crack length in the posterior quadrant was lower than anterior, medial and lateral quadrants. Less than 3% of the cracks were longer than 1 mm, indicating the presence of 'in vivo macroscopic' cracks in bone tissue. It was observed that the 99% of the cracks had angles that were less than 25° with the osteons (median angle of 4.2° with an interquartile range of 5.8°), indicating that the majority in vivo linear microcracks are parallel to osteons. The stagnant crack length and crack orientation across decades of aging suggest that either physiological loading profile leading to these in vivo microcracks are not changing notably with age, or, microcrack and osteonal orientations may be relatively insensitive to age-related changes in locomotion. In conclusion, in vivo linear microcracks of the femoral midshaft grow in planes parallel to osteons and their lengths do not increase with age.

10.1.40 The effects of increased intracortical remodeling on microcrack behaviour in compact bone
Kennedy OD, Brennan O, Mauer P, Rackard SM, O'Brien FJ, Taylor D, Lee TC
Bone 2008;43:889-93

It is not known how cracks behave in areas of increased intracortical remodeling. More remodeling creates wider variation in the properties of osteons. We hypothesized that osteon age would influence microcrack behaviour during propagation. Compact bone (2×2×36 mm) were harvested from the right metatarsal. Samples were cyclically loaded to failure. Cracks were categorized as short (<100 μm), intermediate (100-300 μm) and long (>300 μm). Numerical crack density (Cr.Dn) of long cracks was greater in controls compared with OVX. Controls also displayed a higher crack surface density (Cr.S.Dn) compared with OVX ($p<0.05$). The behaviour of short cracks did not differ between old and new osteons, but intermediate and long cracks preferentially stopped at newer osteons compared with older ones ($p<0.05$). This mechanism may have an important role in terms of prolonging fatigue life. We conclude that recently formed osteons have a unique influence on propagating microcracks compared with older osteons.

10.1.41 Prediction of the fracture load of whole proximal femur specimens by topological analysis of the mineral distribution in DXA-scan images
Boehm HF, Horng A, Notohamiprodjo M, Eckstein F, Burklein D, Panteleon A, Lutz J, Reiser M
Bone 2008;43:826-31

Femoral BMD of 100 hip specimens was obtained by DXA. Maximum compressive strength (MCS) of the specimens was measured in a mechanical loading device simulating a fall on the greater trochanter. The topology of bone mineral distribution in the scan images was evaluated by image processing methods based on the Minkowski functionals (MF) using the optimized topological parameter MF2D. R^2 for the correlation between load-to-failure and BMD varied between 0.73 and 0.79 being highest in the trochanteric ROI. Correlation between load-to-failure of the specimens with the topological parameter MF2D ranged from R^2=0.8 to 0.91. In a multivariate model combining the topological information from all ROIs, correlation with MCS rose to R^2=0.94.

10.1.42 Tissue modulus calculated from beam theory is biased by bone size and geometry: Implications for the use of three-point bending tests to determine bone tissue modulus
van Lenthe GH, Voide R, Boyd SK, Muller R
Bone 2008;43:717-23

Murine femora are not perfect beams. Beam theory underestimates tissue modulus. Femoral geometry and size had strong effects on beam theory-derived tissue moduli. Owing to their relatively thin cortex, underestimation was higher for B6 than C3H. Underestimation was dependent on support width in a strain-specific manner. From our combined experimental-computational approach tissue moduli were 12.0±1.3 GPa and 13.4±2.1 GPa for B6 and C3H, respectively.

10.1.43 Estimation of hydrodynamic shear stresses developed on human osteoblasts cultured on Ti-6Al-4V and strained by four point bending. Effects of mechanical loading to specific gene expression
Kokkinos PA, Zarkadis IK, Panidis TT, Deligianni DD
J Mater Sci Mater Med 2008;[Epub ahead of print]

Homogeneous strain was applied to human bone marrow derived osteoblasts cultured on Ti-6Al-4V, at levels which are considered physiological, by a four-point bending mechanostimulatory system. Mechanical loading contributes to the regulation of osteoblast differentiation by influencing the expression of the osteoblast-specific transcription factor Cbfa1, both at the mRNA and protein level, and also the osteocalcin expression, whereas osteopontin gene expression was unaffected by mechanical loading at all experimental conditions.

10.1.44 Mechanical properties of physiological and pathological models of collagen peptides investigated via steered molecular dynamics simulations
Gautieri A, Vesentini S, Montevecchi FM, Redaelli A
J Biomech 2008;41:3073-7

10.1.45 Effect of LIMK2 RNAi on reorganization of the actin cytoskeleton in osteoblasts induced by fluid shear stress
Fu Q, Wu C, Shen Y, Zheng S, Chen R
J Biomech 2008;[Epub ahead of print]

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Growth

10.1.46 Deiodinase-mediated thyroid hormone inactivation minimizes thyroid hormone signaling in the early development of fetal skeleton
Capelo LP, Beber EH, Huang SA, Zorn TM, Bianco AC, Gouveia CH
Bone 2008;43:921-30

10.1.47 Skeletogenesis in Xenopus tropicalis: Characteristic bone development in an anuran amphibian
Miura S, Hanaoka K, Togashi S
Bone 2008;43:901-9

10.1.48 Cooperative regulation of chondrocyte differentiation by CCN2 and CCN3 shown by a comprehensive analysis of the CCN family proteins in cartilage
Kawaki H, Kubota S, Suzuki A, Lazar N, Yamada T, Matsumura T, Ohgawara T, Maeda T, Perbal B, Lyons KM, Takigawa M
J Bone Miner Res 2008;23:1751-64

10.1.49 Microarray analysis of perichondral and reserve growth plate zones identifies differential gene expressions and signal pathways
Zhang M, Pritchard MR, Middleton FA, Horton JA, Damron TA
Bone 2008;43:511-20

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Remodelling Markers

10.1.50 Bone markers predict cardiovascular events in chronic kidney disease
Fahrleitner-Pammer A, Herberth J, Browning SR, Obermayer-Pietsch B, Wirnsberger G, Holzer H, Dobnig H, Malluche HH
J Bone Miner Res 2008;23:1850-8

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Bone Formation

10.1.51 Granulocyte colony-stimulating factor induces osteoblast apoptosis and inhibits osteoblast differentiation
Christopher MJ, Link DC
J Bone Miner Res 2008;23:1765-74

Long-term treatment with granulocyte colony-stimulating factor (G-CSF) is associated with osteopenia, increased osteoclast activity and number, and a decrease in number of mature osteoblasts. G-CSF treatment in mice leads to decreased numbers of endosteal and trabecular osteoblasts. The effect is specific to mature osteoblasts, because bone-lining cells, osteocytes, and periosteal osteoblasts are unaffected. G-CSF treatment accelerates osteoblast turnover in the marrow by inducing osteoblast apoptosis. In addition, whereas G-CSF increases osteoprogenitor number, differentiation of mature osteoblasts is impaired. Bone marrow transplantation studies show that G-CSF acts through a hematopoietic intermediary to suppress osteoblasts. Finally, G-CSF, through suppression of mature osteoblasts, also leads to a marked decrease in osteoprotegerin expression in the bone marrow, whereas expression of RANKL remains relatively constant, suggesting a novel mechanism contributing to the increased osteoclastogenesis seen with long-term G-CSF treatment. In sum, these findings suggest that the hematopoietic system may play a novel role in regulating osteoblast differentiation and apoptosis during G-CSF treatment.

10.1.52 IGF-I secreted by osteoblasts acts as a potent chemotactic factor for osteoblasts
Nakasaki M, Yoshioka K, Miyamoto Y, Sasaki T, Yoshikawa H, Itoh K
Bone 2008;43:869-79

IGF-I induced cell migration of both MC3T3-E1 cells and primary mouse osteoblasts, and checkerboard analysis revealed that IGF-I induced directional migration (chemotaxis) of osteoblasts. Neutralization of mouse IGF-I with monoclonal antibodies resulted in delayed osteoblast monolayer wound healing and cellular polarization but addition of human IGF-I reversed these effects. IGF-I also promoted cell spreading on fibronectin in an integrin β1-dependent manner. IGF-I induced Akt and Rac activation and localized accumulation of phosphatidylinositol 3,4,5-triphosphate (PtdIns (3,4,5)P3) at the membrane in osteoblasts. The phosphatidyl inositol 3 kinase (PI3K) inhibitor LY294002 inhibited IGF-I-induced cell migration and wound healing.

10.1.53 Bril: A novel bone-specific modulator of mineralization
Moffatt P, Gaumond MH, Salois P, Sellin K, Bessette MC, Godin E, Tambasco de Oliveira P, Atkins GJ, Nanci A, Thomas G
J Bone Miner Res 2008;23:1497-508

10.1.54 Pressure, oxygen tension and temperature in the periosteal callus during bone healing: An in vivo study in sheep
Epari DR, Lienau J, Schell H, Witt F, Duda GN
Bone 2008;43:734-9

10.1.55 B-cell infiltrates induce endosteal bone formation in inflammatory arthritis
Hayer S, Polzer K, Brandl A, Zwerina J, Kireva T, Smolen JS, Schett G
J Bone Miner Res 2008;23:1650-60

10.1.56 Bax deficiency in mice increases cartilage production during fracture repair through a mechanism involving increased chondrocyte proliferation without changes in apoptosis
Rundle CH, Wang X, Sheng MH, Wergedal JE, Lau KH, Mohan S
Bone 2008;43:880-8

10.1.57 Heparanase expression and activity influences chondrogenic and osteogenic processes during endochondral bone formation
Brown AJ, Alicknavitch M, D'Souza SS, Daikoku T, Kirn-Safran CB, Marchetti D, Carson DD, Farach-Carson MC
Bone 2008;43:689-99

10.1.58 Calmodulin-dependent kinase 1beta is expressed in the epiphyseal growth plate and regulates proliferation of mouse calvarial osteoblasts in vitro
Pedersen ME, Fortunati D, Nielsen M, Brorson SH, Lekva T, Nissen-Meyer LS, Gautvik VT, Shahdadfar A, Gautvik KM, Jemtland R
Bone 2008;43:700-7

10.1.59 Dissection of sets of genes that control the character of wnt5a-deficient mouse calvarial cells
Guo J, Jin J, Cooper LF
Bone 2008;43:961-71

10.1.60 Fracture healing in mice deficient in plasminogen activator inhibitor-1
Rundle CH, Wang X, Wergedal JE, Mohan S, Lau KH
Calcif Tissue Int 2008;83:276-84

10.1.61 The endothelin system mediates bone modeling in the late stage of orthodontic tooth movement in rats
Sprogar S, Vaupotic T, Cor A, Drevensek M, Drevensek G
Bone 2008;43:740-7

10.1.62 Molecular basis for affected cartilage formation and bone union in fracture healing of the streptozotocin-induced diabetic rat
Ogasawara A, Nakajima A, Nakajima F, Goto K, Yamazaki M
Bone 2008;43:832-9

10.1.63 Latent TGF-beta binding proteins (LTBPs)-1 and -3 coordinate proliferation and osteogenic differentiation of human mesenchymal stem cells
Koli K, Ryynanen MJ, Keski-Oja J
Bone 2008;43:679-88

10.1.64 PDGF receptor beta is a potent regulator of mesenchymal stromal cell function
Tokunaga A, Oya T, Ishii Y, Motomura H, Nakamura C, Ishizawa S, Fujimori T, Nabeshima Y, Umezawa A, Kanamori M, Kimura T, Sasahara M
J Bone Miner Res 2008;23:1519-28

10.1.65 Use of an alpha-smooth muscle actin GFP reporter to identify an osteoprogenitor population
Kalajzic Z, Li H, Wang LP, Jiang X, Lamothe K, Adams DJ, Aguila HL, Rowe DW, Kalajzic I
Bone 2008;43:501-10

10.1.66 LMP-1 retroviral gene therapy influences osteoblast differentiation and fracture repair: A preliminary study
Strohbach CA, Rundle CH, Wergedal JE, Chen ST, Linkhart TA, Lau KH, Strong DD
Calcif Tissue Int 2008;83:202-11

10.1.67 The peroxisome proliferator activator receptor alpha/delta agonists linoleic acid and bezafibrate upregulate osteoblast differentiation and induce periosteal bone formation in vivo
Still K, Grabowski P, Mackie I, Perry M, Bishop N
Calcif Tissue Int 2008;83:285-92

10.1.68 NMDA enhances stretching-induced differentiation of osteobalsts through the ERK1/2 signaling pathway
Li JL, Cui B, Qi L, Li XY, Deng LF, Ning G, Liu JM
Bone 2008;43:469-75

10.1.69 Wnt and steroid pathways control glutamate signalling by regulating glutamine synthetase activity in osteoblastic cells
Olkku A, Mahonen A
Bone 2008;43:483-93

10.1.70 Electrophysiological properties of a novel ca(2+)-activated k (+) channel expressed in human osteoblasts
Hirukawa K, Muraki K, Ohya S, Imaizumi Y, Togari A
Calcif Tissue Int 2008;83:222-9

10.1.71 Dual delivery of an angiogenic and an osteogenic growth factor for bone regeneration in a critical size defect model
Patel ZS, Young S, Tabata Y, Jansen JA, Wong ME, Mikos AG
Bone 2008;43:931-40

10.1.72 Osteogenesis depending on geometry of porous hydroxyapatite scaffolds
Yoshikawa M, Tsuji N, Shimomura Y, Hayashi H, Ohgushi H
Calcif Tissue Int 2008;83:139-45

10.1.73 MEPE-ASARM peptides control extracellular matrix mineralization by binding to hydroxyapatite: An inhibition regulated by PHEX cleavage of ASARM
Addison WN, Nakano Y, Loisel T, Crine P, McKee MD
J Bone Miner Res 2008;23:1638-49

10.1.74 mRNA expression and protein distribution of fibronectin splice variants and high-molecular weight tenascin-C in different phases of human fracture healing
Kilian O, Dahse R, Alt V, Zardi L, Hentschel J, Schnettler R, Kosmehl H
Calcif Tissue Int 2008;83:101-11

10.1.75 Osteopontin functions as an opsonin and facilitates phagocytosis by macrophages of hydroxyapatite-coated microspheres: Implications for bone wound healing
Pedraza CE, Nikolcheva LG, Kaartinen MT, Barralet JE, McKee MD

Bone 2008;43:708-16

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Bone Resorption

10.1.76 High molecular weight tropomyosins regulate osteoclast cytoskeletal morphology
Kotadiya P, McMichael BK, Lee BS
Bone 2008;43:951-60

Tropomyosins are coiled-coil dimers that bind to the major groove of F-actin and regulate its accessibility to actin-modifying proteins. Osteoclasts, which undergo rounds of polarization and depolarization as they progress through the resorptive cycle, possess an actin cytoskeleton. Osteoclasts express two closely related tropomyosins of the high molecular weight type, which are not expressed in monocytic and macrophage precursors. These isoforms, Tm-2 and Tm-3, are not strongly associated with actin-rich adhesion structures, but are instead distributed diffusely throughout the cell. Tm-2/3 expression occurs late in osteoclastogenesis and continues to increase as cells mature. Knockdown of these isoforms via RNA interference results in flattening and increased spreading of osteoclasts, accompanied by diminished motility and altered resorptive capacity. In contrast, overexpression of Tm-2, but not Tm-3, caused morphological changes that include decreased spreading of the cells and induction of actin patches or stress fiber-like actin filaments, also with effects on motility and resorption. Suppression of Tm-2/3 or overexpression of Tm-2 resulted in altered distribution of gelsolin and microfilament barbed ends. These data suggest that high molecular weight tropomyosins are expressed in fusing osteoclasts to regulate the cytoskeletal scaffolding of these large cells, due at least in part by moderating accessibility of gelsolin to these microfilaments.

10.1.77 Lrp6 hypomorphic mutation affects bone mass through bone resorption in mice and impairs interaction with mesd
Kubota T, Michigami T, Sakaguchi N, Kokubu C, Suzuki A, Namba N, Sakai N, Nakajima S, Imai K, Ozono K
J Bone Miner Res 2008;23:1661-71

10.1.78 Ion transporters involved in acidification of the resorption lacuna in osteoclasts
Henriksen K, Sorensen MG, Jensen VK, Dziegiel MH, Nosjean O, Karsdal MA
Calcif Tissue Int 2008;83:230-42

10.1.79 Plasminogen activators are involved in the degradation of bone by osteoclasts
Everts V, Daci E, Tigchelaar-Gutter W, Hoeben KA, Torrekens S, Carmeliet G, Beertsen W
Bone 2008;43:915-20

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Osteocytes

10.1.80 Osteocyte morphology in fibula and calvaria - Is there a role for mechanosensing?
Vatsa A, Breuls RG, Semeins CM, Salmon PL, Smit TH, Klein-Nulend J
Bone 2008;43:452-8

If osteocytes sense matrix strains directly via their cytoskeleton, the 3D shape and the long axes of osteocytes in fibulae and calvariae will bear alignment to the different mechanical loading patterns. Fibular osteocytes showed a relatively elongated morphology (ratio lengths 5.9:1.5:1), whereas calvarial osteocytes were relatively spherical (ratio lengths 2.1:1.3:1). Osteocyte lacunae in fibulae had higher unidirectional alignment than the osteocyte lacunae in calvariae as demonstrated by their degree of anisotropy (3.33 and 2.10, respectively). The long axes of osteocyte lacunae in fibulae were aligned parallel to the principle mechanical loading direction, whereas those of calvarial osteocyte lacunae were not aligned in any particular direction. The anisotropy of osteocytes and their alignment to the local mechanical loading condition suggest that these cells are able to directly sense matrix strains due to external loading of bone. The relatively spherical morphology of calvarial osteocytes suggests that these cells are more mechanosensitive than fibular osteocytes, which provides a possible explanation of efficient physiological load bearing for the maintenance of calvarial bone despite its condition of relative mechanical disuse.

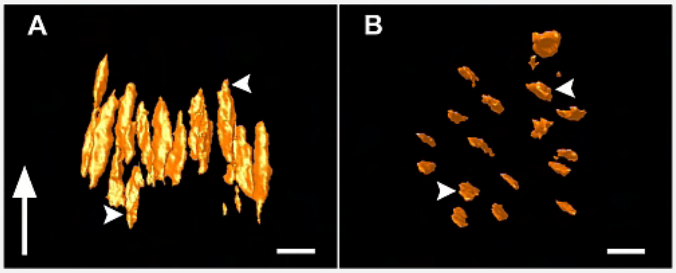

Fig. 10.1.80 3D reconstruction of individual osteocyte lacunae in adult mouse fibula by using nanocomputed tomography scans. A) Longitudinal view, showing the unidirectional alignment of long axes of osteocyte lacunae (arrow heads) parallel to the principle mechanical loading direction (large arrow), in a section of adult mouse fibula. Bar 15 µm. B) Transverse view, showing the thickness of individual lacunae (arrow heads). Bar, 15 µm. Reproduced from Bone, 43:452-8, Copyright (2008), with permission from Elsevier.

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Systemic Factors

10.1.81 Comparison of sex steroid measurements in men by immunoassay versus mass spectroscopy and relationships with cortical and trabecular volumetric bone mineral density
Khosla S, Amin S, Singh RJ, Atkinson EJ, Melton Iii LJ, Riggs BL
Osteoporos Int 2008;19:1465-71

Serum testosterone (T) and non-SHBG bound (or bioavailable) T levels by immunoassay correlated well with the corresponding mass spectroscopy measurements (R=0.90 and 0.95, respectively, P<0.001); the correlations for serum E_2 measured using the two techniques were less robust (R=0.63 for total E_2 and 0.84 for bioavailable E_2, P<0.001).

10.1.82 The relationship of serum osteocalcin concentration to insulin secretion, sensitivity and disposal with hypocaloric diet and resistance training
Fernandez-Real JM, Izquierdo M, Ortega F, Gorostiaga E, Gomez-Ambrosi J, Moreno-Navarrete JM, Fruhbeck G, Martinez C, Idoate F, Salvador J, Forga L, Ricart W, Ibanez J
J Clin Endocrinol Metab 2008;[Epub ahead of print]

In a cross-sectional in 149 men (using minimal model); and 2 longitudinal in 2 independent groups (one formed by 26 women, and the other by 9 men and 11 women), after a mean of 7.3% and 16.8% weight loss; and after a mean of 8.7% weight loss plus regular exercise. In the cross-sectional study, circulating osteocalcin was associated with insulin sensitivity, mainly in lean subjects, and with insulin secretion (only in lean subjects). A mean of 16.8%, but not 7.3% weight loss, led to significant increases in circulating osteocalcin. However, a mean of 8.7% weight loss plus regular exercise led to the more pronounced effects on the serum osteocalcin, which increased in parallel to reduced visceral fat mass, unchanged thigh muscle mass, and increased leg strength and force. The post-intervention serum levels of osteocalcin were associated with both insulin sensitivity (r=0.49, p=0.03) and fasting triglycerides (r=–0.54, p=0.01). The change in visceral fat was the parameter that best predicted the change in serum osteocalcin, once age, BMI and insulin sensitivity changes were controlled for (p=0.002). Circulating osteocalcin could mediate the role of bone as an endocrine organ in humans.

10.1.83 Expression and regulation of the vitamin D receptor in the zebrafish, Danio rerio
Craig TA, Sommer S, Sussman CR, Grande JP, Kumar R
J Bone Miner Res 2008;23:1486-96

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Local Factors

10.1.84 Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23
Yamazaki Y, Tamada T, Kasai N, Urakawa I, Aono Y, Hasegawa H, Fujita T, Kuroki R, Yamashita T, Fukumoto S, Shimada T
J Bone Miner Res 2008;23:1509-18

10.1.85 Overexpression of bone sialoprotein leads to an uncoupling of bone formation and bone resorption in mice
Valverde P, Zhang J, Fix A, Zhu J, Ma W, Tu Q, Chen J
J Bone Miner Res 2008;23:1775-88

10.1.86 SMAD3 functions as a transcriptional repressor of acid-sensing ion channel 3 (ASIC3) in nucleus pulposus cells of the intervertebral disc
Uchiyama Y, Guttapalli A, Gajghate S, Mochida J, Shapiro IM, Risbud MV
J Bone Miner Res 2008;23:1619-28

10.1.87 Annexin-mediated matrix vesicle calcification in vascular smooth muscle cells
Chen NX, O'Neill KD, Chen X, Moe SM
J Bone Miner Res 2008;23:1798-805

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Risk Factors

10.1.88 Case finding for the management of osteoporosis with FRAX®-assessment and intervention thresholds for the UK
Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A
Osteoporos Int 2008;19:1395-408

The FRAX® tool computes the 10-year probability of fractures in from clinical risk factors (CRFs) with or without the measurement of femoral neck BMD. Fracture probabilities were computed using the FRAX® tool calibrated to the epidemiology of fracture and death in the UK. The relationship between cost effectiveness and fracture probability used the source data from a prior publication that examined the cost effectiveness of generic alendronate in the UK. An intervention threshold was set by age in men and women, based on the fracture probability equivalent to that of women with a history of a prior osteoporosis related fracture. Treatment was cost effective at all ages when the 10-year probability of a major fracture exceeded 7%. The intervention threshold at the age of 50 years corresponded to a 10-year probability of a major osteoporotic fracture of 7.5%. This rose progressively with age to 30% at the age of 80 years, so that intervention was cost effective at all ages. Assessment thresholds for testing with BMD (6-9% at the age of 50 years) also rose with age (18-36% at the age of 80 years). The use of these thresholds in a case-finding strategy would identify 6-20% of women as eligible for BMD testing and 23-46% as eligible for treatment, depending on age. The same threshold can be used in men.

10.1.89 Validation of ten-year fracture risk prediction: A clinical cohort study from the Manitoba Bone Density Program
Leslie WD, Tsang JF, Lix LM
Bone 2008;43:667-71

20,579 women age 47.5 years or older at the time of baseline femoral neck BMD were identified. Health service records assessed fracture codes (86,447 person-years follow up, 1173 patients with osteoporotic fractures). Fracture rates were derived for subgroups stratified by age (5-year strata) and estimated risk (5% strata). Direct and actuarial methods gave nearly identical point estimates, but the latter were more precise. There was a strong linear correlation between predicted and observed fracture rates based upon age only (r=0.95) and age plus BMD (r=0.99). For age strata 50 to 75, and for estimated risk strata from 0-5% to 20-25%, the confidence intervals overlapped the line of identity. For women age >77.5 or estimated risk >25%, observed exceeded estimated fracture rates. Corrected for survival bias, women age >77.5 had observed fracture rates no different than predicted. Swedish 10-year fracture risk data are generally applicable to the Canadian female population.

10.1.90 Vertebral fracture assessment (VFA) with a densitometer predicts future fractures in elderly women unselected for osteoporosis
McCloskey EV, Vasireddy S, Threlkeld J, Eastaugh J, Parry A, Bonnet N, Beneton M, Kanis JA, Charlesworth D
J Bone Miner Res 2008;23:1561-8

Women (n=5157) ≥75 yr of age in the community underwent imaging of the spine (T4-L4) with a densitometer (Hologic QDR4500A) at entry to a trial of 800 mg oral clodronate or placebo daily over 3 yr. The proportion of vertebrae interpretable varied from 98.2% at T1) to 57.1% at T4, with >92% interpretable at levels between T8 and L3. By BMD at the total hip, 19.6% of the women had osteoporosis, the prevalence of vertebral fracture was 14.5%. Women with one or more vertebral fractures had a RR for incident osteoporotic fractures of 2.01 (1.64-2.47). The RR for hip fractures was 2.29 (1.63-3.21). After adjustment for age, femoral neck BMD, weight, and treatment, the RR was 1.50 (1.21-1.86) for osteoporotic fractures, with similar results for hip fractures RR=1.41 (0.99-2.02). For women with two or more vertebral fractures, the adjusted RRs were 1.97 (1.24-2.72) and 1.86 (1.14-3.03) for osteoporotic and hip fractures, respectively.

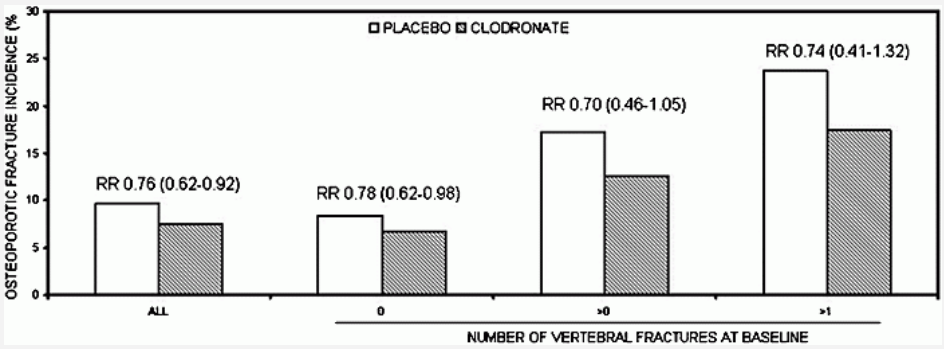

Fig. 10.1.90 Incidence of osteoporotic fractures for the placebo and clodronate-treated groups with respect to baseline vertebral fracture status. Reproduced from J Bone Miner Res 2008;23:1561-8 with permission of the American Society of Bone and Mineral Research.

10.1.91 Hip fractures in institutionalized elderly people: Incidence rates and excess mortality
Rapp K, Becker C, Lamb SE, Icks A, Klenk J
J Bone Miner Res 2008;23:1825-31

A cohort of >69,000 women and men admitted to nursing homes were used to calculate sex- and age-specific incidence rates of hip fractures. To each patient with a hip fracture (n=4342), four residents without hip fracture (n=17,368) were matched by sex, age, and level of care (measure for the need of care). During 91,850 person-years, 4342 hip fractures were observed; incidence rates were 50.8/1000 in women and 32.7/1000 person-years in men. Mortality was increased (women: hazard rate ratio for the first 3 mo after fracture, 1.72; 95% CI 1.59-1.86; men: hazard ratio, 2.14; 95% CI 1.80-2.53), but excess mortality was limited to the first months after injury.

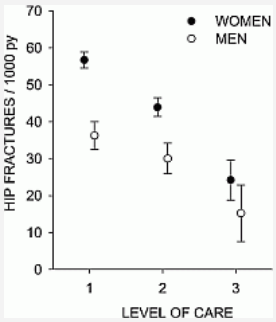

Fig. 10.1.91a Incidence rate of hip fractures stratified by level of care in the cohort of residents admitted to nursing homes in Baden-Württemberg between 2000 and 2005. py, person-years. Reproduced from J Bone Miner Res 2008;23:1825-31 with permission of the American Society of Bone and Mineral Research.

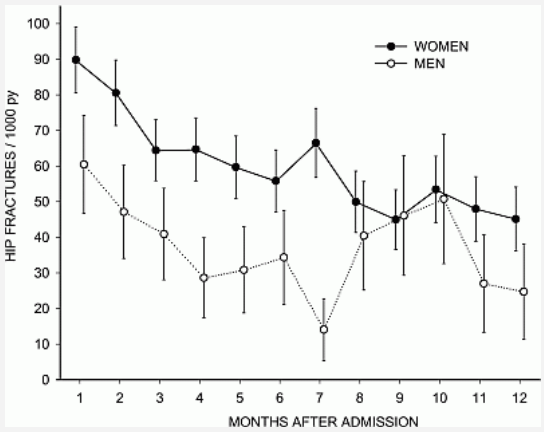

Fig. 10.1.91b Incidence rate of hip fractures stratified by the time distance to home admission in the cohort of residents admitted to nursing homes in Baden-Württemberg between 2000 and 2005. py, person-years. Reproduced from J Bone Miner Res 2008;23:1825-31 with permission of the American Society of Bone and Mineral Research.

10.1.92 Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks
Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV
Osteoporos Int 2008;19:1431-44

The Dubbo Osteoporosis Epidemiology Study was designed as a community-based prospective study, with 1358 women and 858 men aged 60+ years as at 1989. Between 1989 and 2004, 426 women and 149 men had sustained a low trauma fracture (not including morphometric vertebral fractures). Two prognostic models based on the Cox's proportional hazards analysis were considered: model I included age, BMD, prior fracture and falls; and model II included age, weight, prior fracture and fall. Analysis of AUC suggested that model I (AUC=0.75 for both sexes) performed better than model II (AUC=0.72 for women and 0.74 for men). If the 5-year risk of 10% or greater is considered "high risk", then virtually all 80-year-old men with BMD T-scores<–1.0 or 80-year-old women with T-scores<–2.0 were predicted to be in the high risk group. A 60-year-old woman's risk was considered high risk only if her BMD T-scores≤–2.5 and with a prior fracture; however, no 60-year-old men would be in the high risk regardless of their BMD and risk profile.

10.1.93 Relationship of blood lead levels to incident nonspine fractures and falls in older women: The study of osteoporotic fractures
Khalil N, Cauley JA, Wilson JW, Talbott EO, Morrow L, Hochberg MC, Hillier TA, Muldoon SB, Cummings SR
J Bone Miner Res 2008;23:1417-25

This was a prospective cohort of 533 women 65-87 years of age enrolled in the Study of Osteoporotic Fractures at two U.S. research centers (Baltimore, MD; Monongahela Valley, PA) from 1986 to 1988. Blood lead levels (in µg/dl) were measured in 1990-1991 and classified as "low" (≤3; lower 15th percentile, referent); "medium" (4-7); or "high" (≥8; upper 15th percentile). Total hip BMD was measured by DXA twice, 3.55 years apart. The mean blood lead level was 5.3±2.3 (SD) µg/dl (range, 1-21 µg/dl). Baseline BMD was 7% lower in total hip and 5% lower in femoral neck in the highest compared with lowest blood lead group (p<0.02). Hip bone loss tended to be greater in the high lead group, but differences were not significant. In multivariable adjusted models, women with high blood lead levels had an increased risk of nonspine fracture (HR=2.50; 95% CI 1.25, 5.03; p trend=0.016) and higher risk of falls (incident rate ratio=1.62; 95% CI 1.07, 2.45; p trend=0.014) compared with women with lowest lead level.

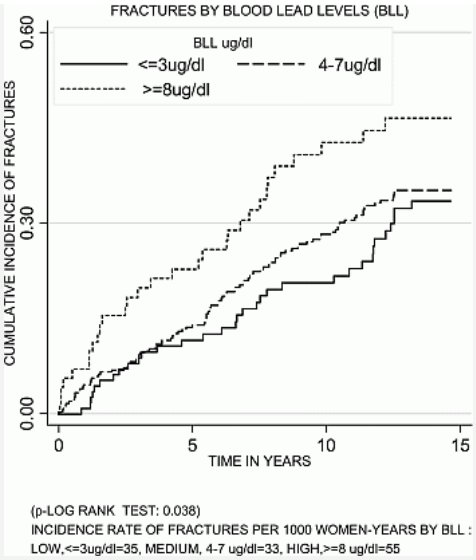

Fig. 10.1.93 Cumulative incidence of fractures in women in SOF across blood lead levels. Reproduced from J Bone Miner Res 2008;23:1417-25 with permission of the American Society of Bone and Mineral Research.

10.1.94 Acid-suppressive medications and risk of bone loss and fracture in older adults
Yu EW, Blackwell T, Ensrud KE, Hillier TA, Lane NE, Orwoll E, Bauer DC
Calcif Tissue Int 2008;83:251-9

In 5755 men and 5339 women, men using either PPIs or H2RAs had lower cross-sectional bone mass. No significant BMD differences were observed among women. However, there was an increased risk of nonspine fracture among women using PPIs (relative hazard [RH]=1.34, 1.10-1.64). PPI use was also associated with an increased risk of nonspine fracture in men but only among those who were not taking calcium supplements (RH=1.49, 95% CI 1.04-2.14). H2RA use was not associated with nonspine fractures, and neither H2RA use nor PPI use was associated with incident hip fractures in men or women. The use of PPIs in older women, and perhaps older men with low calcium intake, may be associated with a modestly increased risk of nonspine fracture.

10.1.95 Grip strength may facilitate fracture prediction in perimenopausal women with normal BMD: A 15-year population-based study
Sirola J, Rikkonen T, Tuppurainen M, Jurvelin JS, Alhava E, Kroger H
Calcif Tissue Int 2008;83:93-100

In 971 perimenopausal women fractures during the 15-year were recorded based on self-reports and validated from medical records. In the total sample and in osteopenic or osteoporotic women (T-score<–1, n=284) grip strength was not associated with fracture-free survival rate (P=nonsignificant in Cox regression). In women with normal baseline BMD (N-BMD, T-score>–1, n=687) the lowest grip strength quartile had a lower fracture-free survival rate in the Cox proportional hazard model (P=0.005, hazard ratio [HR]=2.0). In the multivariate Cox regression model, T-score and grip strength were the only predictors of 15-year fracture-free survival in the N-BMD group and a risk index (RI) was formed according to HRs of these two variables. High RI (0-5 points) was associated with lower 15-year fracture-free survival rate (P=0.001, HR=0.137) in the N-BMD group. In contrast, 5-year T-score was no better a predictor of fractures in the baseline N-BMD group (P=0.04, HR=0.36). In conclusion, grip strength predicts 15-year fracture-free survival with N-BMD, while 5-year DXA does not seem to be any better a predictor of fracture risk.

10.1.96 Relationship between grip strength and bone mineral density in healthy Hong Kong adolescents
Chan DC, Lee WT, Lo DH, Leung JC, Kwok AW, Leung PC
Osteoporos Int 2008;19:1485-95

Cross-sectional data of 169 11- to 12-year-old boys and 173 10- to 11-year-old girls came from the baseline result of a cohort study. Significant correlations were shown between grip strength and bone mass at hip, spine and whole body (boys: BMC:0.72-0.74, BMD:0.38-0.60; girls: BMC:0.71-0.72, BMD:0.44-0.63; p<0.0001). Multiple regressions with all covariates showed that about 70% and 50%, respectively, of the variations in BMC and BMD could be explained but not for whole body BMD. Grip strength was an independent predictor of bone mass, except hip BMD in boys and whole body BMD in girls. Stepwise regression showed that grip strength was a robust predictor in both sexes. Prediction models by grip strength and weight explained about 60% and 40% of the variations in BMC of different sites and in BMD of hip and spine, respectively.

10.1.97 Abdominal aortic calcification, BMD, and bone microstructure: A population-based study
Chow JT, Khosla S, Melton LJ, Atkinson EJ, Camp JJ, Kearns AE
J Bone Miner Res 2008;23:1601-12

Abdominal aortic calcification (AAC), BMD, and bone microstructure in 693 residents was assessed with QCT of the spine and hip and high-resolution pQCT of the radius. In men, AAC did not correlate with lower vertebral trabecular and femoral neck vBMD (p<0.001) after adjustment. BV/TV and Tb.Th inversely correlated with AAC in all men (p<0.001), and Tb.Th remained correlated after age adjustment (p<0.05). Tb.N positively correlated with AAC in younger men (p<0.001) but negatively in older men (p<0.001). The opposite was true with Tb.Sp (p=0.01 and p<0.001, respectively). Lower Tb.N and higher Tb.Sp correlated with AAC in older men even after adjustment. Among all women and postmenopausal women, AAC correlated with lower vertebral and femoral neck vBMD (p<0.001) but not after adjustment. Lower BV/TV and Tb.Th correlated with AAC (p=0.03 and p=0.04, respectively) in women, but not after adjustment. The findings support an age-dependent association between AAC and vBMD. AAC correlates with specific bone microstructural parameters in older men, suggesting a possible common pathogenesis for vascular calcification and deterioration in bone structure.

10.1.98 Treatment with potassium bicarbonate lowers calcium excretion and bone resorption in older men and women
Dawson-Hughes B, Harris SS, Palermo NJ, Castaneda-Sceppa C, Rasmussen HM, Dallal GE
J Clin Endocrinol Metab 2008;[Epub ahead of print]

171 men and women age 50 and older were randomized to placebo or 67.5 mmol/d of potassium bicarbonate, sodium bicarbonate, or potassium chloride for 3 mo. All received calcium (600 mg of calcium as triphosphate) and 525 IU of vitamin D3 daily. Bicarbonate affected the study outcomes whereas potassium did not; the two bicarbonate groups and the two no bicarbonate groups were therefore combined. Subjects taking bicarbonate had reductions in urinary N-telopeptide and calcium excretion, when compared with subjects taking no Bicarbonate. Potassium supplementation did not affect N-telopeptide or calcium excretion. Bicarbonate, but not potassium, had a favorable effect on bone resorption and calcium excretion. This suggests that increasing the alkali content of the diet may attenuate bone loss in healthy older adults.

10.1.99 A bone structural basis for fracture risk in diabetes
Melton LJ, 3rd, Riggs BL, Leibson CL, Achenbach SJ, Camp JJ, Bouxsein ML, Atkinson EJ, Robb RA, Khosla S
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Diabetic and nondiabetic subjects were evaluated in a cross-sectional study. 49 (28 women and 21 men) with type 2 diabetes were compared to age- and sex-matched nondiabetic controls. Adjusted for differences in BMI between cases and controls (29.8 vs. 27.6), hip aBMD was greater in diabetic subjects, but this was accounted for by greater trabecular vBMD. Cortical vBMD was similar in the two groups, as was bone cross-sectional area and cortical thickness. Bone strength measures were generally better in diabetic subjects, but bone loads were higher from their greater weight. Consequently, load to strength ratios (i.e., factor-of-risk) were similar.

10.1.100 Bone mineral density at menopause does not predict breast cancer incidence
Tremollieres FA, Pouilles JM, Laparra J, Ribot C
Osteoporos Int 2008;19:1497-504

2,137 women reviewed 13.1 years after their initial examination. 98 incident breast cancer (BC) cases were recorded throughout the follow-up. Women with incident BC differed from those who had never had BC with regard to age at menarche, age of birth of first child, familial history of BC and postmenopausal hormone therapy use. There was no significant difference between the two groups for baseline DXA of the spine.

10.1.101 Current socio-economic measures, and not those measured during infancy, affect bone mass in poor urban South African children
Norris SA, Sheppard ZA, Griffiths PL, Cameron N, Pettifor JM
J Bone Miner Res 2008;23:1409-16

Understanding the impact of socio-economic status (SES) on bone development in in 9/10-yr-old black children (n=309) living in Soweto and Johannesburg, South Africa. Findings suggest that current SES measures, rather than SES during infancy, are stronger predictors of current whole body bone area (BA) and whole body BMC after adjusting for body size, pubertal development, physical activity, habitual dietary calcium intake, and body composition. SES had no significant effect on either hip or spine bone mass. Caregiver's marital/cohabiting status (indicator of social support) and whether there was a television in the home (indicator of greater income) at age 9/10 years were the most important socio-economic determinants of whole body BA and BMC. SES has a significant independent effect on whole body BMC through its impact on BA. This suggests that poverty alleviation policies in South Africa could have a positive effect on bone health.

10.1.102 Association between quantitative measures of skin color and plasma 25-hydroxyvitamin D
Rockell JE, Skeaff CM, Williams SM, Green TJ
Osteoporos Int 2008;19:1639-42

The aim of this study was to determine the association between constitutive (natural) and sun-induced skin color and 25OHD in a group of Pacific People (n=87) and Europeans (n=255) living in NZ (46° S) in summer. Mean (SD) 25OHD was higher in Europeans than Pacific People, 88 (31) nmol/L vs. 75 (34) nmol/L, respectively. Based on constitutive skin color, 35% of participants were very light, 45% light, 16% intermediate, 4% tanned, and 0% brown or dark. Skin color at the forearm but not constitutive skin color was a predictor of 25OHD. Each 10 degrees lower skin color value at the forearm (more tanning) was associated with a 5 nmol/L higher 25OHD (P<0.001). Tanning but not natural skin color was an important determinant of 25OHD. Further study is needed in a population with a higher proportion of darker skin people.

10.1.103 Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures
Leboff MS, Hawkes WG, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J
Osteoporos Int 2008;19:1283-90

110 community-dwelling women with hip fractures were recruited from Boston, MA (n=30) and Baltimore, MD (n=80) before 1998 and 25(OH)D levels were measured by radioimmunoassay. Vitamin D insufficiency defined as a 25(OH)D ≤32 ng/mL was present in 96% of the women with hip fractures and 38% had extremely low levels ≤9 ng/mL. At one year post-fracture, compared to women with a 25(OH)D >9 ng/mL, those with 25(OH)D ≤9 ng/mL had poorer LEGS performance (p<0.0001) and higher fall rates, without group differences in grip strength or balance.

10.1.104 Vitamin D deficiency and supplementation during pregnancy
Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S
Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

A prospective randomized study 180 women (Indian Asian, Middle Eastern, Black and Caucasian) were recruited at 27 weeks gestation and randomized into a single oral dose of 200,000 IU vitamin D, a daily supplement of 800 IU vitamin D from 27 weeks until delivery and a no treatment group. The final maternal 25-hydroxyvitamin D levels were higher in the supplemented group (daily dose (median) 42 (IQR 31-76) nmol/l, stat dose (median 34 (IQR 30-46) nmol/l vs. median 27 (IQR 27-39) nmol/l in the no treatment; p<0.0001) and fewer women with secondary hyperparathyroidism in the supplemented group (10% in daily dose vs. 12% in stat dose vs. 27% in the no treatment; p<0.05). Cord 25-hydroxyvitamin D levels were higher with supplementation (daily dose median 26 (IQR 17-45) nmol/l, stat dose median 25 (IQR 18-34) nmol/l vs. median 17 (IQR 14-22) nmol/l in no treatment; p=0.001). Single or daily dose improved 25-hydroxyvitamin D levels. However, even with

supplementation, only a small percentage of women and babies were vitamin D sufficient. Further research is required to determine the optimal timing and dosing of vitamin D in pregnancy.

10.1.105 Vitamin D metabolites and calcium absorption in severe vitamin D deficiency
Need AG, O'Loughlin PD, Morris HA, Coates PS, Horowitz M, Nordin BC
J Bone Miner Res 2008;23:1859-63

Vitamin D insufficiency does not cause malabsorption of calcium because serum 1,25(OH)(2)D is maintained by secondary hyperparathyroidism. 319 subjects with a serum 25(OH)D ≤40 nM, in whom calcium absorption, serum calcium, PTH, bone markers, and vitamin D metabolites had been measured. They were grouped into 0-10, 11-20, 21-30, and 31-40 nM 25D and differences between the groups were tested by ANOVA. Serum calcium, 1,25(OH)(2)D, and calcium absorption were decreased and serum PTH and alkaline phosphatase (ALP) and urine hydroxyproline were increased in those with 25(OH)D ≤10 nM. Serum ALP and urine hydroxyproline were more strongly related, inversely, to calcium absorption than to the vitamin D metabolites. Vitamin D deficiency does not reduce calcium absorption, until the serum 25(OH)D falls to approximately 10 nM.

10.1.106 Rapid correction of low vitamin D status in nursing home residents
Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N
Osteoporos Int 2008;19:1621-8

This prospective study included 63 nursing home residents. The 25 with low vitamin D status (serum 25(OH)D ≤25 ng/ml) received oral ergocalciferol 50,000 IU three times weekly for four weeks; the others received no change to their routine care. Mean total 25 (OH)D increased ($p<0.0001$) from 17.3 to 63.8 ng/ml in the treated group and remained unchanged in the comparison group. Serum 25(OH)D(3) remained stable in the comparison group, but declined ($p<0.0001$) with D(2) treatment from 15.4 to 9.1 ng/ml. Serum PTH trended down in the treatment group ($p=0.06$). No treatment-induced improvement in ambulation, cognition or behavior was observed. No hypercalcemia or other adverse effects were observed with ergocalciferol treatment. Four weeks of oral vitamin D (2) supplementation effectively and safely normalizes serum 25(OH)D in nursing home residents.

10.1.107 Circulating 25-hydroxyvitamin D, VDR polymorphisms, and survival in advanced non-small-cell lung cancer
Heist RS, Zhou W, Wang Z, Liu G, Neuberg D, Su L, Asomaning K, Hollis BW, Lynch TJ, Wain JC, Giovannucci E, Christiani DC
J Clin Oncol 2008;[Epub ahead of print]

The relationship between circulating 25-hydroxyvitamin D levels; VDR polymorphisms, including Cdx-2 G>A (rs11568820), FokI C>T (rs10735810), and BsmI C>T (rs144410) was assessed with survival among patients with advanced NSCLC. There were 294 patients and 233 deaths, with median follow-up of 42 months. We found no difference in survival by circulating vitamin D level. The C/C genotype of the FokI polymorphism was associated with improved survival: median survival for C/C was 21.4 months, for C/T was 12.1 months, and for T/T was 15.6 months (log-rank P=0.005). There were no effects on survival by the Cdx-2 or BsMI polymorphism. However, having increasing numbers of protective alleles was associated with improved survival (adjusted hazard ratio for two or more vs. zero to one protective alleles, 0.57; 95% CI, 0.41-0.79; P=0.0008). On haplotype analysis, the G-T-C (Cdx-2-FokI-BsmI) haplotype was associated with worse survival compared with the most common haplotype of G-C-T (adjusted hazard ratio, 1.61; 95% CI, 1.21-2.14; P=0.001). There was no effect of vitamin D level on overall survival in the advanced NSCLC population. The T allele of the VDR FokI>T polymorphism and the G-T-C (Cdx-2-FokI-BsmI) haplotype were associated with worse survival.

10.1.108 Vitamin D depletion induces RANKL-mediated osteoclastogenesis and bone loss in a rodent model
Anderson PH, Sawyer RK, Moore AJ, May BK, O'Loughlin PD, Morris HA
J Bone Miner Res 2008;23:1789-97

Six groups of 10-wk-old male Sprague Dawley rats (n=42) were fed a diet containing 0.4% calcium and various levels of dietary vitamin D(3) for 4 mo to achieve stable mean serum 25D levels ranging between 10 and 115 nM. At 7 mo of age, animals were killed. In the distal femoral metaphysis, trabecular bone mineral volume (BV/TV) showed a positive association with circulating 25D levels ($r^2=0.42$, $p<0.01$) in the animals with serum 25D levels between 20 and 115 nM. Osteoclast surface (Oc. S) levels were positively associated with RANKL:OPG mRNA ratio, higher in groups with lower serum 25D levels. Serum 25D levels <80 nM gave rise to osteopenia as a result of increased osteoclastogenesis, suggesting that levels of 25D >80 nM are needed for optimal bone volume. These data indicate that serum 25D levels are a major determinant of osteoclastogenesis and bone mineral volume and are consistent with the levels of 25D recommended to reduce the risk of fracture in humans.

10.1.109 PPARG by dietary fat interaction influences bone mass in mice and humans
Ackert-Bicknell CL, Demissie S, Marin de Evsikova C, Hsu YH, DeMambro VE, Karasik D, Cupples LA, Ordovas JM, Tucker KL, Cho K, Canalis E, Paigen B, Churchill GA, Forejt J, Beamer WG, Ferrari S, Bouxsein ML, Kiel DP, Rosen CJ
J Bone Miner Res 2008;23:1398-408

A QTL for vBMD, Bmd8, was found on mid-distal chromosome (Chr) 6 in mice. This region is homologous to human Chr 3p25. The B6.C3H-6T (6T) congenic mouse was previously created to study this QTL. Peroxisome proliferator activated receptor gamma (Pparg) was determined to be the most likely candidate gene for the Bmd8 QTL of the 630 genes located in the congenic region. Furthermore, in the C3H/HeJ (C3H) strain, which is the donor strain for the 6T congenic, several polymorphisms were found in the Pparg gene. With a high-fat diet, the 6T mouse has a lower aBMD and BV/TV of the distal femur compared with B6 mice. Interactions between SNPs in the PPARG gene and dietary fat for the phenotype of BMD were examined in the Framingham Offspring Cohort. This analysis showed that there was a similar interaction of the PPARG gene and diet (fat intake) on aBMD in both men and women.

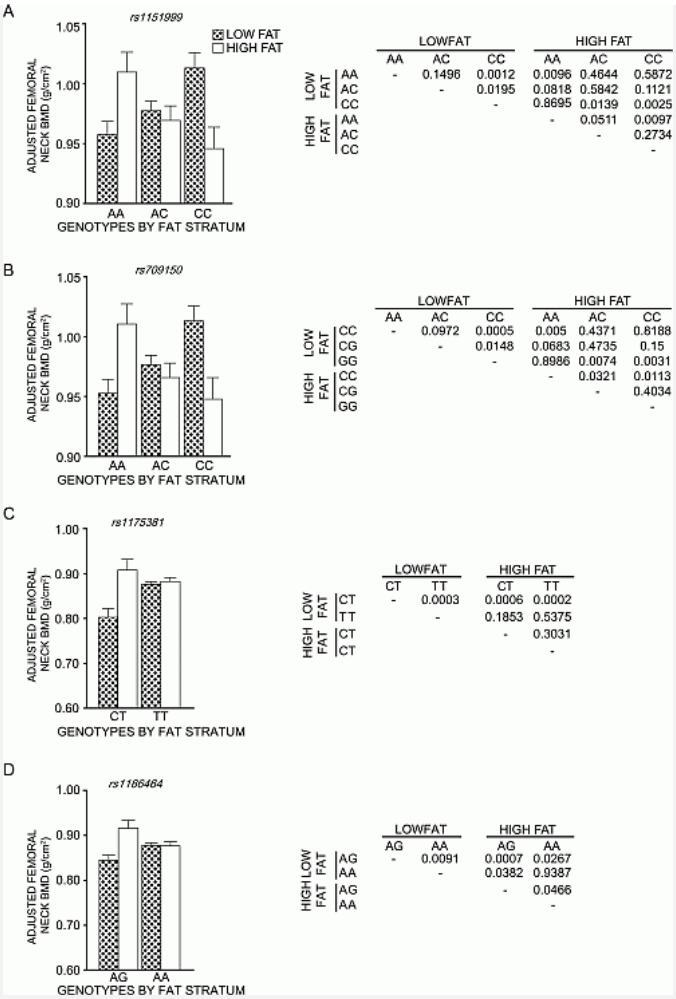

Fig. 10.1.109 Diet by SNP allele interactions in the Framingham Offspring cohort. A significant SNP allele by percent energy derived from dietary fat interaction was observed for SNP 6 (A, rs1151999) and SNP 7 (B, rs709150) in men and for SNP 12 (C, rs1175381) and SNP 13 (D, rs1186464) in women. SNPs 6 and 7 are in strong linkage disequilibrium (LD), with a D' of 0.996 and an r^2 of 0.976, and as a consequence, yielded virtually the same result. In addition, a D' of 1 and an r^2 of 0.338 were noted for SNPs 12 and 13. The p values for the interaction between a given SNP and energy intact (%KJ from total fat) were as follows: SNP 6, p=0.0004; SNP7, p=0.0002; SNP12, p=0.002; SNP13, p=0.002). This interaction is visually presented in for each SNP in the graph. The results to the right of each graph shows the p values obtained from pairwise comparisons by fat stratum and genotypes. Reproduced from J Bone Miner Res 2008;23:1398-408 with permission of the American Society of Bone and Mineral Research.

10.1.110 Leptin treatment prevents type I diabetic marrow adiposity but not bone loss in mice
Motyl KJ, McCabe LR
J Cell Physiol 2008;[Epub ahead of print]

T1-diabetic mice with chronic (28 days) received subcutaneous infusion of leptin or saline. Leptin prevented the increase of marrow adipocytes and the increased aP2 expression that we observed in vehicle-treated diabetic mice. However, leptin did not prevent T1-diabetic decreases in trabecular bone volume fraction or bone mineral density in tibia or vertebrae. Consistent with this finding, markers of bone formation (osteocalcin RNA and serum levels) in diabetic mice were not restored to normal levels with leptin treatment. Interestingly, markers of bone resorption (TRAP5 RNA and serum levels) were decreased in diabetic mice by leptin treatment.

10.1.111 Dextran sodium sulfate-induced colitis causes rapid bone loss in mice
Hamdani G, Gabet Y, Rachmilewitz D, Karmeli F, Bab I, Dresner-Pollak R
Bone 2008;43:945-50

Colitis was induced by adding dextran sodium sulfate (DSS) to the drinking water for 2 weeks to 9-week-old Balb/C male mice. DSS-treated mice exhibited lower bone mass, decreased trabecular number (23%) and connectivity density (37%). No changes were observed in cortical bone indices. Osteopenia resulted from suppressed bone formation, as indicated by decreased trabecular double-labeled surface (dL%) of 90%, mineralizing surface (MS) of 62%, and bone formation rate (BFR) of 67%, and increased bone resorption as indicated by a 34% increase in osteoclast number in DSS-treated mice compared to the controls. Myeloperoxidase activity inversely correlated with trabecular BV/TV (r=−0.67, p=0.02), trabecular number (r=−0.86, p=0.0008) and connectivity density (r=−0.63, p=0.03). Myeloperoxidase activity inversely correlated with the bone formation indices: dL%, MS, and BFR (r=−0.79, p=0.007, r=−0.84, p=0.002, r=−0.83, p=0.003, respectively). DSS-induced colitis is associated with reduced femoral bone mass and altered micro architecture, which results from suppressed bone formation and increased bone resorption. The decrease in indices of bone mass, structure and formation are directly linked to the degree of colonic mucosal inflammation. DSS-induced colitis can be used to study pharmacological interventions for bone loss in colitis.

10.1.112 Geographic variation of bone mineral density and selected risk factors for prediction of incident fracture among Canadians 50 and older
Langsetmo L, Hanley DA, Kreiger N, Jamal SA, Prior J, Adachi JD, Davison KS, Kovacs C, Anastassiades T, Tenenhouse A, Goltzman D
Bone 2008;43:672-8

10.1.113 Sodium and bone health: Impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women
Teucher B, Dainty JR, Spinks CA, Majsak-Newman G, Berry DJ, Hoogewerff JA, Foxall RJ, Jakobsen J, Cashman KD, Flynn A, Fairweather-Tait SJ
J Bone Miner Res 2008;23:1477-85

10.1.114 Relationship of calcification of atherosclerotic plaque and arterial stiffness to bone mineral density and osteoprotegerin in postmenopausal women referred for osteoporosis screening
Frost ML, Grella R, Millasseau SC, Jiang BY, Hampson G, Fogelman I, Chowienczyk PJ
Calcif Tissue Int 2008;83:112-20

10.1.115 The relationship of ghrelin and adiponectin with bone mineral density and bone turnover markers in elderly men
Gonnelli S, Caffarelli C, Del Santo K, Cadirni A, Guerriero C, Lucani B, Franci B, Nuti R
Calcif Tissue Int 2008;83:55-60

10.1.116 BMD and bone geometry in transtibial and transfemoral amputees
Sherk VD, Bemben MG, Bemben DA
J Bone Miner Res 2008;23:1449-57

10.1.117 Bone steady-state is established at reduced bone strength after spinal cord injury: A longitudinal study using peripheral quantitative computed tomography (pQCT)
Frotzler A, Berger M, Knecht H, Eser P
Bone 2008;43:549-55

10.1.118 Increased cortical remodeling after osteotomy causes posttraumatic osteopenia
Augat P, Claes L
Bone 2008;43:539-43

10.1.119 Relationship between arterial calcification and bone loss in a new combined model rat by ovariectomy and vitamin d(3) plus nicotine
Park JH, Omi N, Iemitsu M, Maeda S, Kitajima A, Nosaka T, Ezawa I
Calcif Tissue Int 2008;83:192-201

10.1.120 The magnitude and rate of bone loss in ovariectomized mice differs among inbred strains as determined by longitudinal in vivo micro-computed tomography
Klinck J, Boyd SK
Calcif Tissue Int 2008;83:70-9

10.1.121 Increased longitudinal growth in rats on a silicon-depleted diet
Jugdaohsingh R, Calomme MR, Robinson K, Nielsen F, Anderson SH, D'Haese P, Geusens P, Loveridge N, Thompson RP, Powell JJ
Bone 2008;43:596-606

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 1, 2008

Falls

10.1.122 Factors associated with hip fracture-related falls among patients with a history of recurrent falling
Formiga F, Navarro M, Duaso E, Chivite D, Ruiz D, Perez-Castejon JM, Lopez-Soto A, Pujol R
Bone 2008;43:941-4

In 1225 patients admitted because of a hip fracture secondary to a fall (index fall), those patients with a history of three or more falls (recurrent fallers) in the year prior to the index fall were identified as high-risk fallers; those with less than three falls were considered to be sporadic fallers. The mean number of falls in the year prior to the index fall was 1.7±6.5; 227 patients (22%) had experienced three or more falls within that period. Most index falls (880, 71.8%) took place at the patient's home, 232 (18.95%) in the street and 113 (9.2%) elsewhere; most (892, 72.9%) took place during day time. Recurrent fallers were characterized by poorer baseline independence for activities of the daily living, a prior diagnosis of dementia, greater use of prescription drugs and a greater use of neuroleptics. For frequent fallers, the index fall was more often associated with an intrinsic factor than for sporadic fallers.

10.1.123 Hip axis length variation: Its correlation with anthropometric measurements in women from three ethnic groups
Clark P, Tesoriero LJ, Morton DJ, Talavera JO, Karlamangla A, Schneider DL, Wooten WJ, Barrett-Connor E
Osteoporos Int 2008;19:1301-6

157 non-Hispanic white women from the Rancho Bernardo Study, 292 women from the Health Assessment Study of African-American Women, and 210 women from the Skeletal Health of Mexican-American Women Project had ethnic differences in the unadjusted hip axis length (HAL) measurement, after adjusting for hip circumference, there were no residual differences in HAL with regard to ethnicity: 10.7 cm in Mexican-American women vs. 10.8 in non-Hispanic white women and African-American women (p=0.61). There were no ethnic differences in HAL in women from the three ethnic groups. Differences in fracture risk among these groups cannot be explained by ethnic differences in HAL.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 1, 2008

Treatment

10.1.124 Benefit of adherence with bisphosphonates depends on age and fracture type: Results from an analysis of 101,038 new bisphosphonate users

Curtis JR, Westfall AO, Cheng H, Lyles K, Saag KG, Delzell E

J Bone Miner Res 2008;23:1435-41

In conjunction with fracture incidence rates among the nonadherent, estimates were used to compute the number needed to treat with high adherence to prevent one fracture, by age and fracture type. Among 101,038 new bisphosphonate users, the proportion of persons with high adherence at 1, 2, and 3 years was 44%, 39%, and 35%, respectively. Among 65- to 78-yr-old persons with a physician diagnosis of osteoporosis, the crude and adjusted rate of hip fracture among the nonadherent was 1.96 (95% CI 1.48-2.60) and 1.74 (95% CI 1.30-2.31), respectively, resulting in a number needed to treat with high adherence to prevent one hip fracture of 107. The impact of high adherence was substantially less for other types of fractures and for younger persons. Analysis of adherence in a non-time-dependent fashion artifactually magnified differences in fracture rates between adherent and nonadherent persons. The antifracture effectiveness associated with high adherence to oral bisphosphonates varied substantially by age and fracture type.

10.1.125 Fracture outcomes related to persistence and compliance with oral bisphosphonates

Gallagher AM, Rietbrock S, Olson M, van Staa TP

J Bone Miner Res 2008;23:1569-75

The General Practice Research database was used to identify patients ≥18 yr of age prescribed alendronate or risedronate in 44,531 patients; 58.3% continued bisphosphonate for >1 yr and 23.6% for >5 yr. The risk of hip/femur fracture [RR], 0.78; 95% CI 0.64-0.94) and osteoporotic fracture (RR, 0.85; 95% CI 0.76-0.94) were lower with current than past bisphosphonate use. The largest reduction in hip/femur and osteoporotic fracture risk was observed in patients treated for at least 6 mo and no reduction in those treated for <6 mo. The risks of hip/femur and osteoporotic fractures followed the pattern of nonosteoporotic fractures in the first 6 mo but then started to reduce after 6-12 mo of treatment. Increased risks were found in patients with low compliance. Use of bisphosphonates was associated with fracture risk reductions after 6-12 mo of treatment, but only 58% of the patients were treated for at least 1 year.

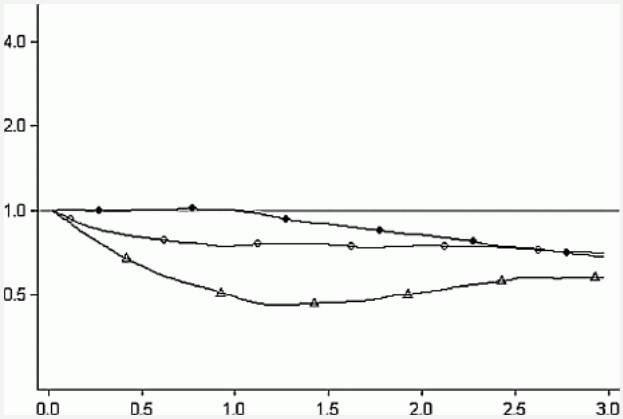

Fig. 10.1.125a Ratio of the hazard rates of osteoporotic or hip/femur fracture compared with non-osteoporotic fractures with duration of bisphosphonate treatment (○, osteoporotic fractures; ●, hip/femur fractures; △, vertebral fractures). The smoothed hazard rates were estimated for each fracture type over 100 periods of time during current bisphosphonate use; the ratio of osteoporotic (or hip/femur) over nonosteoporotic were estimated and standardized to the ratio in the first time period after starting bisphosphonates. y axis, RR; x axis, duration of bisphosphonate treatment (yr). Reproduced from J Bone Miner Res 2008;23:1569-75 with permission of the American Society of Bone and Mineral Research.

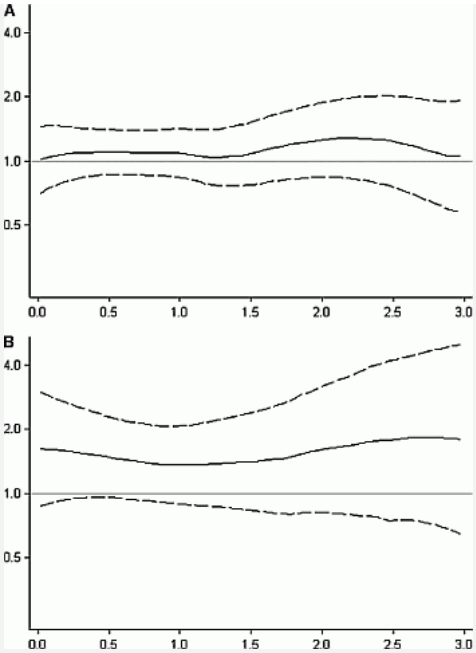

Fig. 10.1.125b Ratio of hazard rates of osteoporotic and hip/femur fractures during current bisphosphonate use in patients who started with risedronate compared with those who started alendronate. y axis, RR; x axis, duration of bisphosphonate treatment (yr). Reproduced from J Bone Miner Res 2008;23:1569-75 with permission of the American Society of Bone and Mineral Research.

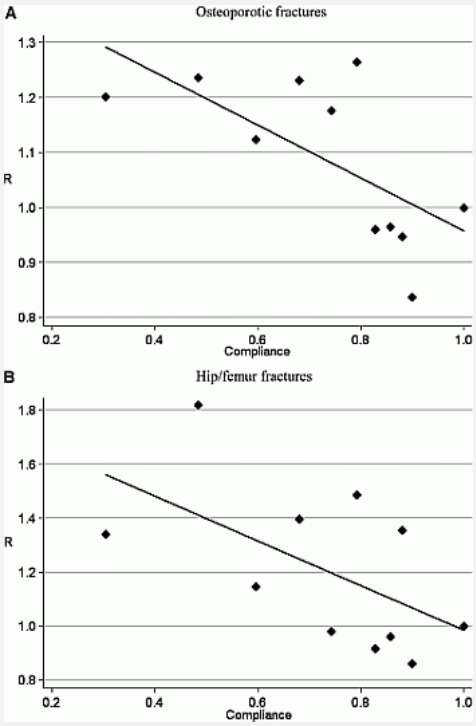

Fig. 10.1.125c RR of osteoporotic and hip/femur fracture for different levels of compliance during current bisphosphonate use. The reference group consisted of patients with compliance 0.90-1.0; patients with compliance <0.90 were divided into 10 subgroups based on the deciles of compliance, and RRs were estimated within each subgroup. The line represents a linear regression of the RRs. y axis, RR; x axis, compliance. Reproduced from J Bone Miner Res 2008;23:1569-75 with permission of the American Society of Bone and Mineral Research.

10.1.126 Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization
Sunyecz JA, Mucha L, Baser O, Barr CE, Amonkar MM
Osteoporos Int 2008;19:1421-9

Two claims databases were used to identify women ≥45 years of age and who filled a new bisphosphonate prescription during 2000-2002. In 32,944 women (mean age, 64 years) who filled a new prescription for daily or weekly alendronate (n=26,581) or risedronate (n=6,363). At 3 years, 37% of women were compliant and 21% of women were persistent. Unadjusted total mean health care costs were lower for the compliant vs. non-compliant and persistent vs. non-persistent cohorts. After adjusting for potential confounders, total health care costs were reduced by 8.9% for persistent patients (p<0.001) and 3.5% for compliant patients (p=0.014). Persistence decreased the likelihood of inpatient admission by 47%. At 3 years, women who were persistent and compliant with bisphosphonate therapy had lower total costs compared with nonpersistent and noncompliant women, after controlling for relevant risk factors.

10.1.127 Risk of hip fracture after bisphosphonate discontinuation: Implications for a drug holiday
Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG
Osteoporos Int 2008;19:1613-20

Recent data suggest that hip fracture risk was not increased among women receiving 5 years of bisphosphonate who were subsequently randomized to placebo. We studied older women compliant with bisphosphonates ≥2 years to evaluate the risk of hip fracture after bisphosphonate discontinuation. Using administrative databases from a large U.S. healthcare organization, we identified women initiating bisphosphonate compliant (Medication Possession Ratio, MPR ≥66%) for 2 years. At 2 years, 9063 women were eligible for analysis. Hip fracture incidence among women who discontinued bisphosphonates versus those who did not was 8.43 versus 4.67 per 1000 person years (p=0.016). The adjusted hazard ratio of hip fracture per 90 days following discontinuation was 1.2 (1.1-1.3). For women with higher compliance at 2 years (MPR ≥80%) or compliant for 3 years, there were no significant differences in risk associated with discontinuation. The rate of hip fracture was increased among women compliant with bisphosphonate therapy for 2 years who subsequently discontinued, suggesting that discontinuation is not advisable under these conditions. This association was attenuated with higher compliance and a longer duration of previous bisphosphonate therapy.

10.1.128 Bisphosphonate-induced osteopetrosis: Novel bone modeling defects, metaphyseal osteopenia, and osteosclerosis fractures after drug exposure ceases
Whyte MP, McAlister WH, Novack DV, Clements KL, Schoenecker PL, Wenkert D
J Bone Miner Res 2008;23:1698-707

A 12-yr-old boy developed osteopetrosis (OPT) receiving pamidronate (PMD) for bone pain and elevation in alkaline phosphatase. Now 17 yr of age, he had less pain but further fractures. His growth plates were fused, hyperphosphatasemia persisted. He had fractures of a metacarpal, an osteosclerotic distal radius, and a dense diaphyseal ulna "chalkstick" break remained incompletely healed after 2 yr. There was new L(4) spondylolysis, and previous L(5) spondylolysis had caused spondylolisthesis. Modeling disturbances of OPT persisted, but partial recovery was shown by metaphyseal surfaces with a unique concave shape. Metaphyseal osteosclerosis had remodeled imperfectly to become focal areas of dense, diaphyseal bone. Newer metaphyseal bone was unexpectedly osteopenic, especially in his distal femurs where cortices were thin and a paucity of trabeculae was documented by CT. Femoral necks had become short and wide with an abnormal contour. A "bone-within-bone" configuration was now present throughout his skeleton. In vertebrae, endplates were thin, and trabecular osteopenia was present central and peripheral to the bands of osteosclerosis. BMD Z-scores assessed by DXA had decreased into the normal range. Iliac crest biopsy showed active bone formation, with much less accumulated primary spongiosa than during the PMD infusions. Osteoclasts that had been dysmorphic, round cells without polarization and off of bone surfaces were now unremarkable in number, location, and appearance.

10.1.129 Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis
Lewiecki EM, Keaveny TM, Kopperdahl D, Genant HK, Engelke K, Fuerst T, Kivitz A, Davies RY, Fitzpatrick LA
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Women aged 55-80 years with BMD T-scores≤–2.0 to ≥–5.0 (N=93), oral ibandronate 150 mg/mo (n=47) or placebo (n=46) was administered for 12 months and increased integral total hip QCT BMD and DXA areal BMD more than placebo at 12 months (differences: 2.2%, P=0.005; 2.0%, P=0.003). FEA-derived hip strength-to-density ratio and femoral, peripheral, and trabecular strength increased with ibandronate versus placebo (differences: 4.1%, P<0.001; 5.9%, P<0.001; 2.5%, P=0.011; 3.5%, P=0.003, respectively). Ibandronate improved vertebral, peripheral, and trabecular strength and anteroposterior bending stiffness versus placebo [7.1% (P<0.001), 7.8% (P<0.001), 5.6% (P=0.023), and 6.3% (P<0.001), respectively]. HSA-estimated femoral narrow neck cross-sectional area and moment of inertia and outer diameter increased with ibandronate versus placebo (respectively 3.6%, P=0.003; 4.0%, P=0.052; 2.2%, P=0.049). Once-monthly oral Ibandronate for 12 months improved hip and spine BMD measured by QCT and DXA and strength estimated by FEA of QCT scans.

10.1.130 Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer
Saarto T, Vehmanen L, Blomqvist C, Elomaa I
J Clin Oncol 2008;26:4289-95

268 pre- and postmenopausal, node-positive breast cancer patients were randomly assigned to clodronate, 1.6 g orally administered daily, or to control groups for 3 years. Premenopausal women were treated with adjuvant CMF chemotherapy; and postmenopausal women were treated with antiestrogens, either 20 mg tamoxifen or 60 mg toremifene, for 3 years. 89 disease-free patients were included in the analyses of osteoporosis-free survival. During 10-years, 24 of 89 patients were diagnosed with osteoporosis. 14 patients developed spinal osteoporosis (3 of 41 in the clodronate group, and 11 of 48 in the control group), and 14 of 89 patients were diagnosed with hip osteoporosis (7 of 41 in the clodronate group, and 7 of 48 in the control group). The 10-year spinal, osteoporosis-free survival rate was 92.7% in the clodronate group, and 77.0% in the control group (P=0.035). No difference was seen in the frequency of hip osteoporosis (85.4% v 82.9%; P=0.92). Three years of clodronate reduces the incidence of spine osteoporosis.

10.1.131 Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer
Hershman DL, McMahon DJ, Crew KD, Cremers S, Irani D, Cucchiara G, Brafman L, Shane E
J Clin Oncol 2008;26:4739-45

This study is a randomized, double-blind, multicenter, phase III trial comparing ZA (4 mg intravenously every 3 months) versus placebo for 1 year. Premenopausal women underwent serial BMD measurements before initiating chemotherapy and at 6 and 12 months. Of 101 women randomly assigned and completed baseline evaluation, 96 completed the 6-month evaluation, and 85 completed the 12-month evaluation. Placebo was associated with decline in LS BMD at both 6 (2.4%) and 12 (4.1%) months. Similarly, total hip BMD declined by 0.8% at 6 months and 2.6% at 12 months. BMD remained stable in ZA patients.

10.1.132 Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling
McDonald MM, Dulai S, Godfrey C, Amanat N, Sztynda T, Little DG
Bone 2008;43:653-62

Saline, a Bolus dose of 0.1 degrees mg/kg zoledronic acid (ZA) or 5 weekly divided doses of 0.02 degrees mg/kg of ZA commenced 1 week post operatively in a rat closed fracture model. ZA did not alter the rate of endochondral fracture union. All fractures united by 6 weeks. ZA increased hard callus bone mineral content (BMC), volume and increased callus strength at 6 and 26 weeks post fracture. Hard callus remodeling commenced at 4 weeks post fracture with Bolus ZA treatment but was delayed until after

6 weeks in the Weekly ZA group. By 12 and 26 weeks, Bolus ZA had equivalent callus content of remodelled neocortical bone to the Saline controls, whereas Weekly ZA remained reduced. Callus material properties such as peak stress were reduced in both ZA groups at 6 weeks. At 26 weeks, Bolus ZA treated calluses generated peak stress equivalent to control values, whereas Weekly ZA callus peak stress remained reduced, indicating remodeling delay. Osteoclast inhibition with ZA does not delay endochondral fracture repair in healthy rats. Bolus ZA increased net callus size and strength at 6 weeks while allowing hard callus remodeling to proceed in the long term, albeit more slowly than control. Prolonged bisphosphonate dosing during repair does not delay endochondral ossification but can significantly affect remodeling long after the drug is ceased.

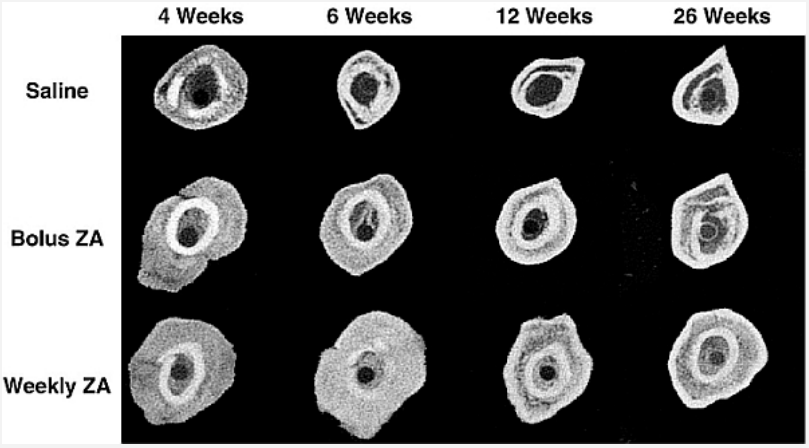

Fig. 10.1.132a Representative images from QCTcross sectional scans of the fracture calluses. Samples of callus at 4, 6, 12 and 26 weeks post-fracture for Saline, Bolus ZA and Weekly ZA groups. Note the extensive increases in callus size and delayed formation of the neo-cortex with ZA treatment. Reproduced from Bone, 43:653-62, Copyright (2008), with permission from Elsevier.

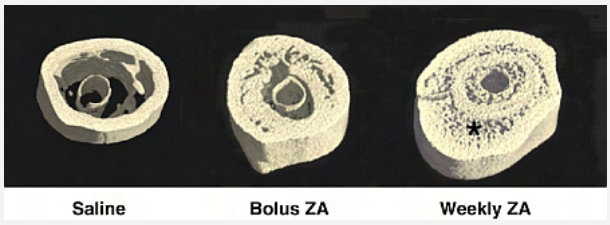

Fig. 10.1.132b 3-dimensional reconstruction images of cross section images from the central fracture region generated from microCT scans. Representative samples at 26 weeks for each treatment group. Weekly ZA demonstrates extensive retention of unremodeled primary bone (*) compared to Saline and Bolus ZA. Further, Saline samples show complete removal of the original cortical bone at this stage, this original cortex is still evident in both the Bolus and Weekly ZA samples. Reproduced from Bone, 43:653-62, Copyright (2008), with permission from Elsevier.

10.1.133 Short-term effects of high-dose zoledronic acid treatment on bone mineralization density distribution after orthotopic liver transplantation
Misof BM, Bodingbauer M, Roschger P, Wekerle T, Pakrah B, Haas M, Kainz A, Oberbauer R, Muhlbacher F, Klaushofer K
Calcif Tissue Int 2008;83:167-75

Bone mineralization density distribution in paired transiliacal biopsies (at and 6 months after OLT) from patients (control CON n=18, treatment group ZOL n=21, the latter treated with i.v. ZOL at doses of 4 mg/month) was assessed. Trabecular bone displayed a decrease in mean and most frequent calcium concentration (Ca(MEAN) -2.9% and Ca(PEAK) -2.8%, respectively; both P<0.001), increased heterogeneity of mineralization (Ca(WIDTH) +12.2%, P=0.01), and increased percentage of bone areas with low mineralization (Ca(LOW) +32.4%, P=0.02) compared to normal; however, there were no differences compared to cortical bone. Six months after OLT, ZOL-treated trabecular bone displayed reduced Ca(LOW) (-32.0%, P=0.047), cortical bone increased Ca(MEAN) (+4.2%, P=0.009), increased Ca(PEAK) (+3.3%, P=0.040), and decreased Ca(LOW) (-55.7, P=0.038) compared to CON and increased Ca(MEAN) compared to baseline (+1.9, P=0.032) without any signs of hyper- or defective mineralization.

10.1.134 Impact of raloxifene or tamoxifen use on endometrial cancer risk: A population-based case-control study
DeMichele A, Troxel AB, Berlin JA, Weber AL, Bunin GR, Turzo E, Schinnar R, Burgh D, Berlin M, Rubin SC, Rebbeck TR, Strom BL
J Clin Oncol 2008;26:4151-9

A case-control study of white and African American women age 50-79 years diagnosed with endometrial cancer between July 1999 and June 2002. Controls were identified through random-digit dialling. In 547 cases and 1410 controls among cases, 3.3% had taken raloxifene; 6.2% had taken tamoxifen. Among controls, 6.6% had taken raloxifene; 2.4% had taken tamoxifen. After adjustment for other risk factors, the odds of endometrial cancer among raloxifene users was 50% that of nonusers (odds ratio [OR]=0.50; 95% CI 0.29-0.85), whereas tamoxifen users had three times the odds of developing endometrial cancer compared with raloxifene users (OR=3.0; 95% CI 1.3-6.9). Endometrial tumors in raloxifene users had a more favorable histologic profile and were predominantly International Federation of Gynecology and Obstetrics stage I and low grade. Raloxifene users had lower odds of endometrial cancer compared with both tamoxifen users and SERM nonusers, suggesting a role for raloxifene in endometrial cancer prevention and individualization of SERM therapy.

10.1.135 The calcium-sensing receptor is involved in strontium ranelate-induced osteoclast apoptosis: New insights into the associated signalling pathways
Hurtel AS, Mentaverri R, Caudrillier A, Cournarie F, Wattel A, Kamel S, Terwilliger EF, Brown EM, Brazier M
J Biol Chem 2008;[Epub ahead of print]

Using primary mature rabbit osteoclasts, strontium (Sr2+o) dose-dependently stimulates the apoptosis of on mature osteoclasts mediated by the Ca2+o-sensing receptor (CaR), which in turn, stimulates a PLC-dependent signalling and nuclear translocation of NF-κB. Unlike Ca2+o, Sr2+o-induced osteoclast apoptosis was shown to depend on PKCII activation and

to be independent of IP3 action. Sr2+o and Ca2+o in combination were shown to exert a greater effect on mature osteoclast apoptosis than did either divalent cation by itself.

10.1.136 Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer
Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, Fan M, Jun S
J Clin Oncol 2008;26:4875-82

Eligible women with hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy were stratified by duration of aromatase inhibitor therapy (≤ 6 vs. >6 months), received calcium and vitamin D, and were randomly assigned to placebo (n=125) or subcutaneous denosumab 60 mg (n=127) every 6 months. At 12 and 24 months, spine BMD increased by 5.5% and 7.6%, respectively, in the denosumab group versus placebo (P<0.0001 at both time points). Increases were observed as early as 1 month and were not influenced by duration of aromatase inhibitor therapy. Increases in BMD were also observed at the total hip, total body, femoral neck, and the predominantly cortical one-third radius. Bone turnover markers decreased with denosumab treatment.

10.1.137 Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment
Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S, Audran M, Barker C, Anastasilakis AD, Fraser WD, Nickelsen T
J Bone Miner Res 2008;23:1591-600

503 postmenopausal women with osteoporosis received teriparatide for 24 mo, treatment-naive (n=84); pretreated with no evidence of inadequate treatment response (n=134); and pretreated showing an inadequate response to antiresorptive (AR) (n=285), which was predefined based on the occurrence of fractures, persistent low BMD, and/or significant BMD loss while on therapy. Lumbar spine BMD increased from baseline at 6, 12, 18, and 24 mo in all three groups. The mean gain in spine BMD over 24 mo was greater in the treatment-naive group (0.095 g/cm^2; 13.1%) than in the AR pretreated (0.074 g/cm^2; 10.2%; p<0.005) and inadequate AR responder (0.071 g/cm^2; 9.8%; p<0.001) groups. The corresponding increases in total hip BMD were 3.8%, 2.3%, and 2.3%, respectively. Early decreases in hip BMD in the inadequate AR responder group were reversed by 18 mo of treatment. Increases in BMD between 18 and 24 mo were significant. Teriparatide for 24 mo is associated with an increase in BMD in patients with and without previous AR use.

10.1.138 Effects of PTH and alendronate on type I collagen isomerization in postmenopausal women with osteoporosis: The PaTH study
Garnero P, Bauer DC, Mareau E, Bilezikian JP, Greenspan SL, Rosen C, Black D
J Bone Miner Res 2008;23:1442-8

In the first year of the PaTH study, postmenopausal women with osteoporosis were assigned to PTH(1-84) (100 µg/d; n=119), ALN (10 mg/d; n=60), or both (n=59). During the second year, women on PTH in the first year were reallocated to placebo (n=31) or ALN (n=32) and women with ALN continued on ALN. During the first year, there was no change in αα/ββ CTX ratio with PTH or ALN. At 24 mo, there was a marked increase of the αα/ββ CTX ratio in women who received PTH during the first year, followed by a second year of placebo (median: +45.5, p<0.001) or ALN (+55.2%, p<0.001). Conversely, the αα/ββ CTX ratio only slightly increased (+16%, p<0.05) after 2 yr of continued ALN. PTH(1-84) for 1 yr followed by 1 yr of placebo or ALN may be associated with decreased type I collagen isomerization.

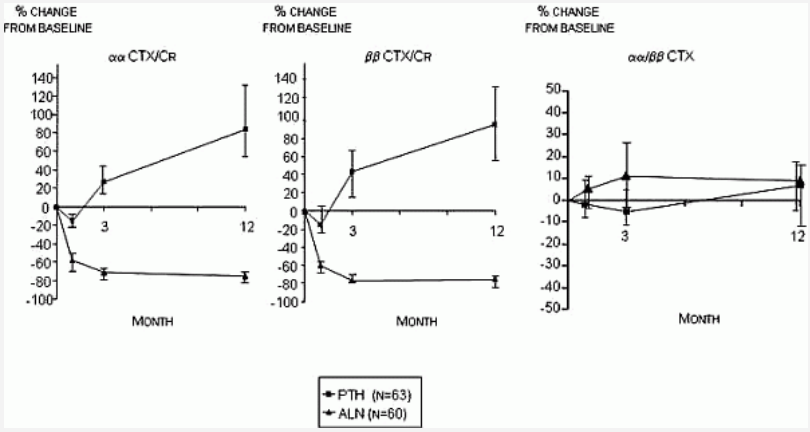

Fig. 10.1.138a Changes of urinary αα CTX/cr, ββ CTX/Cr, and ratio αα/ββ CTX in postmenopausal women treated with PTH(1-84) or alendronate for 1 yr. The graphs show the median and the 95% CIs of the percent changes from baseline. Reproduced from J Bone Miner Res 2008;23:1326-33 with permission of the American Society of Bone and Mineral Research.

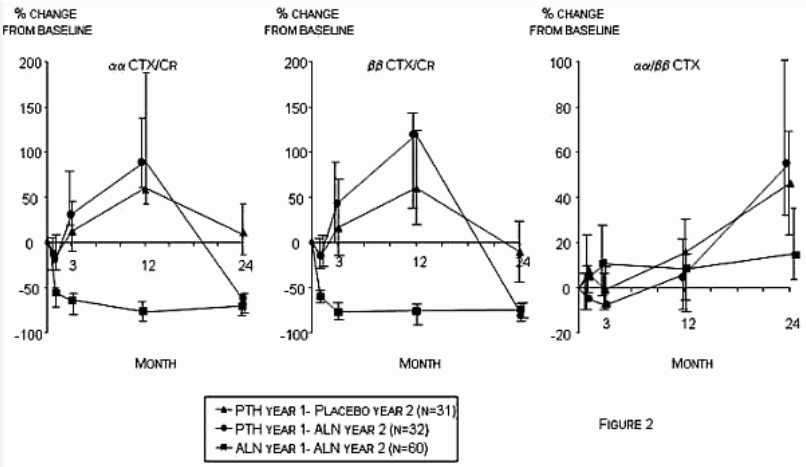

Fig. 10.1.138b Changes of urinary αα CTX/cr, ββ CTX/Cr, and ratio αα/ββ CTX in postmenopausal women treated with 2 yr of continued alendronate, 1 yr of PTH, followed by 1 yr of placebo and 1 yr of PTH followed by 1 yr of alendronate. The graphs show the median and 95% CIs of the percent changes from baseline. Reproduced from J Bone Miner Res 2008;23:1326-33 with permission of the American Society of Bone and Mineral Research.

10.1.139 Parathyroid hormone(1-84) treatment of postmenopausal women with low bone mass receiving hormone replacement therapy
Fogelman I, Fordham JN, Fraser WD, Spector TD, Christiansen C, Morris SA, Fox J
Calcif Tissue Int 2008;83:85-92

Subjects were randomized to 100 µg PTH(1-84) or placebo injections daily for 24 months (n=90/group). At 18 months, the mean increase in lumbar spine BMD was 7.9% for PTH(1-84) subjects vs. 1.5% for those receiving HRT alone; between-group differences were significant at 6 months and persisted throughout the study. Lumbar spine BMD increased in 94% of women receiving PTH(1-84) compared to 59% for HT alone. Femoral neck BMD and bone turnover markers were higher in PTH(1-84)-treated subjects, but the changes in total hip and distal radius BMD were not significant. Addition of PTH(1-84) to stable HRT produced marked increases in lumbar spine BMD.

10.1.140 Suppression of parathyroid hormone and bone resorption by calcium carbonate and calcium citrate in postmenopausal women
Thomas SD, Need AG, Tucker G, Slobodian P, O'Loughlin PD, Nordin BE
Calcif Tissue Int 2008;83:81-4

25 healthy postmenopausal women were recruited in this double blind crossover study. The subjects were randomly allocated to 1000 mg of elemental calcium as carbonate or 500 mg of calcium as citrate. They were given the alternate calcium dose one week later. Analysis of variance found no difference between measures for the two salts. Tests for equivalence indicated that 500 mg of calcium citrate may be superior to 1000 mg of calcium carbonate in raising serum total and ionized calcium (P=0.04 and 0.05, respectively). For all parameters measured, 500 mg of calcium citrate was at least as beneficial as 1000 mg of calcium carbonate. Calcium citrate is at least as effective as calcium carbonate in suppressing PTH and C-terminal telopeptide crosslinks, at half the dose.

10.1.141 Hyperlipidemia impairs osteoanabolic effects of PTH
Huang MS, Lu J, Ivanov Y, Sage AP, Tseng W, Demer LL, Tintut Y
J Bone Miner Res 2008;23:1672-9

Intermittent PTH has differential osteoanabolic effects in wildtype (C57BL/6) and hyperlipidemic (LDLR(-/-)) mice. Induction of IEGs in calvarial tissue, 45 min after a single dose of recombinant hPTH(1-34), was attenuated in LDLR(-/-) mice compared with C57BL/6 mice. Daily hPTH(1-34) injections for 5 wk increased total and cortical BMD and BMC, assessed by pQCT, in C57BL/6 mice. However, this induction was completely abrogated in LDLR(-/-) mice. Similarly, PTH(1-34) failed to increase BMD in another hyperlipidemic mouse model, ApoE(-/-) mice. Histomorphometric analysis showed that trabecular bone of both mice responded similarly to PTH(1-34). Structural parameters improved in response to PTH(1-34) in both mouse strains, although to a lesser degree in LDLR(-/-) mice. With PTH(1-34), osteoblast surface trended toward an increase in C57BL/6 mice and increased in LDLR(-/-) mice. PTH(1-34) did not alter resorption parameters, except for the eroded surface (ES/BS), which was reduced in the C57BL/6 but not in the LDLR(-/-) mice. PTH(1-34) has adverse effects on cortical bones of the hyperlipidemic mice, suggesting that the therapeutic effects of PTH.

10.1.142 Additive benefit of higher testosterone levels and vitamin D plus calcium supplementation in regard to fall risk reduction among older men and women
Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B
Osteoporos Int 2008;19:1307-14

199 men and 246 women age 65+ living at home were followed for 3 years. Compared to the lowest quartile, men and women in the highest quartile of total testosterone had a decreased odds of falling (men: OR=0.22; 95% CI 0.07,0.72 / women: OR=0.34; 95% CI 0.14,0.83); if those individuals also took vitD+cal, the fall reduction was enhanced (men: OR=0.16; 95% CI 0.03,0.90 / women: OR=0.15; 95% CI 0.04,0.57). Similarly, women in the top quartile of dihydroepiandrosterone sulfate (DHEA-S) had a lower risk of falling (OR=0.39; 95% CI 0.16,0.93). Other sex hormones and SHBG did not predict falling in men or women.

10.1.143 Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women
Syed FA, Oursler MJ, Hefferanm TE, Peterson JM, Riggs BL, Khosla S
Osteoporos Int 2008;19:1323-30

Reanalysis of bone biopsies from a randomized, placebo-controlled trial involving 56 postmenopausal osteoporotic women (mean

age, 64 years) treated either with placebo (PL, n=27) or transdermal estradiol (0.1 mg/d, n=29) for 1 year showed adipocyte volume/tissue volume (AV/TV) and adipocyte number (Ad#) increased (by approximately 20%, P<0.05) in the PL group, but were unchanged (Ad#) or decreased (AV/TV, by -24%, P<0.001) in the E group. E treatment also prevented increases in mean adipocyte size over one year.

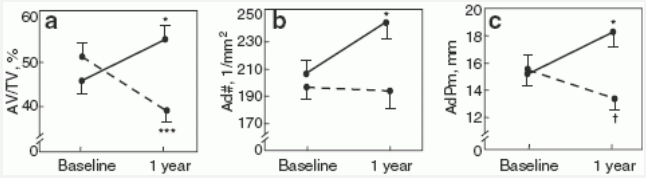

*Fig. 10.1.143a Changes in (a) adipocyte volume/tissue volume (AV/TV), (b) adipocyte number (AD#), and (c) adipocyte perimeter (AdPm) in the placebo (solid circles and lines) and E (open circles and dashed lines) groups over one year. *P<0.05, ***P<0.001, and †P=0.059 for comparison with baseline. P-values for comparison of change in placebo versus change in E groups are as follows: AV/TV, <0.001; AD#, 0.075; and AdPm, <0.005. Reproduced from Osteoporos Int 2008;19:1323-30 with permission from Springer.*

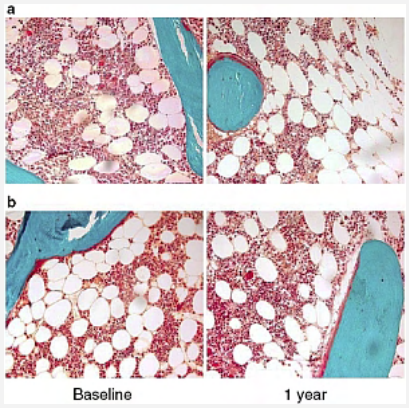

Fig. 10.1.143b Representative serial sections of Goldner's stained iliac crest biopsies from a patient either on placebo (Panel A) or on E (Panel B) at the start (baseline) and end of treatment (1 year). Photomicrographs taken at 40× magnification. Reproduced from Osteoporos Int 2008;19:1323-30 with permission from Springer.

10.1.144 Prevention of trabecular bone loss induced by estrogen deficiency by a selective p38alpha inhibitor
Caverzasio J, Higgins L, Ammann P
J Bone Miner Res 2008;23:1389-97

Increased bone remodelling with estrogen deficiency is mediated by the production of cytokines such as TNFα and interleukin-1. The p38 pathway mediates cytokines effects on enhanced bone turnover in postmenopausal osteoporosis. The p38α inhibitor, SD-282 blunted the increase in the bone resorption marker DPD/Cr induced by OVX in adult rats. Associated with this effect, SD-282 did not reduce enhanced by 2-fold the rise in the bone formation marker serum osteocalcin observed in OVX animals and blocked vertebral bone loss associated with estrogen deficiency. A partial preventive effect was observed in long bones with reduction of trabecular bone loss and enhancement of cross-sectional area of the diaphysis. Prevention of trabecular bone loss and increased in cortical bone area were associated with improvement of biomechanical resistances.

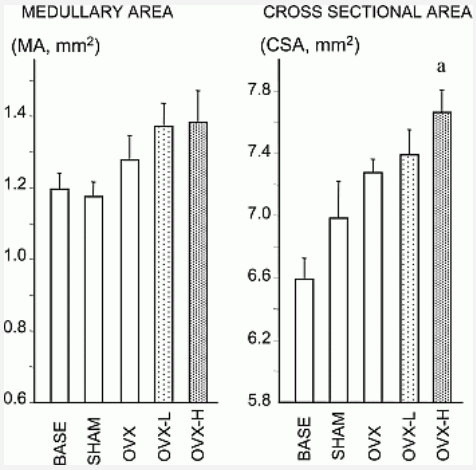

Fig. 10.1.144 Effect of SD-282 on midshaft medullary and crosssectional area. Medullary (MA) and cross-sectional (CSA) areas of the left tibia were determined in intact (baseline [BASE]) and either Sham or OVX rats treated orally twice a day, 6 d/wk for 8 wk with vehicle or 15 or 45 mg/kg of SD-282. Values are means±SE. [a]p<0.02 compared with Sham. Reproduced from J Bone Miner Res 2008;23:1389-97 with permission of the American Society of Bone and Mineral Research.

10.1.145 The effects of oral calcitonin on bone collagen maturation: Implications for bone turnover and quality
Karsdal MA, Byrjalsen I, Leeming DJ, Delmas PD, Christiansen C
Osteoporos Int 2008;19:1355-61

168 postmenopausal women treated with placebo, 0.15, 0.4, 1, or 2.5 mg calcitonin daily. The non-isomerized ααCTX and isomerized ββCTX were measured in 24-hour urine samples at baseline, and after 1 day, 1 month and 3 months. Calcitonin

dose-dependently inhibited bone resorption by up to 50% as measured by αCTX and isomerized ββCTX. Bone collagen maturation measured as the ratio between αCTX and ββCTX remained unchanged during treatment. Calcitonin reduced both αCTX to ββCTX levels in urine without affecting the αCTX to ββCTX ratio.

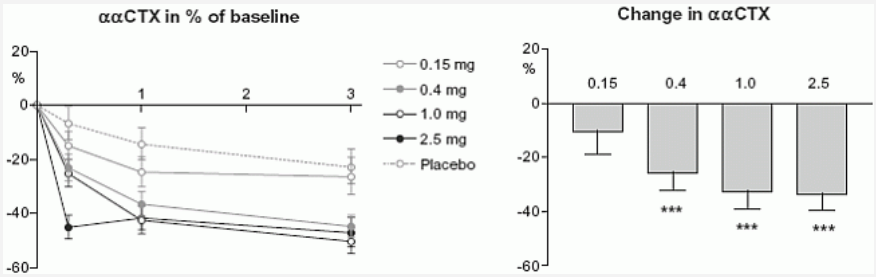

*Fig. 10.1.145a Urinary αCTX in percentage of baseline values during 3 months of therapy. The left figure shows the changes relative to baseline, and right figure shows the placebo-corrected time-averaged mean during the treatment period. Values shown are geometric mean ±1SEM. The level of significance denotes difference from the placebo group: ***p<0.001. Reproduced from Osteoporos Int 2008;19:1355-61 with permission from Springer.*

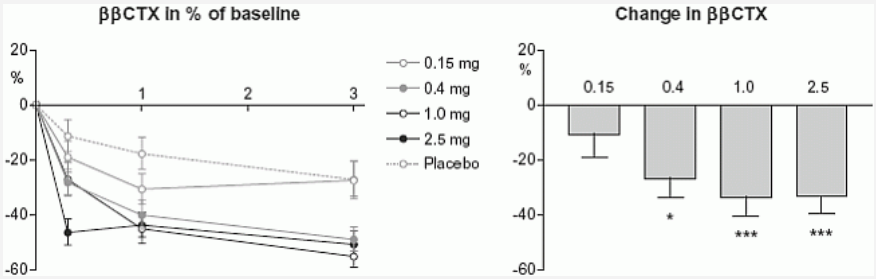

*Fig. 10.1.145b Urinary ββCTX in percentage of baseline values during 3 months of therapy. The left figure shows the changes relative to baseline, and right figure shows the placebo-corrected time-averaged mean during the treatment period. Values shown are geometric mean ±1SEM. The level of significance denotes difference from the placebo group: *p<0.05; ***p<0.001. Reproduced from Osteoporos Int 2008;19:1355-61 with permission from Springer.*

10.1.146 Minodronic acid (ONO-5920/YM529) prevents decrease in bone mineral density and bone strength, and improves bone microarchitecture in ovariectomized cynomolgus monkeys
Mori H, Tanaka M, Kayasuga R, Masuda T, Ochi Y, Yamada H, Kishikawa K, Ito M, Nakamura T
Bone 2008;43:840-8

Mature female cynomolgus monkeys, aged 9-17 years, were ovariectomized or sham-operated. Minodronic acid was administered orally once a day in doses of 0, 0.015, and 0.15 mg/kg from the day after surgery for 17 months. Treatment inhibited bone turnover markers and the decrease in lumbar vertebral BMD; 0.15 mg/kg completely prevented these changes. At 17 months after surgery, minodronic acid also suppressed Oc.S/BS and N.Oc/BS, OS/BS, MS/BS, MAR, BFR/BS, and BFR/BV in the lumbar vertebral bodies and tibia. In the mechanical tests, ultimate load on lumbar vertebral bodies and femoral neck of the OVX-control animals were reduced compared to the sham. Minodronic acid prevented these reductions in strength at 0.15 mg/kg. There was correlation between BMD and bone strength. In microCT analysis of the lumbar vertebral bodies, minodronic acid improved trabecular architecture, converting rod structures into plate structures, and preventing the increase in trabecular disconnectivity at 0.15 mg/kg.

10.1.147 Long-term minodronic acid (ONO-5920/YM529) treatment suppresses increased bone turnover, plus prevents reduction in bone mass and bone strength in ovariectomized rats with established osteopenia
Tanaka M, Mori H, Kayasuga R, Ochi Y, Kawada N, Yamada H, Kishikawa K
Bone 2008;43:894-900

Female F344/DuCrj rats, aged 14 weeks, were OVX or sham operated. After 3 months, the OVX rats showed an increase in bone turnover, and a decrease in bone mass and strength. Minodronic acid orally once a day for 12 months at doses of 0, 0.006, 0.03 and 0.15 mg/kg from 3 months after OVX inhibited the decrease in BMD of lumbar vertebrae and femur. In the femur, treatment with 0.15 mg/kg minodronic acid increased the BMD of distal and mid sites to sham levels. Minodronic acid dose-dependently suppressed OVX-induced increase in urinary deoxypyridinoline, decreased serum osteocalcin. In bone histomorphometric analysis after 12 months, OVX rats showed an increase in Oc.S/BS and N.Oc/BS, MS/BS and BFR/BV at lumbar vertebral bodies. Trabecular bone volume, trabecular thickness and trabecular number of lumbar vertebral bodies were decreased after OVX. Minodronic acid increased these structural indices, indicating that it prevented the deterioration in trabecular architecture. In a mechanical test at 12 months of treatment, ultimate load of lumbar vertebral bodies and mid femur in the OVX-control group was decreased compared to the sham group. Minodronic acid prevented the reduction in bone strength at both sites. In particular, in the mid-femur, treatment with 0.03 and 0.15 mg/kg increased bone strength to sham levels or greater.

10.1.148 Identification of material parameters based on Mohr-Coulomb failure criterion for bisphosphonate treated canine vertebral cancellous bone
Wang X, Allen MR, Burr DB, Lavernia EJ, Jeremic B, Fyhrie DP
Bone 2008;43:775-80

33 canine lumbar vertebrae from dogs were treated daily for one year with oral alendronate, risedronate, or saline. Two sets of elastic modulus and hardness values were calculated for each specimen using the Continuous Stiffness Measurement (CSM) method (E(CSM) and H(CSM)) from the loading segment and the Oliver-Pharr method (E(O-P) and H(O-P)) from the unloading segment, respectively. Young's modulus (E(FE)), cohesion (c), and friction angle (varphi) were identified using a finite element model for each nanoindentation. Bisphosphonate had a significant effect on Oliver-Pharr hardness and the Mohr-Coulomb cohesion was larger for the risedronate-treated compared to vehicle. This result suggests that bisphosphonate increases the hardness and shear strength of bone tissue. Shear strength was linearly predicted by modulus and hardness measured by the Oliver-Pharr method (r^2=0.99). These results show that bisphosphonate-induced changes in

Mohr-Coulomb material properties, including tissue shear cohesive strength, can be accurately calculated from Oliver-Pharr measurements of Young's modulus and hardness.

10.1.149 Recovery of trabecular and cortical bone turnover after discontinuation of risedronate and alendronate therapy in ovariectomized rats

Fuchs RK, Phipps RJ, Burr DB

J Bone Miner Res 2008;23:1689-97

210 six-month-old female Sprague Dawley rats were ovariectomized and 6 wk later were randomized into baseline controls vehicle-treated controls, ALN (2.4 μg/kg), low-dose RIS (RIS low; 1.2 μg/kg), and high-dose RIS (RIS high; 2.4 μg/kg) treated for 8 wk. After 8 wk of treatment, trabecular bone turnover rates were suppressed in all drug-treated animals. Trabecular bone formation rate (BFR/BS) remained lower than vehicle in bisphosphonate-treated animals through 12 wk. Sixteen weeks after treatment withdrawal, trabecular BFR/BS in the proximal tibia was re-established in animals treated with RIS but not in animals treated with ALN compared with controls. BMD of the fifth lumbar vertebra remained significantly higher than controls 16 wk after treatment withdrawal in ALN-treated animals but not in RIS-treated animals. Despite reductions in BMD and increases in bone turnover, ultimate force of the fifth lumbar vertebra remained higher in all drug-treated animals through 16 wk after withdrawal.

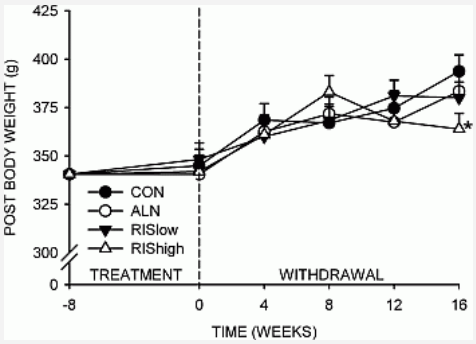

*Fig. 10.1.149a Body weight changes with treatment withdrawal. *Significantly different from vehicle-treated CON (p<0.05). Reproduced from J Bone Miner Res 2008;23:1689-97 with permission of the American Society of Bone and Mineral Research.*

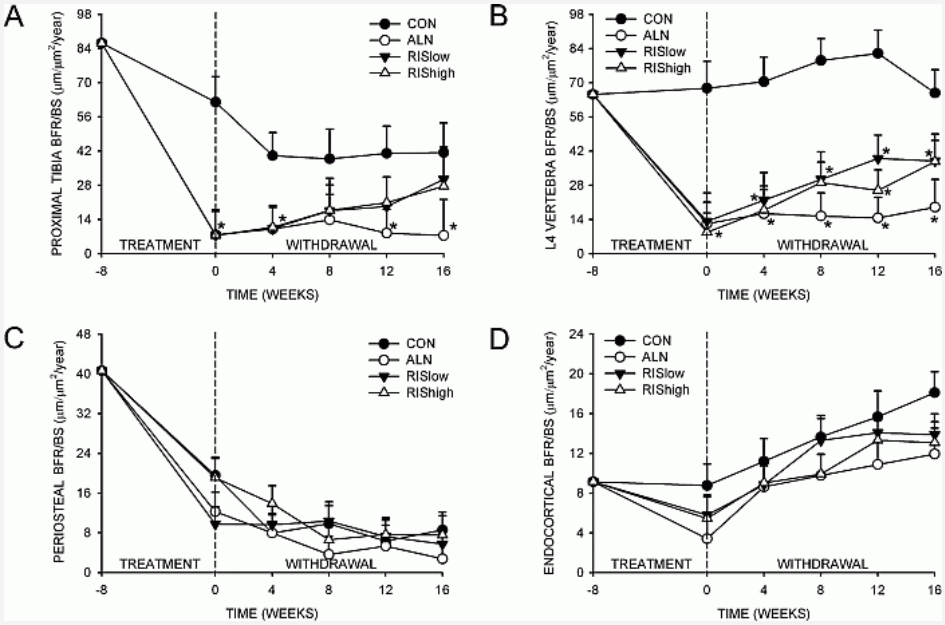

*Fig. 10.1.149b Effect of bisphosphonate treatment and withdrawal on BFR/BS of the proximal tibial metaphysis (A), fourth lumbar vertebra (B), periosteal surface of the tibial middiaphysis (C), and endocortical surface of the tibial mid-diaphysis (D). *Significantly different from vehicle-treated CON (p<0.05). Reproduced from J Bone Miner Res 2008;23:1689-97 with permission of the American Society of Bone and Mineral Research.*

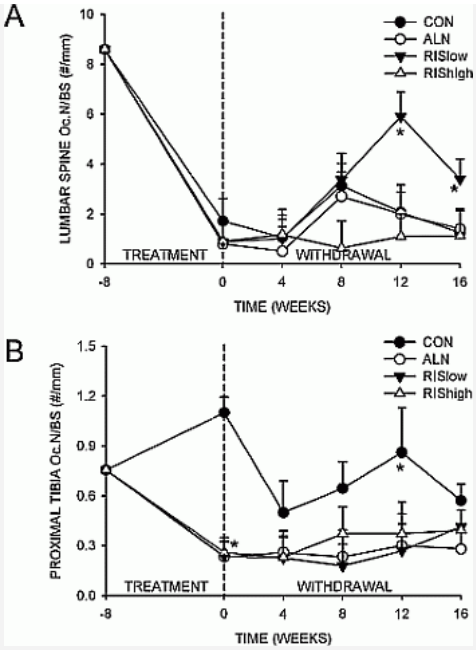

*Fig. 10.1.149c Effect of bisphosphonate treatment and withdrawal on N.Oc/BS for the (A) fourth lumbar vertebra and (B) proximal tibial metaphysis. *Significantly different from vehicle-treated CON (p<0.05). Reproduced from J Bone Miner Res 2008;23:1689-97 with permission of the American Society of Bone and Mineral Research.*

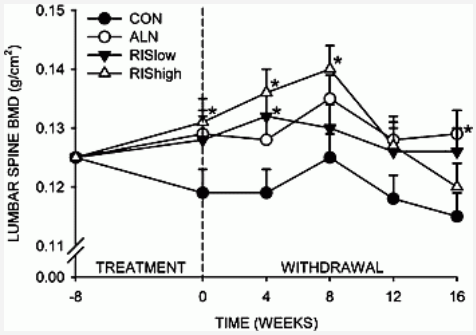

*Fig. 10.1.149d Effect of bisphosphonate treatment and withdrawal on BMD of the fifth lumbar vertebra. *Significantly different from vehicle-treated CON (p<0.05). Reproduced from J Bone Miner Res 2008;23:1689-97 with permission of the American Society of Bone and Mineral Research.*

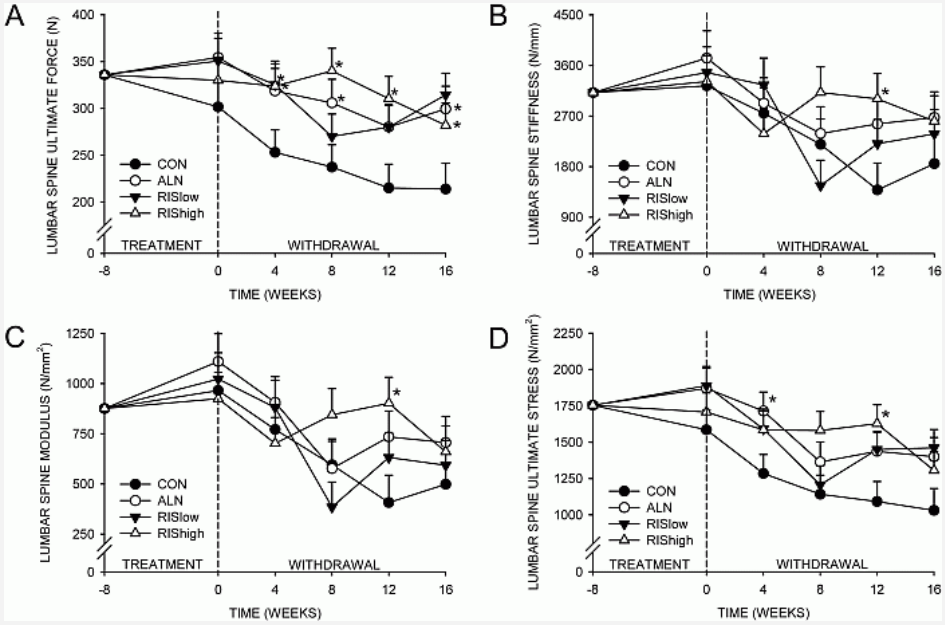

*Fig. 10.1.149e Effect of bisphosphonate treatment and withdrawal on bone strength of the L5 vertebrae. (A) Ultimate force. (B) Stiffness. (C) Modulus. (D) Ultimate stress. *Significantly different from vehicle-treated CON (p<0.05). Reproduced from J Bone Miner Res 2008;23:1689-97 with permission of the American Society of Bone and Mineral Research.*

10.1.150 Influence of early and late zoledronic acid administration on vertebral structure and strength in ovariectomized rats
Brouwers JE, van Rietbergen B, Bouxsein ML
Calcif Tissue Int 2008;83:186-91

Twenty-nine female 35-week-old Wistar rats were divided into SHAM-OVX (n=9), OVX (n=5), OVX and early ZOL (n=8), and OVX

and late ZOL (n=7). ZOL was given once (20 µg/kg body weight s.c.) at OVX in the early ZOL group and 8 weeks later in the late ZOL group; rats were killed 16 weeks after OVX. Compared to SHAM-OVX, OVX rats had lower BV/TV; SMI, Tb.N, Tb.Sp, and Conn.D tended to be deteriorated in lumbar vertebrae, while both ZOL groups did not differ from the SHAM-OVX group. Both ZOL groups had higher BV/TV than OVX; the early ZOL group also had lower SMI and higher Tb.Th. OVX tended to decrease mechanical properties, while early and late ZOL inhibited OVX-induced degeneration. Neither OVX nor ZOL induced changes in the trabecular microarchitecture of caudal vertebrae.

10.1.151 Connexin 43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts in vivo
Plotkin LI, Lezcano V, Thostenson J, Weinstein RS, Manolagas SC, Bellido T
J Bone Miner Res 2008;23:1712-21

Connexin (Cx)43 is required for inhibition of osteocyte and osteoblast apoptosis by bisphosphonates in vitro. Mice in which Cx43 was deleted from osteocytes and osteoblasts. Cx43(DeltaOb-Ot/-) 5-mo-old female mice were given alendronate (2.3 µmol/kg/d) daily in (n=6-11) for 31 days, starting 3 days before implantation of pellets releasing prednisolone (2.1 mg/kg/d). Cx43(DeltaOb-Ot/-) mice and their littermates (Cx43(fl/-), Cx43(DeltaOb-Ot/+), and Cx43(fl/+)) gained bone from 2 to 4.5 mo of age normally. Prednisolone induced a similar increase in osteocyte and osteoblast apoptosis in Cx43(DeltaOb-Ot/-) or in control Cx43 (fl/-) littermates. Alendronate prevented prednisolone-induced apoptosis in control Cx43(fl/-) mice, not Cx43(DeltaOb-Ot/-) mice. Alendronate inhibited glucocorticoid-induced bone loss in both type of animals, suggesting that inhibition of resorption is the predominant effect of alendronate against the early phase of glucocorticoid-induced bone loss. Cx43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts.

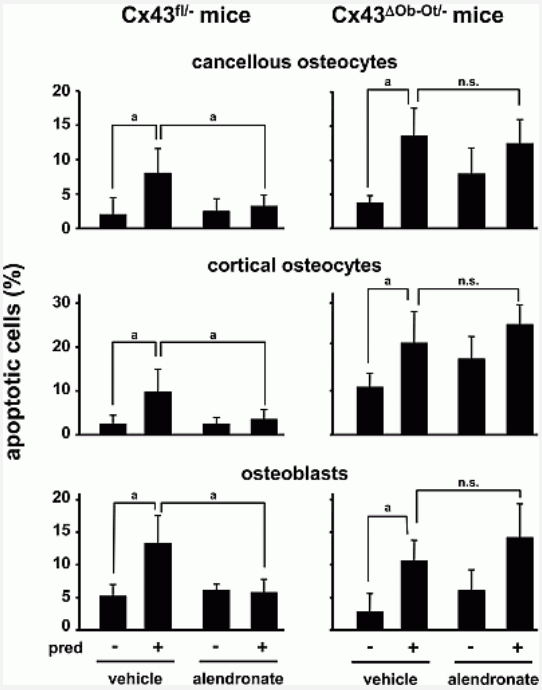

Fig. 10.1.151 Alendronate prevents glucocorticoid-induced cancellous and cortical osteocyte and osteoblast apoptosis in Cx43$^{fl/-}$ but not in Cx43$^{\Delta Ob\text{-}Ot/-}$ mice lacking Cx43 in osteocytes and osteoblasts. Mice were treated with daily alendronate injections, starting 3 days before pellet implantation. Twenty-eight days after pellet implantation, mice were killed, and apoptosis was determined. pred, prednisolone; n.s., not significant. [a]p<0.05 by generalized linear models, n=4-9 mice. Reproduced from J Bone Miner Res 2008;23:1712-21 with permission of the American Society of Bone and Mineral Research.

10.1.152 Strontium ranelate does not stimulate bone formation in ovariectomized rats
Fuchs RK, Allen MR, Condon KW, Reinwald S, Miller LM, McClenathan D, Keck B, Phipps RJ, Burr DB
Osteoporos Int 2008;19:1331-41

Strontium ranelate (SrR) in ovariectomized (OVX) rats (25 or 150 mg/kg/day) for 90 days did not increase bone formation on trabecular or periosteal bone surfaces, and failed to inhibit bone resorption of trabecular bone regardless of Ca intake. There were no improvements in bone mass, volume or strength with either dose of SrR given normal Ca.

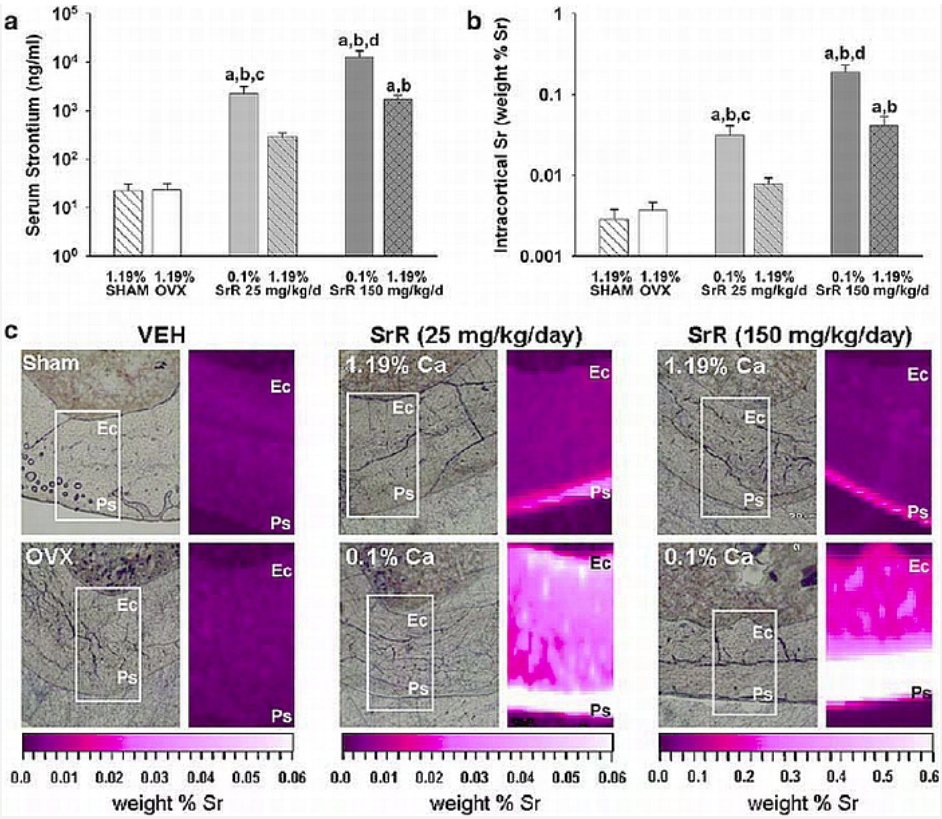

Fig. 10.1.152a Strontium concentrations in serum and cortical bone. (a) Serum strontium (ng/ml) presented as a log scale; (b) Intracortical strontium (weight % Sr) presented as a log scale; and (c) Pictoral representation of the distribution of strontium in cortical bone of the tibial midshaft. The periosteal (Pc) surface contained ~5 times more strontium than the intracortical bone, and significantly more strontium was deposited into the bone of animals given the low Ca diet regardless of Sr level. Dark purple areas represent regions with the lowest concentration of strontium, and white areas represent regions with the highest concentration of Sr. Note that the scale for the concentration of strontium is 10 fold higher for the strontium 150 mg group (0.0% - 0.6% for 150 mg/kg/day strontium vs 0.0% - 0.06% for strontium 25 mg/kg/day). [a]Significantly different from OVX; [b]Significantly different from SHAM; [c]Significantly different between Sr 25 mg Ca groups; [d]Significantly different between Sr 150 mg Ca dosages ([a, b, c, d]p<0.05). Reproduced from Osteoporos Int 2008;19:1331-41 with permission from Springer.

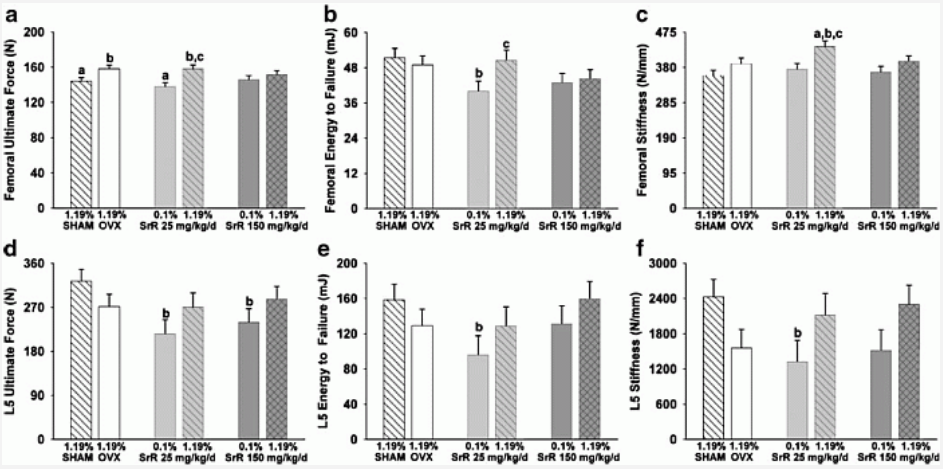

Fig. 10.1.152c Mechanical properties of the femur and L5 vertebrae. (a) Femoral ultimate force (N); (b) Femoral energy to failure (mJ); (c) Femoral stiffness (N/mm); (d) L5 ultimate force (N); (e) L5 energy to failure (mJ); (f) L5 stiffness (N/mm). [a]Significantly different from OVX; [b]Significantly different from SHAM; [c]Significantly different between SrR 25 mg/kg/day calcium groups ([a, b, c]p<0.05). Reproduced from Osteoporos Int 2008;19:1331-41 with permission from Springer.

10.1.153 Transdermal lovastatin enhances fracture repair in rats

Gutierrez GE, Edwards JR, Garrett IR, Nyman JS, McCluskey B, Rossini G, Flores A, Neidre DB, Mundy GR

J Bone Miner Res 2008;23:1722-30

Statins stimulate BMP2 transcription and bone formation. Lovastatin (LV) given transdermally (TD) for 5 days after fracture (0.1-5 mg/kg/d) was compared with vehicle-treated control rats and rats treated with LV by oral gavage (PO) at 5-25 mg/kg/d for 5 days post fracture showed enhanced fracture repair at 2 and 6 wk. BMD in the callus area at 6 wk was also increased in the TD group compared with vehicle-treated controls ($p < 0.05$). The force required to break TD-treated bones (0.1 mg/kg/d for 5 days) was 42% greater than vehicle-treated controls ($p<0.02$), and there was a 90% increase in stiffness ($p<0.01$). PO LV at much higher doses (10 and 25 mg/kg/d) showed increased stiffness. An increase was observed in the size of the callus, surrounding proliferating cell nuclear antigen-positive cells, and osteoblast and osteoclast number in TD-treated rats compared with controls at day 8 after fracture (n=6). TD LV accelerates fracture healing, whereas 10-fold the lipid-lowering dose was required to produce any effect orally.

10.1.154 Effects of estrogen receptor alpha- and beta-selective substances in the metaphysis of the tibia and on

serum parameters of bone and fat tissue metabolism of ovariectomized rats
Seidlova-Wuttke D, Prelle K, Fritzemeier KH, Wuttke W
Bone 2008;43:849-55

OVX rats were s.c. injected for 4 weeks with 3 doses of the ERα agonist 16α-LE2 or the ERβ agonist 8β-VE2 or with E2. The intermediate doses were antagonized by an additional daily treatment with ICI (1.53 mg). By QCT, density of tibial cancellous metaphyseal was reduced in the controls which was prevented by E2 and the ERα agonist. Endosteal surface, endosteal, periosteal circumferences and fat depots were largest in the controls and the ERβ treated animals and lowest in the E2 and the 16α-LE2 injected ovx rats. Osteocalcin and the CrossLaps were highest in the ovx controls and reduced by E2 and the ERα agonist. Serum osteocalcin was stimulated by the ERβ agonist. The strain strength index (SSI) in relation to the bodyweight was lowest in controls and increased dose dependently in the E2 and in the ERα treated animals. Most effects in the bone and fat were exerted by mechanisms involving the ERα but the ERβ agonist appears to stimulate osteoblasts.

10.1.155 Local application of statin promotes bone repair through the suppression of osteoclasts and the enhancement of osteoblasts at bone-healing sites in rats
Ayukawa Y, Yasukawa E, Moriyama Y, Ogino Y, Wada H, Atsuta I, Koyano K
Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;[Epub ahead of print]

Simvastatin was injected into a rat bony defect for 3 days from surgery. Five or ten days after the injection, new bone tissue was collected, and the gene expressions of bone-related proteins were examined. At day 5, the statin group demonstrated larger new bone area. The number of tartrate-resistant acid phosphatase-positive multinucleated cells was less than in the control and the expressions of both alkaline phosphatase and bone morphogenetic protein 2 mRNA increased. In contrast, the expression of cathepsin K was suppressed. Although the levels of both RANK and osteoprotegerin were not affected by statin, the expression of RANKL was depressed. At day 10, there were no differences among the groups in either histomorphometric or reverse transcription polymerase chain reaction analyses. New bone area increased under the influence of simvastatin; however, the effect did not continue when the administration was terminated. Osteoclast suppression may be the consequence of RANKL depression.

10.1.156 A combination of granulocyte colony-stimulating factor and stem cell factor ameliorates steroid-associated osteonecrosis in rabbits
Wu X, Yang S, Duan D, Liu X, Zhang Y, Wang J, Yang C, Jiang S
J Rheumatol 2008;[Epub ahead of print]

ON was induced by low dose lipopolysaccharide and subsequent pulsed high-dose methylprednisolone. Rabbits in the treated group were subjected to subcutaneous injections of G-CSF at a dose of 100 μg/kg and SCF 25 μg/kg per day for 5 days; rabbits in the control group were given saline. The mean number of leukocytes and relative numbers of mononuclear cells increased after mobilization. All rabbits displayed a marked increase in osteocalcin protein expression in response to G-CSF/SCF. MRI scans showed a reactive interface between the necrotic and reparative zones after G-CSF/SCF. Quantitative analysis showed that new vessel formation was 3.3-fold greater and vessel density was 2.6-fold greater in the treatment than the control. The histologic and histomorphometric analysis revealed that the new bone volume was higher in the G-SCF/SCF group than in the control group at 4 weeks. G-CSF/SCF-induced mobilization of BMSC in the necrotic foci may represent a promising strategy for promoting functional bone repair of early stage ON.

10.1.157 Effects of vitamin k(2) and risedronate on bone formation and resorption, osteocyte lacunar system, and porosity in the cortical bone of glucocorticoid-treated rats
Iwamoto J, Matsumoto H, Takeda T, Sato Y, Liu X, Yeh JK
Calcif Tissue Int 2008;83:121-8

49 female Sprague Dawley rats, 3 months of age, were randomized into five groups according to control, GC, and GC with vitamin K_2, risedronate, or vitamin K_2 + risedronate. At the end of the 8-weeks, GC decreased percent cortical bone area and increased percent marrow area as a result of decreased periosteal bone formation, and increased endocortical bone erosion, and increased cortical porosity. Vitamin K_2 prevented a reduction in periosteal bone formation but did not affect percent cortical bone and marrow areas. Risedronate prevented a reduction in periosteal bone formation and an increase in endocortical bone erosion, resulting in prevention of alterations in percent cortical bone and marrow areas. Both increased osteocyte density and lacunar occupancy and prevented a GC-induced increase in cortical porosity. Vitamin K_2 and risedronate had additive effects on osteocyte density and lacunar occupancy and a synergistic effect on cortical porosity.

10.1.158 Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: A clinical practice guideline from the American College of Physicians
Qaseem A, Snow V, Shekelle P, Hopkins R, Jr., Forciea MA, Owens DK
Ann Intern Med 2008;149:404-15

10.1.159 Effect of the women's health initiative on prescription anti-osteoporosis medication utilization
Farley JF, Blalock SJ, Cline RR
Osteoporos Int 2008;19:1603-12

10.1.160 Effects of three years of low-dose thiazides on mineral metabolism in healthy elderly persons
Ott SM, Lacroix AZ, Scholes D, Ichikawa LE, Wu K
Osteoporos Int 2008;19:1315-22

10.1.161 Bone resorption inhibitor alendronate normalizes the reduced bone thickness of TRPV5(-/-) mice
Nijenhuis T, van der Eerden BC, Hoenderop JG, Weinans H, van Leeuwen JP, Bindels RJ
J Bone Miner Res 2008;23:1815-24

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 1, 2008

Exercise

10.1.162 Meta-analysis of walking for preservation of bone mineral density in postmenopausal women
Martyn-St James M, Carroll S
Bone 2008;43:521-31

Eight trials were eligible for inclusion. Treatment duration ranged from 6 to 24 months. Meta-analysis showed no change in BMD at this site [WMD (fixed-effect) 0.007 g/cm^2, 95% CI -0.001 to 0.016; P=0.09]. BMD data at the femoral neck were available from five trials among postmenopausal women. Results were inconsistent (I^2=51.4%) in showing a positive effect of walking on BMD at this site [WMD (random-effects) 0.014 g/cm^2, 95% CI 0.000 to 0.028; P=0.05]. Insufficient data were available for meta-analysis of the total hip site. Funnel plots showed some asymmetry for negative lumbar spine BMD outcomes. Trial quality scores ranged from 0 to 3 from the Jadad scale of 0 to 5. Regular walking has no effect on preservation of BMD at the spine in postmenopausal women, whilst significant positive effects at femoral neck are evident. However, diverse methodological and reporting discrepancies are apparent in the published trials on which these conclusions are based. Other forms of exercise that provide greater targeted skeletal loading may be required to preserve bone mineral density in this population.

10.1.163 Habitual and low-impact activities are associated with better bone outcomes and lower body fat in older women
Ilich JZ, Brownbill RA
Calcif Tissue Int 2008;83:260-71

In Caucasian women, aged 68.6±7.1 years, subjects with more walking hours/week had higher BMD/BMC of several skeletal sites (P<0.05). Stratification by cumulative (over 3 years) median for heavy housework, walking, sports/recreational, and total activities revealed higher BMD and BMC in the femur and spine (P=0.01) in subjects with those activities above median. Multivariate analysis of covariance results revealed that weight had the strongest influence on BMD and BMC, followed by bone-free lean mass (BFL). Various modes of PA were negatively associated with BMI and fat but not with BFL.

10.1.164 Competitive physical activity early in life is associated with bone mineral density in elderly Swedish men
Nilsson M, Ohlsson C, Eriksson AL, Frandin K, Karlsson M, Ljunggren O, Mellstrom D, Lorentzon M
Osteoporos Int 2008;19:1557-66

In this population-based study, 498 men, 75.2±3.3 (mean±SD) years old, were included. Subjects in the highest frequency group of CS in the early period (10-35 years), had higher BMD at the total body (4.2%, p<0.01), total hip (7.0%, p<0.01), trochanter (8.7%, p<0.01), and lumbar spine (7.9%, p<0.01), than subjects not involved in CS. A stepwise linear regression model showed that frequency of CS in the early period independently positively predicted present BMD at the total body (β=0.12, p<0.01), total hip (β=0.11, p<0.01), trochanter (β=0.12, p<0.01), and lumbar spine (β=0.11, p=0.01). PA in CS early in life is associated with BMD in 75-year-old Swedish men, indicating that increases in BMD following PA are preserved longer than previously believed.

10.1.165 Functional adaptation to loading of a single bone is neuronally regulated and involves multiple bones
Sample SJ, Behan M, Smith L, Oldenhoff WE, Markel MD, Kalscheur VL, Hao Z, Miletic V, Muir P
J Bone Miner Res 2008;23:1372-81

To determine whether adaptation may be neuronally regulated load-induced responses in the left and right ulnas and humeri were determined after loading of the right ulna in male Sprague Dawley rats (69±16 days of age). After a single period of loading at -760, -2000, or -3750 με initial peak strain, rats were given calcein. In one group, temporary neuronal blocking was achieved by perineural anesthesia of the brachial plexus during loading. Right ulna loading induces adaptive responses in other bones in both thoracic limbs compared with Sham controls and that neuronal blocking during loading abrogated bone formation in the loaded ulna and other thoracic limb bones. Skeletal adaptation was more evident in distal long bones compared with proximal long bones. The single period of loading modulated bone neuropeptide concentrations persistently for 10 days. Functional adaptation to loading of a single bone in young rapidly growing rats is neuronally regulated and involves multiple bones. Persistent changes in bone neuropeptide concentrations after a single loading period suggest that plasticity exists in the innervation of bone.

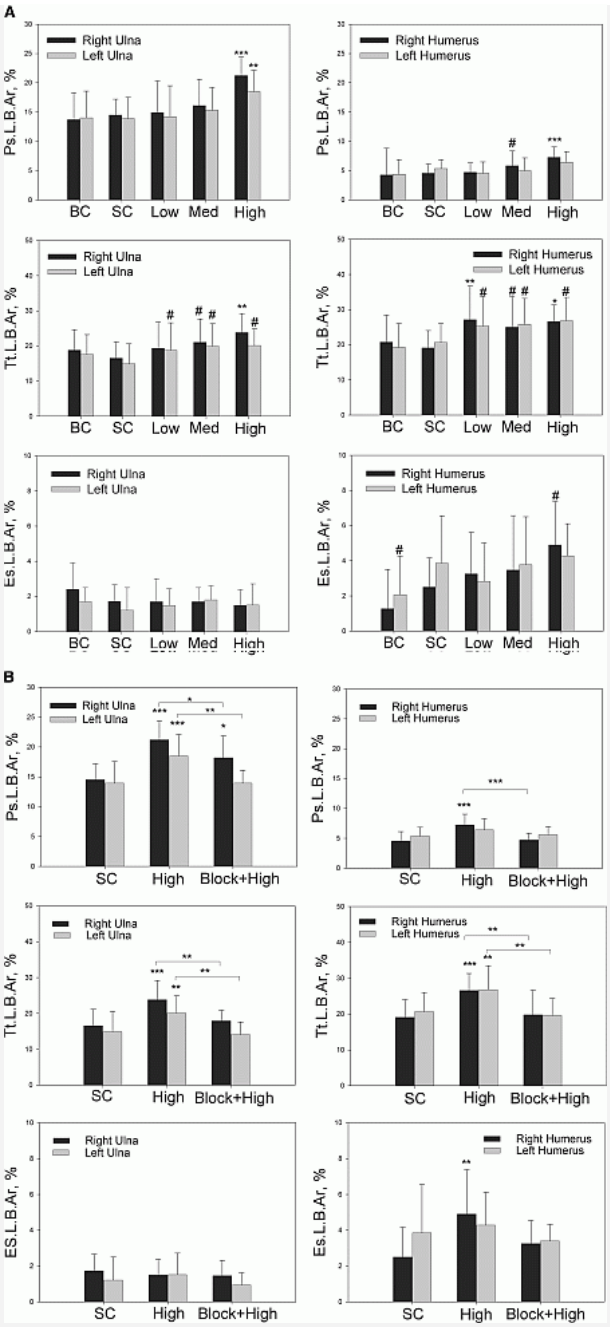

*Fig. 10.1.165a Load-induced bone formation in thoracic limb long bones was most pronounced in the periosteal bone envelope. Neuronal mechanotransduction regulated the majority of adaptive bone formation in distant bones and a large proportion of bone formation in the loaded (right) ulna. (A) Formation of calcein-labeled new bone in thoracic limb bones of Sprague-Dawley rats in response to unilateral cyclic loading of the right ulna. In the high strain group, normalized periosteal labeled bone area (Ps.L.B.Ar) was increased in both the loaded (right) ulna and the contralateral (left) ulna. Similar but reduced responses were also seen in the humerii that were not directly loaded. Changes in total labeled bone area (Tt.L.B.Ar) in response to mechanical loading were less evident. Increased endosteal labeled bone area (Es.L.B.Ar) was only found in the right humerus after high strain loading. Bone formation in baseline and Sham control groups of rats was not significantly different. (B) Adaptive bone formation after brachial plexus blocking and loading at high strain was not significantly different from Sham control, except Ps.L.B.Ar in the loaded (right) ulna, which was reduced 45% by neuronal blocking. BC, baseline control; SC, Sham control; low, loading at -3.3 N, initial peak strain, -760 με; med, loading at -10 N, initial peak strain = -2000 με; high, loading at -18 N, initial peak strain = -3750 με; block + high, loading at high initial peak strain after brachial plexus blocking. *p<0.05; **p<0.01; ***p<0.001; #p<0.15 vs. the relevant Sham control. Differences between the group loaded at high strain and the blocked + loaded group are also indicated. Error bars represent SD. Loaded groups, n=16; Sham control group, n=12; blocked + loaded group, n=8; baseline control group, n=8. Reproduced from J Bone Miner Res 2008;23:1372-81 with permission of the American Society of Bone and Mineral Research.*

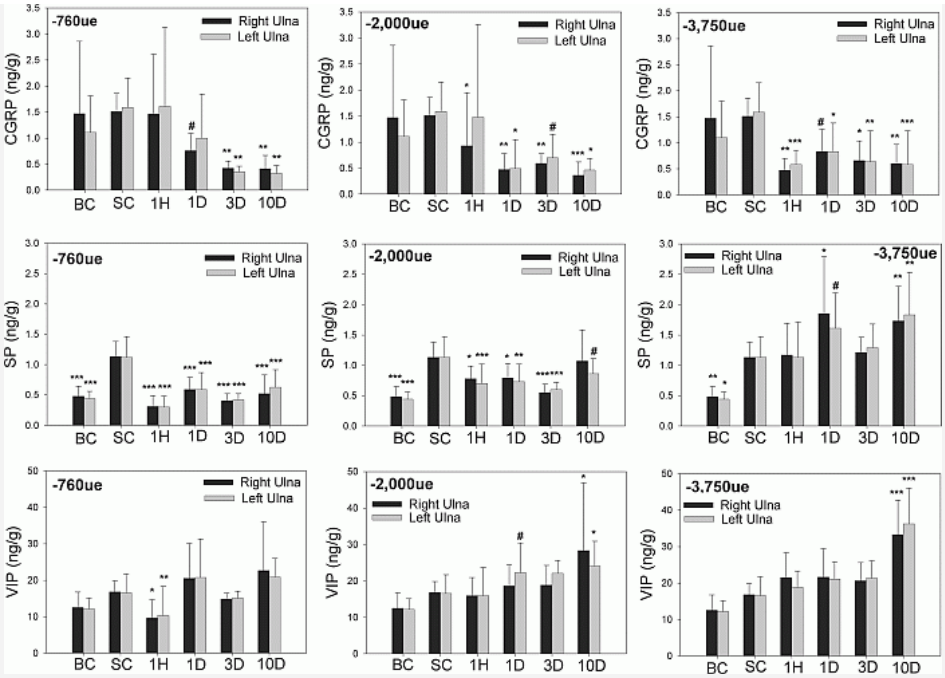

*Fig. 10.1.165b Unilateral cyclic loading of the right ulna induced persistent changes in bone neuropeptide concentrations in both the loaded (right) ulna and the contralateral (left) ulna. Unilateral cyclic loading of the right ulna induced bilateral decreases in ulnar CGRP concentrations that persisted for the 10-day experimental period. Loading with low and medium initial peak strain also induced similar changes in ulnar SP concentrations; these effects were not evident with high strain loading. Ulnar VIP concentrations were also increased bilaterally at 10 days in response to loading at high strain. The Sham control group was not significantly different from the baseline control group for CGRP and VIP, whereas bone concentrations of SP were increased in the Sham control group. BC, baseline control; SC, Sham control; 1H, 1 h after loading; 1D, 1 day after loading; 3D, 3 days after loading; 10D, 10 days after loading; -760 με, loading at low initial peak strain using -3.3 N; -2000 με, loading at medium initial peak strain using -10 N; -3750 με, loading at high initial peak strain using -18 N. *p<0.05; **p<0.01; ***p<0.001; #p<0.15 vs. the relevant Sham control. Error bars represent SD. Loaded groups, n=12; Sham control group, n=9; baseline control group, n=12. Reproduced from J Bone Miner Res 2008;23:1372-81 with permission of the American Society of Bone and Mineral Research.*

10.1.166 The effect of weight loading and subsequent release from loading on the postnatal skeleton
Reich A, Sharir A, Zelzer E, Hacker L, Monsonego-Ornan E, Shahar R
Bone 2008;43:766-74

The tibial growth plates from chicks subjected to load and controls, immediately after loading and following 5 days of load release, were studied. At the end of the loading period, the tibias of the experimental group were shorter and their growth plate narrower than in controls. After a further 5 days of no external load, bones and growth plates demonstrated 'catch-up': the thickness of the growth plate exceeded that of the control; however the relative expression of genes controlling chondrocyte differentiation (collagen II and X) did not change, while the expression of factors related to growth plate ossification (osteopontin, alkaline phosphatase) and cartilage and bone calcification (matrix and bone Gla proteins) was upregulated as a result of the catch-up process. At this time, however, the tibiae of the experimental group showed inferior mechanical and structural properties relative to the control group. External loading during bone elongation negatively affects the mechanical and structural properties of the skeleton.

10.1.167 Skeletal effects of estrogen and mechanical loading are structurally distinct
Pajamaki I, Sievanen H, Kannus P, Jokihaara J, Vuohelainen T, Jarvinen TL
Bone 2008;43:748-57

Thirty 3-week-old littermates of female Sprague Dawley rats were randomly assigned into bilateral sham (E(+)) or ovariectomy (E(-)) surgery after which, the left hindlimb each study animal was cast immobilized (L(-)) while the right limb served as locomotively loaded control (L(+)), a classic 2x2 factorial study design. The loading-induced effects were identical in the estrogen-replete (E(+)) and estrogen-deplete (E(-)) groups. Femoral neck: +78% vs. +69% in the tCSA, +74% vs. +55% in the tBMC, -6.0% vs. -7.2% in the tBMD, and +33% vs. +58% in the F(max); Femoral midshaft: +6.9% vs. +3.9% in the cCSA, +13% vs. +13% in the tCSA, +23% vs. +16% in the cBMC, +5.2% vs. +5.1% in the cBMD, and +8.0% vs. +8.0% in the F(max), respectively. All comparisons (NS), challenging the alleged modulatory effect of estrogen on skeletal mechanosensitivity. Estrogen did not have an independent effect on the periosteal apposition at any of the evaluated bone regions. Instead, according to its primary reproductive function, the effects of estrogen were restricted to accrual of bone mass only, the stimulus being apparent at the endosteal surface of cortex and trabecular structure of the distal metaphysis. In conclusion, the present results indicate that that the actions of estrogen and loading on bone structure are independent and additive in nature.

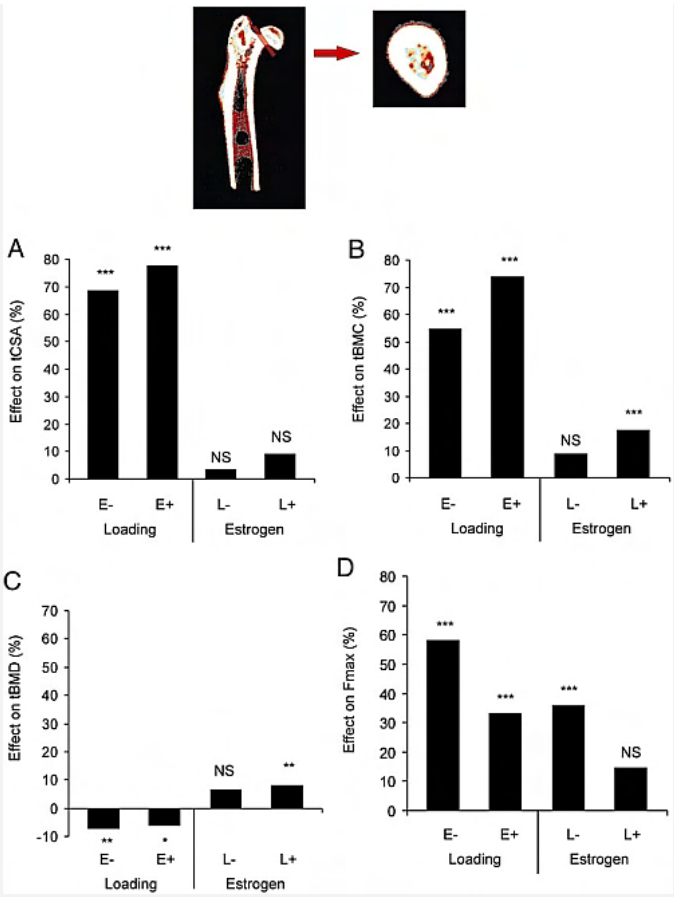

Fig. 10.1.167a Influence of mechanical loading and estrogen on the structural strength (Fmax) and its major components (cross-sectional area, tCSA; mineral mass, BMC; and mineral density, tBMD) of the femoral midneck. Reproduced from Bone, 43:748-57, Copyright (2008), with permission from Elsevier.

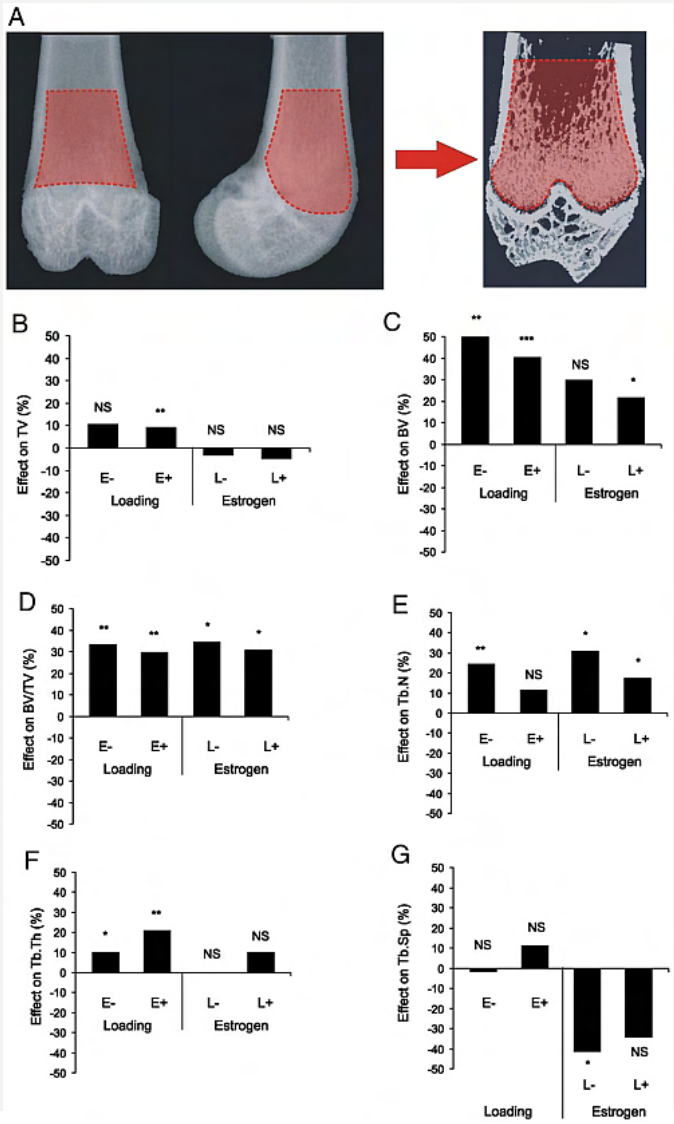

Fig. 10.1.167b Microcomputed tomography (μCT) of the distal femoral metaphysic. (A) An image derived from the distal femur, the red zone indicating the volume of interest (VOI) used for the analysis. (B-G) Effects of mechanical loading and estrogen on the trabecular bone in the distal femoral metaphysis. Loading (p=0.002), but not estrogen (p=0.280), had a significant effect on the total bone volume (TV). However, both factors displayed a significant stimulatory effect on the trabecular bone volume (BV, both p<0.01) and the trabecular bone volume fraction (BV/TV, both p<0.01) of the region. The mechanism of action of the two factors on the trabecular structurewas shown to be very distinct: loading increased the trabecular number (Tb.N, p=0.006) and thickness (Tb.Th, p<0.001) without influencing trabecular spacing (Tb.Sp, p=0.775), while the estrogen-effect was mediated through increased trabecular number (p=0.007) and decreased trabecular spacing without affecting trabecular thickness (p=0.244). Reproduced from Bone, 43:748-57, Copyright (2008), with permission from Elsevier.

10.1.168 Does a novel school-based physical activity model benefit femoral neck bone strength in pre- and early pubertal children?
Macdonald HM, Kontulainen SA, Petit MA, Beck TJ, Khan KM, McKay HA
Osteoporos Int 2008;19:1445-56

10.1.169 A 3-year physical activity intervention program increases the gain in bone mineral and bone width in prepubertal girls but not boys: The Prospective Copenhagen School Child Interventions Study (CoSCIS)
Hasselstrom HA, Karlsson MK, Hansen SE, Gronfeldt V, Froberg K, Andersen LB
Calcif Tissue Int 2008;83:243-50

10.1.170 The effect of moderate impact exercise on skeletal integrity in master athletes
Velez NF, Zhang A, Stone B, Perera S, Miller M, Greenspan SL
Osteoporos Int 2008;19:1457-64

10.1.171 High-intensity exercise induces structural, compositional and metabolic changes in cuboidal bones: Findings from an equine athlete model
Tidswell HK, Innes JF, Avery NC, Clegg PD, Barr AR, Vaughan-Thomas A, Wakley G, Tarlton JF
Bone 2008;43:724-33

10.1.172 The BPAQ: A bone-specific physical activity assessment instrument
Weeks BK, Beck BR
Osteoporos Int 2008;19:1567-77

10.1.173 Climbing exercise enhances osteoblast differentiation and inhibits adipogenic differentiation with high expression of PTH/PTHrP receptor in bone marrow cells
Menuki K, Mori T, Sakai A, Sakuma M, Okimoto N, Shimizu Y, Kunugita N, Nakamura T
Bone 2008;43:613-20

Volume 10, Issue 1, 2008

Men

10.1.174 Vertebral fracture assessment in healthy men: Prevalence and risk factors
El Maghraoui A, Mounach A, Gassim S, Ghazi M
Bone 2008;43:544-8

In 216 healthy men aged between 50 and 79 (mean age, weight and BMI of 63.8 years, 73.3 kg and 25.7 kg/m^2, respectively), 93% of vertebrae from T4-L4 and 98% from T8-L4 were adequately visualized on VFA. Vertebral fractures were detected in 29.6% (64/216) of these men: 34/216 (15.7%) had grade 1 and 30/216 (13.8%) had grades 2 or 3. Twenty-one of men with VFA-identified fracture (32.8%) had only a single vertebral fracture, while the other 67.2% had two or more. The prevalence of VFA-detected fractures increased with age and as BMD declined. This group of men had a lower weight, height, calcium consumption and T-score than those without a VFA-identified vertebral fracture. Regression analysis showed that presence of vertebral fracture was mainly related to the osteoporotic status (OR: 9.0; 95% CI 3.5-22.8).

10.1.175 Constant adaptation of bone to current physical activity level in men: A 12-year longitudinal study
Tervo T, Nordstrom P, Neovius M, Nordstrom A
J Clin Endocrinol Metab 2008;[Epub ahead of print]

This 12-year longitudinal study investigated whether a high BMD from previous high physical activity is maintained with reduced activity later in life. Three groups were investigated with a mean age of 17 years at baseline; 51 athletes who stopped their active careers during follow-up (former athletes), 16 who were active throughout follow-up (active athletes), and 25 controls. After adjustment for age, weight, and height, the former athletes were found to have higher BMD at all sites at every follow-up visit except the last one, when compared to controls ($p<0.05$). The active athletes were found to have significantly higher BMD at all measured locations when compared to controls throughout the entire study ($p<0.05$). From the first to the final follow-up visit, the former athletes were found to have lost more femoral neck BMD than both the active athletes (mean difference, 0.12 g/cm^2; $p=0.003$) and controls (mean difference 0.08 g/cm^2; $p=0.02$). Increased BMD due to previous high physical activity may not prevent osteoporosis in later years.

10.1.176 Renal function and rate of hip bone loss in older men: The Osteoporotic Fractures in Men Study
Ishani A, Paudel M, Taylor BC, Barrett-Connor E, Jamal S, Canales M, Steffes M, Fink HA, Orwoll E, Cummings SR, Ensrud KE
Osteoporos Int 2008;19:1549-56

Serum cystatin C, serum creatinine and total hip BMD measured at baseline in a cohort of 404 older men followed for 4.4 years showed the mean rate of decline in total hip BMD increased with increase in cystatin C (mean annualized percent change -0.29, -0.34, -0.37 and -0.65% for quartiles 1 to 4; p for trend =0.004). Similarly, adjusted rates of hip bone loss were higher among men with lower eGFR as defined by the modification of diet in renal disease formula (mean annualized percent change -0.58, -0.39, -0.37, and -0.31 for quartiles 1 to 4; p for trend=0.02), but not among men with lower eGFR as defined by the Cockcroft-Gault formula (mean annualized percent change -0.47, -0.44, -0.31 and -0.43 for quartiles 1 to 4; p for trend=0.48). Older men with reduced renal function are at increased risk of hip bone loss. Healthcare providers should consider renal function when evaluating older men for risk factors for bone loss and osteoporosis.

10.1.177 Incidence and risk factors for low trauma fractures in men with prostate cancer
Ahlborg HG, Nguyen ND, Center JR, Eisman JA, Nguyen TV
Bone 2008;43:556-60

43 men aged 60+ years reported a history of prostate cancer; among whom, 22 men received androgen deprivation therapy (ADT), and 21 men did not. Men with prostate cancer had higher lumbar spine BMD than those without cancer (p=0.013). During the follow-up period, 15 men with prostate cancer had sustained a fracture, yielding the age-adjusted incidence of fracture among this group was 31.6 per 1000 person-years, which was greater than those without cancer (22.1 per 1000 person-years). The age-adjusted incidence of fracture was more pronounced among those with prostate cancer on ADT (40.2 per 1000 person-years). After adjusting for age, the increase in fracture risk among prostate cancer patients was associated with lower femoral neck BMD (hazard ratio [HR] per SD=1.8, 95% CI 1.0-3.4) and increased rate of bone loss (HR 2.3, 1.2-4.6).

10.1.178 Prevalence of vertebral fractures in men with acromegaly
Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A, Pontecorvi A, De Marinis L, Giustina A
J Clin Endocrinol Metab 2008;[Epub ahead of print]

40 males with acromegaly (25 patients with controlled disease and 15 patients with active disease) and in 31 control males, with age and gonadal status comparable to the patients. Although BMD was not different between acromegalic patients and control subjects, the prevalence of vertebral fractures was higher in acromegalic patients as compared with the controls (57.5% vs. 22.6%; Chi-square: 8.7; p=0.003). Fractured and non fractured acromegalic patients showed no significant difference in age and BMD Z-score. However, acromegalic patients with fractures had serum IGF-I values significantly higher and duration of active disease significantly longer with respect to patients without fractures. Moreover, patients with fractures showed longer untreated hypogonadism as compared to patients without fractures and duration of active acromegaly was the only risk factor significantly correlated with the occurrence of fractures (odds ratio: 1.1, C.I. 1.04-1.6).

10.1.179 Older men with low serum estradiol and high serum SHBG have an increased risk of fractures
Mellstrom D, Vandenput L, Mallmin H, Holmberg AH, Lorentzon M, Oden A, Johansson H, Orwoll ES, Labrie F, Karlsson MK, Ljunggren O, Ohlsson C
J Bone Miner Res 2008;23:1552-60

In older men (n=2639; mean, 75 yr of age) of MrOS Sweden follow-up of 3.3 yr fracture was 20.9/1000 person-years. Estradiol (E2; hazard ratio [HR] per SD decrease, 1.34; 95% CI 1.22-1.49), free estradiol (fE2; HR per SD decrease, 1.41; 95% CI 1.28-1.55), testosterone (T; HR per SD decrease, 1.27; 95% CI 1.16-1.39), and free testosterone (fT; HR per SD decrease, 1.32; 95% CI 1.21-1.44) were all inversely, whereas sex hormone-binding globulin (SHBG; HR per SD increase, 1.41; 95% CI 1.22-1.63) was directly related to fracture risk. fE2 and SHBG ($p<0.001$), but not fT, were independently associated with fracture risk. fE2 was inversely associated with clinical vertebral fractures (HR per SD decrease, 1.57; 95% CI 1.36-1.80), nonvertebral osteoporosis fractures (HR per SD decrease, 1.42; 95% CI 1.23-1.65), and hip fractures (HR per SD decrease, 1.44; 95% CI 1.18-1.76). The inverse relation between serum E2 and fracture risk was nonlinear with a strong relation <6 pg/ml for E2 and 0.3 pg/ml for fE2.

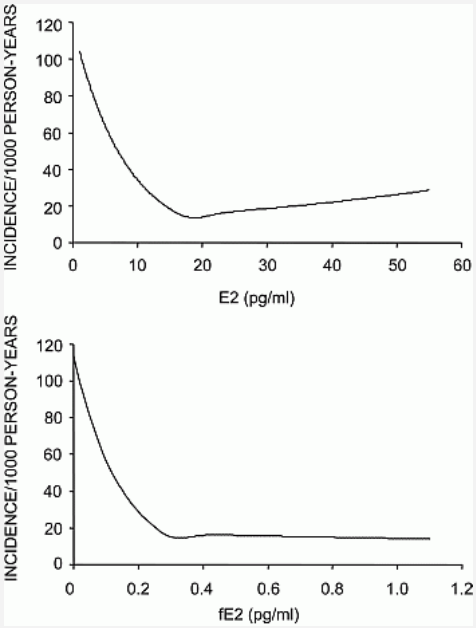

Fig. 10.1.179 Yearly incidence of fractures in relation to total E2 and fE2. Poisson regression models were used to determine the relation between serum hormone levels and fracture risk (all validated fractures). Reproduced from J Bone Miner Res 2008;23:1552-60 with permission of the American Society of Bone and Mineral Research.

10.1.180 Targeting of androgen receptor in bone reveals a lack of androgen anabolic action and inhibition of osteogenesis: A model for compartment-specific androgen action in the skeleton

Wiren KM, Semirale AA, Zhang XW, Woo A, Tommasini SM, Price C, Schaffler MB, Jepsen KJ

Bone 2008;43:440-51

Transgenic mice overexpressing androgen receptor showed no difference in body composition, testosterone, or 17ss-estradiol levels. Transgenic males have reduced serum osteocalcin, CTx and TRAPC5b. In cortical bone, there was no difference in periosteal perimeter but a reduction in cortical bone area due to an enlarged marrow cavity. Endocortical formation was inhibited. Biomechanical analyses showed decreased whole bone strength and quality. Trabecular morphology was altered, with increased bone volume comprised of more trabeculae that were closer together but not thicker. Expression of genes involved in bone formation and bone resorption was reduced. Anabolic effects were exclusively at periosteal surfaces, but in mature osteoblasts androgens inhibited osteogenesis with detrimental effects on matrix quality, bone fragility and whole bone strength. Thus, the present data demonstrate that enhanced androgen signaling targeted to bone results in low bone turnover and inhibition of bone formation by differentiated osteoblasts. These results indicate that direct androgen action in mature osteoblasts is not anabolic.

10.1.181 In vivo microMRI-based finite element and morphological analyses of tibial trabecular bone in eugonadal and hypogonadal men before and after testosterone treatment

Zhang XH, Liu XS, Vasilic B, Wehrli FW, Benito M, Rajapakse CS, Snyder PJ, Guo XE

J Bone Miner Res 2008;23:1426-34

Ten untreated hypogonadal and 10 eugonadal men were selected. The hypogonadal men were treated with a testosterone gel for 24 mo. Changes in microarchitecture were also quantified using individual trabeculae segmentation (ITS)-based and standard morphological analyses. Significant differences in four estimated anisotropic elastic material constants and most morphological parameters were detected. No change in estimated elastic moduli and morphological parameters was detected in the eugonadal group over 24 mo. After 24 mo of treatment, increases in estimated elastic moduli E(22) (9.0%), E(33) (5.1%), G(23) (7.2%), and G(12) (9.4%) of hypogonadal men were detected accompanied by increases in trabecular plate thickness.

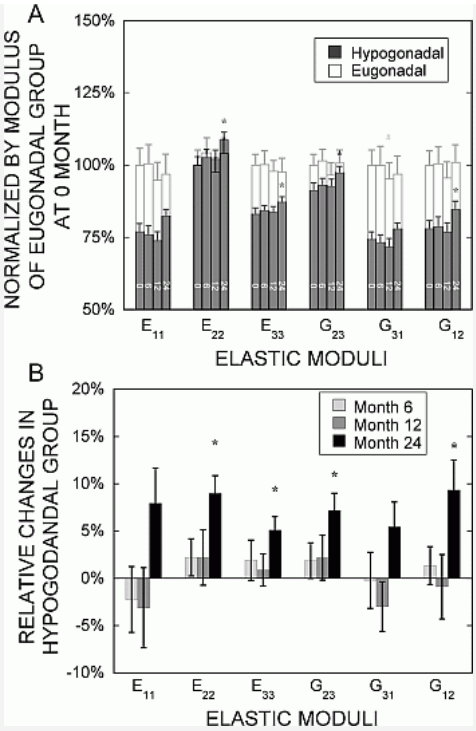

*Fig. 10.1.181a (A) Normalized elastic moduli of both hypogonadal and eugonadal groups (normalized by the corresponding modulus in the eugonadal group at baseline). (B) Relative changes in elastic moduli of the hypogonadal group from baseline at 6, 12, and 24 mo of treatment. Values shown are means±SE. #p<0.05 and *p<0.01 indicate significant difference compared with the baseline. Reproduced from J Bone Miner Res 2008;23:1426-34 with permission of the American Society of Bone and Mineral Research.*

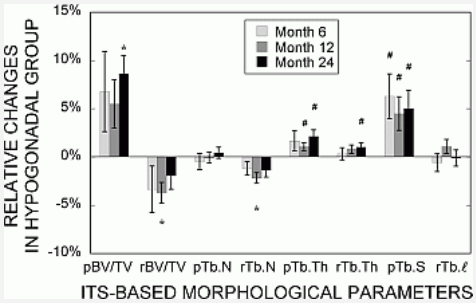

*Fig. 10.1.181b Changes of ITS-based morphological parameters in the hypogonadal group after 6, 12, and 24 mo of treatment relative to the baseline. Values shown are means±SE. #p<0.05 and *p<0.01 indicate significant difference compared with the baseline. Reproduced from J Bone Miner Res 2008;23:1426-34 with permission of the American Society of Bone and Mineral Research.*

10.1.182 Association of Parkinson's disease with accelerated bone loss, fractures and mortality in older men: The Osteoporotic Fractures in Men (MrOS) study

Fink HA, Kuskowski MA, Taylor BC, Schousboe JT, Orwoll ES, Ensrud KE

Osteoporos Int 2008;19:1277-82

10.1.183 Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy

Greenspan SL, Nelson JB, Trump DL, Wagner JM, Miller ME, Perera S, Resnick NM

J Clin Oncol 2008;26:4426-34

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editor E. Seeman

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Osteoporos Int 2008;19:1505-9

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Osteoporos Int 2008;19:1517-25

10.1.190 Nonclassic actions of vitamin D
Bikle D
J Clin Endocrinol Metab 2008;[Epub ahead of print]

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J Bone Miner Res 2008;23:1353-68

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Vashishth D
Bone 2008;43:794-7

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10.1.197 Special report on the 2007 adult and pediatric Position Development Conferences of the International Society for Clinical Densitometry
Lewiecki EM, Gordon CM, Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Silverman S, Bishop NJ, Leonard MB, Bianchi ML, Kalkwarf HJ, Langman CB, Plotkin H, Rauch F, Zemel BS
Osteoporos Int 2008;19:1369-78

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10.1.198 The effect of the microscopic and nanoscale structure on bone fragility
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Osteoporos Int 2008;19:1251-65

10.1.199 Measurement of the toughness of bone: A tutorial with special reference to small animal studies
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Bone 2008;43:798-812

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10.1.200 Recommendations for the registration of agents for prevention and treatment of glucocorticoid-induced osteoporosis: An update from the Group for the Respect of Ethics and Excellence in Science
Compston J, Reid DM, Boisdron J, Brandi ML, Burlet N, Cahall D, Delmas PD, Dere W, Devogelaer JP, Fitzpatrick LA, Flamion B, Goel N, Korte S, Laslop A, Mitlak B, Ormarsdottir S, Ringe J, Rizzoli R, Tsouderos Y, Van Staa T, Reginster JY
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Osteoporos Int 2008;19:1379-94

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Osteoporos Int 2008;19:1363-8

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J Bone Miner Res 2008;23:1548-51

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Campaign Description

Campaign Vision

The IOF Invest in Your Bones campaign vision is of a world without osteoporotic fractures through increasing awareness and understanding of osteoporosis. The emphasis is also on improving quality of life and on the healthcare budget. In addition, the Invest in Your Bones campaign aims to sensitise health professionals, including general practitioners, radiologists and orthopaedic surgeons.

About the Campaign

In 2002, IOF inaugurated the first phase of the Invest in Your Bones Campaign. The campaign, now in its fourth phase (beginning in 2008), supports projects aimed at improving access to, and reimbursement of, diagnosis and proven therapies in individuals at high risk of fragility fracture. It has a geographic focus on France, Germany, Italy, Spain and the UK.

The campaign also helps the IOF to support the 'Call for Action' at the EU, through various policy and lobbying activities, including support to the European Parliament Osteoporosis Interest Group and EU Osteoporosis Consultation Panel.

Other key ongoing projects supported by the campaign include the Osteoporosis Education Program to Improve the Recognition and Reporting of Vertebral Fractures by Radiologists; an initiative involving orthopaedic surgeons aimed at optimizing the care of fragility fracture patients; the development of health economics studies in osteoporosis; and support to the development of new guidelines for assessing fracture risk in individuals.

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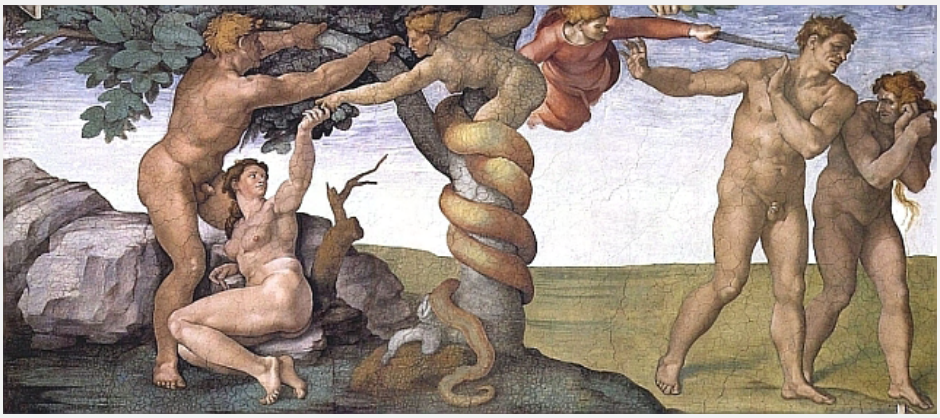

Michelangelo (1475-1564): Center of the ceiling: Original Sin and Expulsion from the Garden of Eden [before restoration], Vatican, Sistine Chapel ©1990. Photo Scala, Florence

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Progress in Osteoporosis is a quarterly review journal that provides a summary of the most important literature published in the field of osteoporosis in the preceding 3-4 months.

Managing Editor: Fina Liu

International Osteoporosis Foundation

Progress In Osteoporosis Volume 10, Issue 2, 2009

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Invest In Your Bones Campaign

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IOF WCO–ECCEO10
May 5 - 8, 2010
Florence, Italy
More information

FRAX® – WHO Fracture Risk Assessment Tool
Helping health professionals worldwide to improve identification of patients at high risk of fracture for treatment .
More information

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I loved you in the morning, our kisses deep and warm,
your hair upon the pillow like a sleepy golden storm,
yes, many loved before us, I know that we are not new,
in city and in forest they smiled like me and you,
but now it's come to distances and both of us must try,
your eyes are soft with sorrow,
Hey, that's no way to say goodbye.

I'm not looking for another as I wander in my time,
walk me to the corner, our steps will always rhyme
you know my love goes with you as your love stays with me,
it's just the way it changes, like the shoreline and the sea,
but let's not talk of love or chains and things we can't untie,
your eyes are soft with sorrow,
Hey, that's no way to say goodbye.

From 'Hey, That's No Way to Say Goodbye'
Leonard Cohen

Overview

Ibandronate

Lewiecki et al report that once-monthly oral ibandronate administered for 12 months increased integral total hip QCT BMD and DXA areal BMD. FEA-derived hip strength to density ratio and femoral, peripheral, and trabecular strength increased with ibandronate while improved vertebral, peripheral, and trabecular strength and anteroposterior bending stiffness vs. placebo improved. HSA-estimated femoral neck outer diameter increased, the latter is probably an artefact given the drug is not an anabolic agent. **J Clin Endocrinol Metab 2009;94:171-80**

Zoledronate

Grey et al make an important contribution to therapeutics by demonstrating that the beneficial effects of zoledronic acid may persist during two years. In 50 postmenopausal women with osteopenia, zoledronate decreased markers of bone turnover for 2 years. Between-groups differences in markers of bone turnover and bone mineral density were similar at 12 and 24 months. Mild secondary hyperparathyroidism was present throughout the study in the zoledronate group. **J Clin Endocrinol Metab 2009;94:538-44**

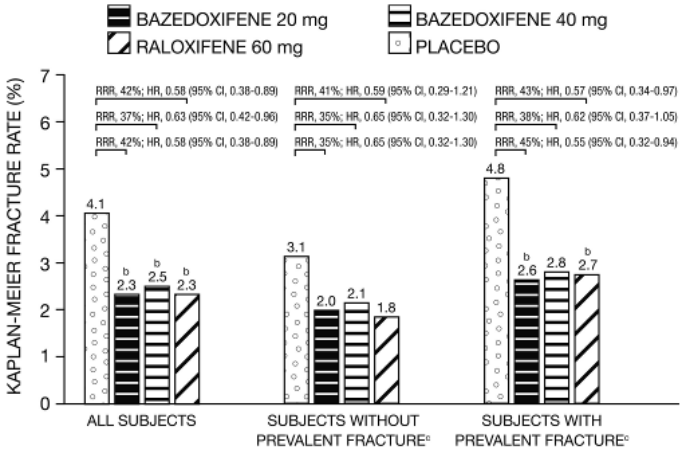
PTH – stimulating the phagocytes, or does it?

Jilka et al confront the challenging issue of why PTH cannot seem to stimulate periosteal apposition, at least in human subjects. The investigators make the point that the anabolic action on the endosteal surface thrives on the ability to inhibit apoptosis of the many osteoblasts cells produced by high remodeling. The periosteum is a pretty quiet place after completion of growth and so PTH does not have many cells to inhibit the apoptosis of. Instead it must exert pro-differentiating and/or pro-survival effects on postmitotic preosteoblasts. **Bone 2009;44:275-86**

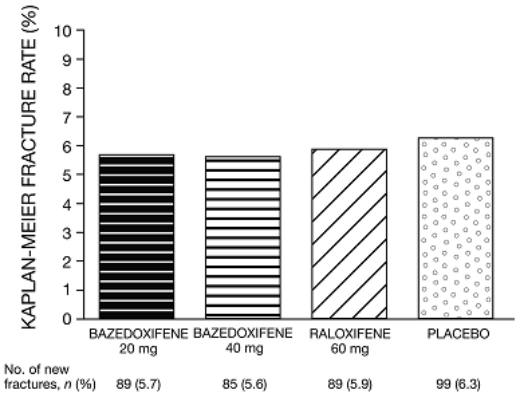
Recker et al report 100 µg PTH(1-84) given for 18 (n=8) or 24 (n=7) months and 8 placebo treated subjects. Cancellous bone volume was 45-48% higher due to higher trabecular number (Tb.N) and produced by intratrabecular tunneling. Trabecular thickness and connectivity density was higher. Cancellous bone formation rate was 2-fold higher because of greater mineralizing surface. Osteoclast and eroded surface were unaffected and there were no effects on cortical thickness, or endocortical, or periosteal BFR; porosity tended to be higher. **Bone 2009;44:113-9**

Bazedoxifene

Silverman et al report that in a 3-year, randomized, double-blind, placebo-controlled study, 6847 women with osteoporosis (55-85 years of age) received bazedoxifene 20 or 40 mg/d, raloxifene 60 mg/d, or placebo. New vertebral fractures were lower with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) than placebo (4.1%); relative risk reductions of 42%, 37%, and 42%, respectively. In a post hoc analysis of women at higher fracture risk, bazedoxifene 20 mg showed a 50% and 44% reduction in nonvertebral fractures relative to placebo (p=0.02) and raloxifene 60 mg (p=0.05), respectively. **J Bone Miner Res 2008;23:1923-34**



Incidence of new vertebral fractures and corresponding fracture risk reductions by baseline prevalent vertebral fracture status.[a] RRR, relative risk reduction; HR, hazard ratio; CI, confidence interval. [a]Intent-to-treat population; n=6847. [b]p<0.05 vs. placebo. [c]p=0.89 for treatment by prevalent fracture status interaction. Reproduced from J Bone Miner Res 2008;23:1923-34 with permission of the American Society of Bone and Mineral Research.



Incidence of nonvertebral fractures in each treatment group.[a] [a]Overall population; N=7492. Reproduced from J Bone Miner Res 2008;23:1923-34 with permission of the American Society of Bone and Mineral Research.

Epidemiology in Taiwan

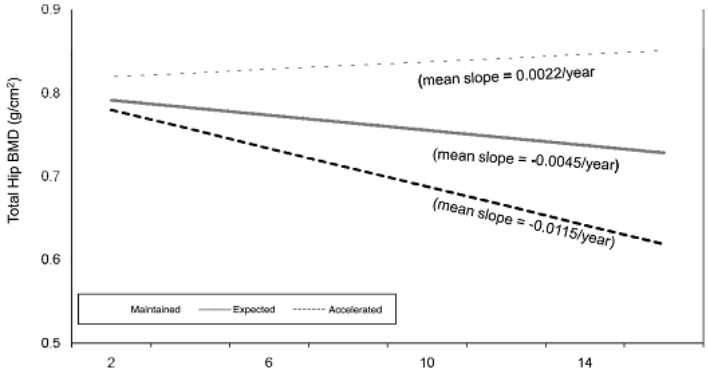
Shao et al report that 75,482 hip fractures occurred during 7 years with an incidence rate of 57.54 per 10,000 per year but increasing by 30% during 7 years and more greatly in males (36%) than in females (22%). The average female-to-male ratio was 1.76, lower than those in many countries. In females, cervical fracture was higher than that of trochanteric fractures, while the incidence of trochanteric fractures was higher than cervical fractures in males (p<0.0001). **Bone 2009;44:125-9**

Renin

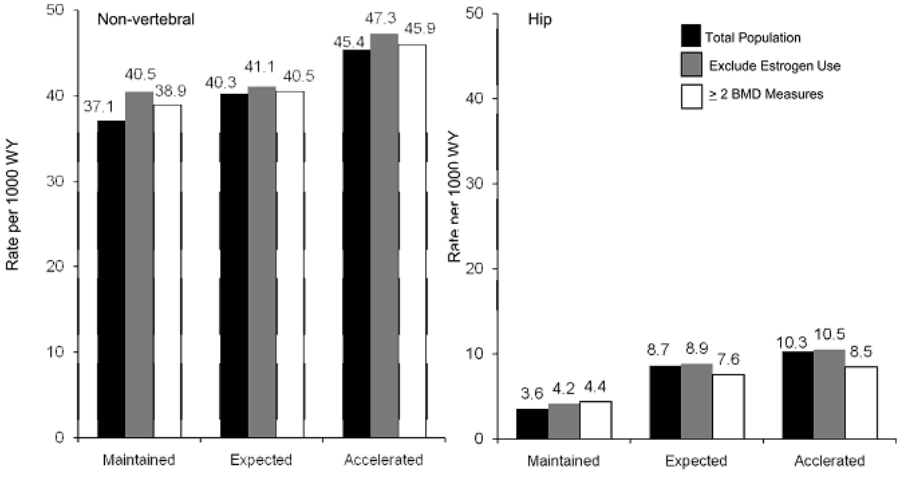
Asaba et al report that activation of the renin-angiotensin system activation induces high turnover osteoporosis with accelerated bone resorption. Angiotensin II (AngII) acted on osteoblasts and increased RANKL and vascular endothelial growth factor stimulating formation of osteoclasts. Knockdown of AT2 receptor inhibited the AngII activity, whereas silencing of the AT1 receptor enhanced it. ACE inhibitor, enalapril, improved osteoporosis; whereas losartan exacerbated the low bone mass phenotype.

Successful skeletal aging

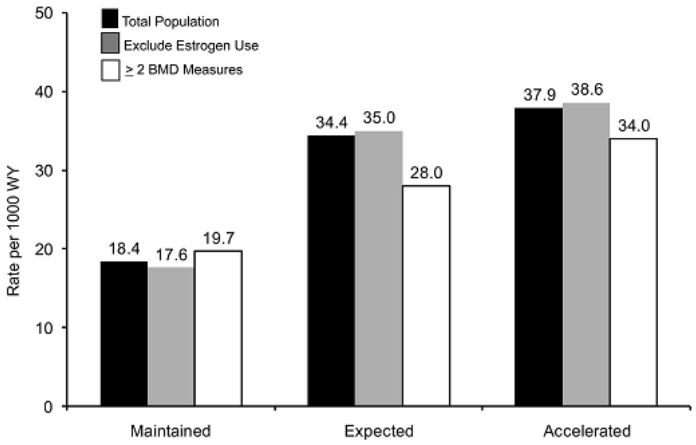
Cauley et al present an interesting study suggesting there is a group of women who lose little or no bone with advancing age. If this is the case, then the pathogenetic mechanisms identifying those who lose little bone and those who lose a great deal of bone need to be studied. Out of 8224 subjects measured over 15 years, about 10% lost little or no BMD. These subjects had a 20% lower risk of nonspine fracture and 67% lower risk of hip fracture. Mortality risks were also lower. **J Bone Miner Res 2009;24:134-43**



Total hip BMD over 15 yr of follow-up. *Estimated from random effects regression. Reproduced from J Bone Miner Res 2009;24:134-43 with permission of the American Society of Bone and Mineral Research.



Age-adjusted incidence rate (per 1000 women-years) of nonspine fracture and hip fracture: women who maintained hip BMD, experienced expected hip bone loss, or experienced accelerated bone boss. Reproduced from J Bone Miner Res 2009;24:134-43 with permission of the American Society of Bone and Mineral Research.



Age-adjusted mortality rate (per 1000 women-years): women who maintained hip BMD, experienced expected bone loss, or experienced accelerated bone boss. Reproduced from J Bone Miner Res 2009;24:134-43 with permission of the American Society of Bone and Mineral Research.

Coupling factor?

Walker et al report that cardiotrophin (CT-1) signals through gp130 and the LIF receptor is expressed in osteoclasts and increases osteoblast activity and mineralization in vitro and in vivo. In neonate CT-1(-/-) mice, low bone mass associated with reduced osteoblasts and many large osteoclasts, but increased cartilage remnants within the bone suggest impaired resorption. Cultured marrow from CT-1(-/-) mice generated osteoclasts and mineralized poorly. As the CT-1(-/-) mice aged, the reduced osteoblast surface (ObS/BS) was no longer detected, but impaired bone resorption continued resulting in an osteopetrotic phenotype. CT-1 is an osteoclast-derived stimulus of bone formation and resorption. **J Bone Miner Res 2008;23:2025-32**

CatK knockout

Pennypacker et al report that CatK null mice have osteopetrosis. CatK (-/-) mice had less lamellar cortical bone. Higher bone volume, trabecular thickness, and trabecular number were observed at the distal femur with a smaller marrow cavity a sign of decreased endocortical resorption. **Bone 2009;44:199-207**

The guilty undertaker sighs,
The lonesome organ grinder cries,
The silver saxophones say I should refuse you.
The cracked bells and washed-out horns
Blow into my face with scorn,
But it's not that way,
I wasn't born to lose you.
I want you, I want you,
I want you so bad,
Honey, I want you.

The drunken politician leaps
Upon the street where mothers weep
And the saviors who are fast asleep,
They wait for you.
And I wait for them to interrupt
Me drinkin' from my broken cup
And ask me to
Open up the gate for you.
I want you, I want you,
I want you so bad,
Honey, I want you.

From 'I Want You'
Bob Dylan

Note from the Editor

The purpose of *Progress in Osteoporosis* is to provide the reader with a summary of the most important literature published in the preceding three to four months in the field of osteoporosis. Most reviews and original research are cited. In addition, summaries and figures are provided for readers who may not have easy access to all the specialist literature. The summaries are based on the contents of abstracts, which have been abbreviated to concisely convey the main theme. The contents of the abstracts and figures should be used only as a means of directing the reader to the original literature and should not be quoted verbatim or cited as a reference. The opinions expressed in the Overview are my own and do not necessarily reflect those of the International Osteoporosis Foundation.

Ego Seeman

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OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 2, 2009

Epidemiology

10.2.1 Incidence of fractures compared to cardiovascular disease and breast cancer: The Women's Health Initiative observational study
Cauley JA, Wampler NS, Barnhart JM, Wu L, Allison M, Chen Z, Hendrix S, Robbins J, Jackson RD
Osteoporos Int 2008;19:1717-23

In 83,724 women, aged 70-79 the projected number of fractures was similar to or exceeded the combined number of cardiovascular events and breast cancers. Over an average of 7.7±2.6 years the annualized (%) incidence of fracture was greatest in whites (2.4%) and American Indians (2.8%) and lowest among blacks (1.3%). The majority of hip fractures occurred in white women. In 10,000 black women, an estimated 153 women would experience CVD, and 35 women, breast cancer compared to 126 women expected to fracture in one year.

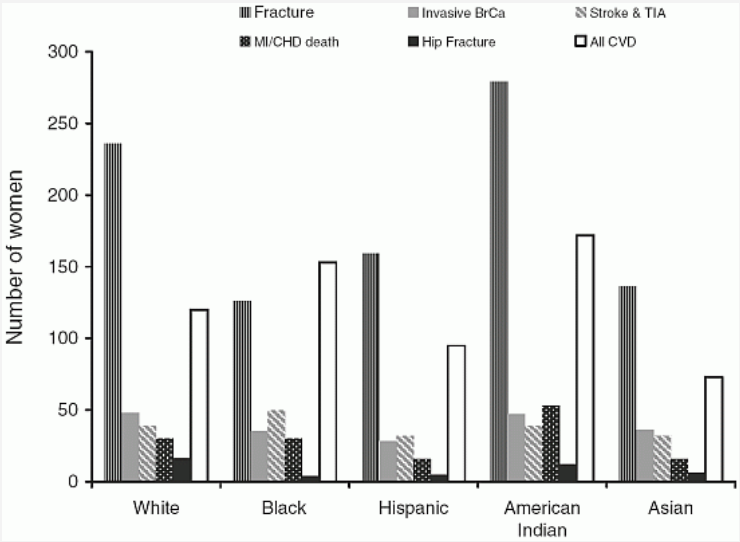

Fig. 10.2.1 The estimated number of cases that will occur in 10,000 women in one year: total fractures, hip fractures, invasive breast cancer, stroke and TIA, MI, CHD death and all CVD (including MI, CHD death, angina, CHF, DVT, coronary revascularization, TIA and stroke). Reproduced from Osteoporos Int 2008;19:1717-23 with permission from Springer.

10.2.2 Geographical variations in hip fracture risk for women: Strong effects hidden in standardised ratios
Barbier S, Ecochard R, Schott AM, Colin C, Delmas PD, Jaglal SB, Couris CM
Osteoporos Int 2009;20:371-7

The study population included women aged 50-85 who were living in France in 2004. Hip fracture cases were identified in the French Diagnosis Related Groups (DRG)-like database using the diagnosis code for closed hip fractures and procedural codes for treatment. The Moran index and a spatial model using latitude and longitude were used to assess the geographical heterogeneities of cumulative incidence risk (CIR) and age effect. A total of 29,218 hip fracture cases were identified. A south-to-north CIR gradient ranging from 7-16% was observed. The variation in the number of years until double hip fracture incidence was 75% (i.e., 1.49 to 2.57 years). In the south, and more markedly in southwest France, the women are at higher risk of hip fracture at a younger age. The risk of fracture may be different between women of the same age.

10.2.3 The prevalence of radiographic vertebral fractures in Latin American countries: The Latin American Vertebral Osteoporosis Study (LAVOS)
Clark P, Cons-Molina F, Deleze M, Ragi S, Haddock L, Zanchetta JR, Jaller JJ, Palermo L, Talavera JO, Messina DO, Morales-Torres J, Salmeron J, Navarrete A, Suarez E, Perez CM, Cummings SR
Osteoporos Int 2009;20:275-82

An age-stratified random sample of 1922 women aged 50 years and older from Argentina, Brazil, Colombia, Mexico, and Puerto Rico showed a standardized prevalence of 11.18 (95% CI 9.23-13.4) of fractures. The prevalence was similar in all five countries, increasing from 6.9% (95% CI 4.6-9.1) in women aged 50-59 years to 27.8% (95% CI 23.1-32.4) in those 80 years and older (p for trend <0.001). Among different risk factors, self-reported height loss OR=1.63 (95% CI 1.18-2.25), and previous history of fracture OR=1.52 (95% CI 1.14-2.03) were (p<0.003 and p<0.04, respectively) associated with radiographic vertebral fractures. In the bivariate analyses HRT was associated with a 35% lower risk OR=0.65 (95% CI 0.46-0.93) and physical activity with a 27% lower risk of having a vertebral fracture OR=0.73 (95% CI 0.55-0.98), but were not statistically significant in multivariate analyses.

10.2.4 A nationwide seven-year trend of hip fractures in the elderly population of Taiwan
Shao CJ, Hsieh YH, Tsai CH, Lai KA
Bone 2009;44:125-9

A total of 75,482 hip fractures occurred during the study period with an incidence rate of 57.54 per 10,000 per year. Overall incidence increased by 30% (p<0.0001), from 49.56 to 64.37 per 10,000 per year during 7 years. The increase in rates was greater in males (36%) than in females (22%). The average female-to-male ratio was 1.76, lower than those in many countries. In females,

the annual incidence of cervical fracture was higher than that of trochanteric fractures throughout the 7 years, while the incidence of trochanteric fractures was higher than cervical fractures each year in males (p<0.0001). The average annual incidence of patients older than 85 years was 9.9 times higher than that of aged 65-69 years in females and 7.9 times in males.

10.2.5 Declining incidence of low-trauma knee fractures in elderly women: Nationwide statistics in Finland between 1970 and 2006

Kannus P, Niemi S, Parkkari J, Sievanen H, Palvanen M
Osteoporos Int 2009;20:43-6

The number and incidence (per 100,000 persons) of low-trauma knee fractures among elderly people in Finland was assessed from 1970 to 2006. The number and incidence of low-trauma knee fractures among 60-year-old or older Finnish women sharply rose between 1970 and 1997, from 218 (number) and 55 (incidence) in 1970 to 733 and 124 in 1997. However, thereafter both the number and incidence of fractures declined so that there were only 626 fractures in these women in 2006 (incidence 94). In the age-adjusted fracture incidence, the findings were similar. During 1970-1997, the age-adjusted incidence of low-trauma knee fractures rose (from 60 to 118), but thereafter, this incidence declined to 85 in 2006. In men, the fracture incidence did not show consistent trend changes over time (30 in 1970 and 36 in 2006). The sharp rise in the incidence of low-trauma knee fractures in Finnish elderly women from early 1970s until late 1990s has been followed by a declining fracture rate.

10.2.6 Hip fractures cluster in space: An epidemiological analysis in Portugal

de Pina MF, Alves SM, Barbosa M, Barros H
Osteoporos Int 2008;19:1797-804

Of 25,634 hip fractures in individuals aged 50 years or more caused by low or moderate impact, 19,759 occurred in women (age, mean±SD, 80.6±8.6 years) and 5875 in men (age 77.7±10.0 years). Incidence rates increased exponentially with age, being higher in women nationwide (female to male ratio from 1.5 to 5.1). Significant geographic differences were found: the incidence rates (95% CI) varied from 154.4 (153.6-155.3) to 572.2 (569.5-575.0) in women and 77.3 (76.64-78.05) to 231.5 (229.9-233.0) in men per 100,000 inhabitants. Spatial autocorrelation values (Moran index) were 0.56 and 0.45 for women and men, respectively. Spatial clusters of high incidences were identified. Geographic differences in incidence rates were about 3-fold.

10.2.7 Reversal of the hip fracture secular trend is related to a decrease in the incidence in institution-dwelling elderly women

Guilley E, Chevalley T, Herrmann F, Baccino D, Hoffmeyer P, Rapin CH, Rizzoli R
Osteoporos Int 2008;19:1741-7

All hip fracture patients aged 60 years and over were identified in a well defined area. Incidence of hip fracture, age- and sex-adjusted to the 2000 Geneva population, was computed in community- and institution-dwelling elderly. From 1991 to 2000, 1624 (41%) hip fractures were recorded in institutionalized-dwelling elderly and 2327 (59%) in community-dwelling elderly. The standardized fracture incidence decreased by 1.3% per year in women (p=0.039), but remained unchanged in men (+0.5%; p=0.686). Among institution-dwelling women, hip fracture incidence fell by 1.9% per year (p=0.044), whereas it remained stable among community-dwelling women (+0.0%, p=0.978). In men, no significant change in hip fracture incidence occurred among institution- or community-dwelling elderly. The decrease in the standardized hip fracture incidence in institution-dwelling women is responsible for the reversal in secular trend.

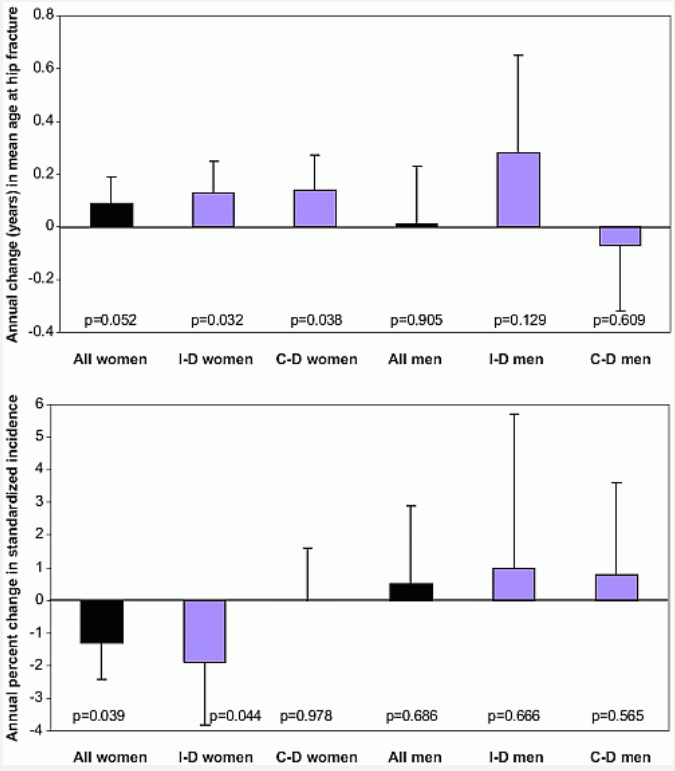

Fig. 10.2.7 Estimated annual change (years) in mean age at hip fracture (upper part) and annual percentage change in standardized incidence of hip fracture (bottom part) over a 10-year period (1991-2000), according to gender and place of residence (institution-dwelling [I-D] and community [C-D]). The shaded bars represent the estimated annual changes and the thin bars their 95% CI (the symmetric 95% CI being omitted). Reproduced from Osteoporos Int 2008;19:1741-7 with permission from Springer.

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Morbidity/Mortality

10.2.8 Relationship between bone quantitative ultrasound and mortality: A prospective study
Gonzalez-Macias J, Marin F, Vila J, Carrasco E, Benavides P, Castell MV, Magana JE, Chavida F, Diez-Perez A
Osteoporos Int 2009;20:257-64

5201 women (72.3±5.3 years) were studied. 100 (1.9%) women died during a median of 36.1 months follow-up, for a total of 14,999 patient-years, 42 because of vascular events (both cardiovascular and cerebrovascular). After adjusting for age, none of the QUS variables showed significant differences between the patients who died and the survivors. In the final multivariate model, SOS was marginally nonsignificant: (HR: 1.19; 0.97-1.45). However, each 1 SD reduction in SOS was associated with a 39% increase in vascular mortality (HR: 1.39; 1.15-1.66).

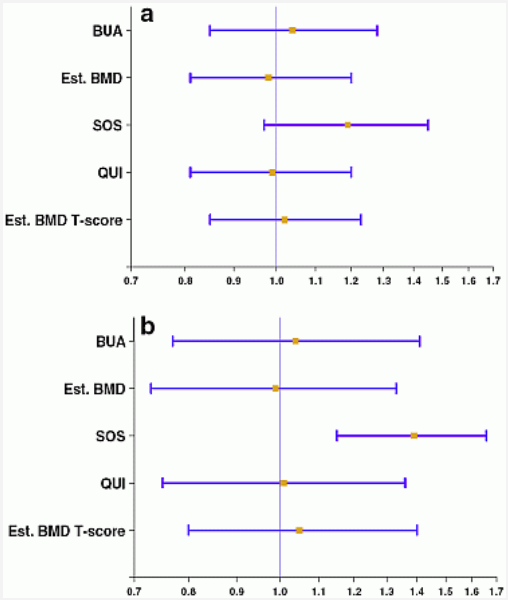

Fig. 10.2.8 Adjusted hazard rates for a) overall, and b) vascular mortality per 1 SD decrease in heel QUS variables. *adjusted for age, thyroxine and hypoglycemic drug treatment, history of chronic obstructive pulmonary disease/asthma, and decreased visual acuity. BMD: bone mineral density; BUA: broadband ultrasound attenuation; SOS: speed of sound; QUI: quantitative ultrasound index (stiffness index). Reproduced from Osteoporos Int 2009;20:257-64 with permission from Springer.*

10.2.9 Relative survival after hospitalisation for hip fracture in older people in New South Wales, Australia
Hindmarsh DM, Hayen A, Finch CF, Close JC
Osteoporos Int 2009;20:221-9

A total of 16,836 cases of hip fracture were assessed. Relative survival 3-36 months postadmission by 10-year age groups and sex was calculated, using NSW life tables for 2002-2004. Relative excess risk was modelled using a generalised linear model with Poisson error structure, using the life table data. One-year cumulative relative survival in 65- to 74-year-olds was 82% (men), 90% (women); in 85+-year-olds 65% (men), 80% (women). Men have a relative excess risk of death of 2.2 (95% CI 2.03-2.38) times that of women. Only 21% of deaths mention the hip fracture as contributing to death.

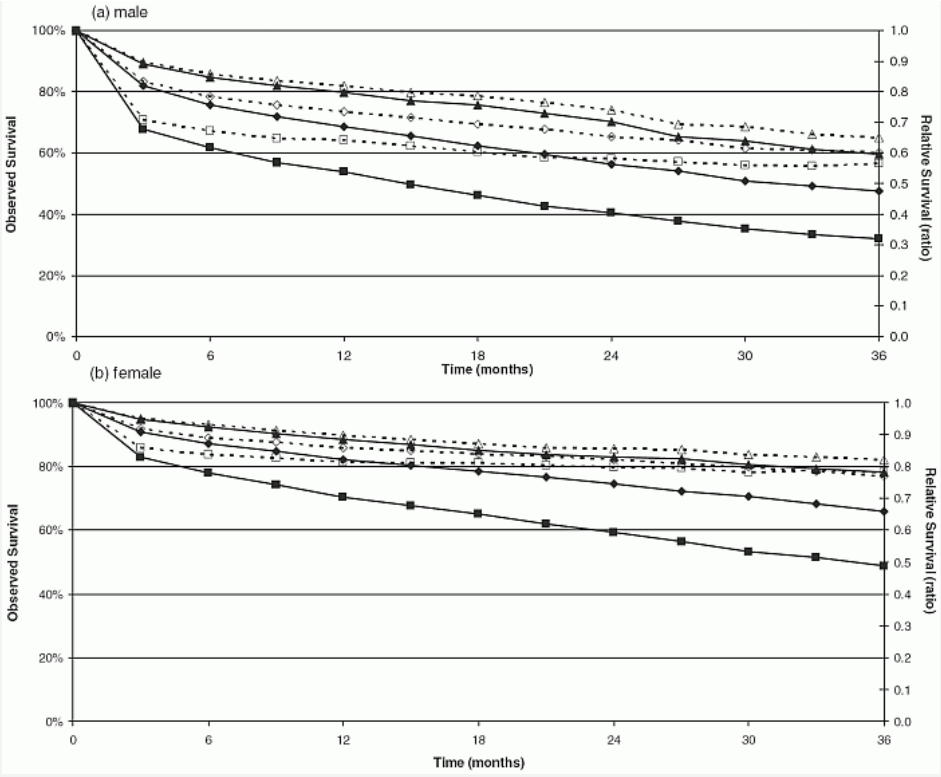

Fig. 10.2.9a Cumulative observed and cumulative relative survival after hospitalisation for fall-related hip fracture by age for a men and b women, NSW, July 2000-December 2003. Reproduced from Osteoporos Int 2009;20:221-9 with permission from Springer.

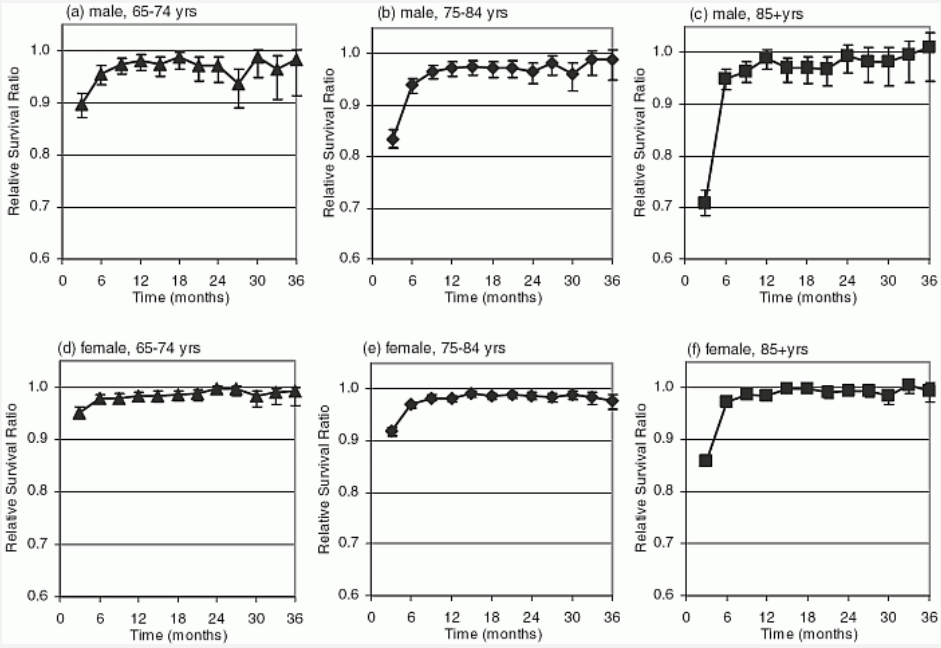

Fig. 10.2.9b Interval-specific relative survival after hospitalisation for fall-related hip fracture, by sex and age group, NSW, July 2000-December 2003. Reproduced from Osteoporos Int 2009;20:221-9 with permission from Springer.

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Genetics

10.2.10 The Val432Leu polymorphism of the CYP1B1 gene is associated with differences in estrogen metabolism and bone density

Napoli N, Rini GB, Serber D, Giri T, Yarramaneni J, Bucchieri S, Camarda L, Di Fede G, Camarda MR, Jain S, Mumm S, Armamento-Villareal R

Bone 2009;44:442-8

Polymorphisms of the CYP450 genes that encode for the enzymes that metabolize estrogen are linked to hormone-related cancers. 468 postmenopausal Caucasian women, 220 from St. Louis, MO, USA (mean age = 63.5±0.53 years) and 248 from Palermo, Italy (mean age = 72.9±0.44 years) participated. Analysis among the Americans for the Valine432Leucine polymorphism showed that, compared to women with the Val/Val genotype, women with the Leu allele (Val/Leu and Leu/Leu) had higher log-transformed values of total urinary estrogen metabolite (ng/mg-creatinine) levels (1.23±0.04, 1.35±0.02, and 1.34 ±0.03; p=0.03), and lower BMD (gm/cm^2) in the lumbar spine (1.009±0.02, 0.955±0.01 and 0.931±0.02; p=0.03) and the femoral neck (0.748±0.02, 0.717±0.01 and 0.693±001, p=0.03) for the Val/Val, Val/Leu and Leu/Leu genotypes, respectively. There were no differences in the urinary metabolites and BMD in the genotypes for the Alanine119Serine polymorphism among the American women. Among the Italian women, no differences in BMD in the different genotypes for the two polymorphisms was observed. In conclusion, women with the Leu allele for the CYP1B1 Val432 polymorphism have increased estrogen catabolism, as indicated by higher urinary estrogen metabolites, compared to those with Val/Val genotype. This may lead to relative hypoestrogenism and lower BMD in the lumbar spine and femoral neck in these women. The Val432Leu polymorphism of the CYP1B1 gene may represent as a possible genetic risk factor for osteoporosis in American women.

10.2.11 Genetic influences on bone loss in the San Antonio Family Osteoporosis study

Shaffer JR, Kammerer CM, Bruder JM, Cole SA, Dyer TD, Almasy L, MacCluer JW, Blangero J, Bauer RL, Mitchell BD

Osteoporos Int 2008;19:1759-67

The 5-year change in BMD in 300 Mexican Americans (>45 years of age) from the San Antonio Family Osteoporosis Study and autosome-wide linkage analysis was carried out using 460 microsatellite markers at a mean 7.6 cM interval density. Rate of BMD change was heritable at the forearm (h(2)=0.31, p=0.021), hip (h(2)=0.44, p=0.017), spine (h(2)=0.42, p=0.005), but not whole body (h(2)=0.18, p=0.123). Covariates associated with rapid bone loss (advanced age, baseline BMD, female sex, low baseline weight, postmenopausal status, and interim weight loss) accounted for 10% to 28% of trait variation. No evidence of linkage was observed at any skeletal site.

10.2.12 Muscle cross-sectional area and structural bone strength share genetic and environmental effects in older women

Mikkola TM, SipilÃ¤ S, Rantanen T, SievÃ¤nen H, Suominen H, Tiainen K, Kaprio J, Koskenvuo M, Kauppinen M, Heinonen A

J Bone Miner Res 2009;24:338-45

pQCT from 102 monozygotic (MZ) and 113 dizygotic (DZ) 63- to 76-year-old female twin pairs to estimate the mCSA of the lower leg, structural bending strength of the tibial shaft (BSIbend), and compressive strength of the distal tibia (BSIcomp). Phenotypic variances were divided into common and trait-specific additive genetic (A), shared environmental (C), and individual environmental (E) effects. The age-adjusted trivariate independent pathway model showed that the total relative contributions of A, C, and E were, respectively, 75%, 0%, and 25% for mCSA, 55%, 20%, and 25% for BSIbend, and 40%, 37%, and 23% for BSIcomp. BSIbend and BSIcomp had shared environmental factors and were also influenced by trait-specific genetic factors.

10.2.13 Characterization of the bone phenotype in ClC-7-deficient mice

Neutzsky-Wulff AV, Karsdal MA, Henriksen K

Calcif Tissue Int 2008;83:425-37

Mice deficient in the chloride channel ClC-7, which is likely involved in acidification of the resorption lacuna, display osteopetrosis. Splenocytes were differentiated into osteoclasts using M-CSF and RANKL. Mature osteoclasts were seeded on calcified or decalcified bone slices, and CTX-I, Ca(2+), and TRAP were measured. ClC-7(-/-) osteoclasts were unable to resorb calcified bone in vitro. However, osteoclasts were able to degrade decalcified bone. Acid influx in bone membrane vesicles was reduced by 70% in ClC-7(-/-) mice. Serum ALP was increased by 30% and TRAP5b was increased by 250% in ClC-7(-/-) mice, whereas the CTX/TRAP5b ratio was reduced to 50% of the wildtype level. Calvarial ClC-7(-/-) osteoblasts showed normal osteoblastogenesis. In summary, we present evidence supporting a pivotal role for ClC-7 in acidification of the resorption lacuna and evidence indicating that bone formation and bone resorption are no longer balanced in ClC-7(-/-) mice.

10.2.14 Cellular mechanism of decreased bone in Brtl mouse model of OI: Imbalance of decreased osteoblast function and increased osteoclasts and their precursors

Uveges TE, Collin-Osdoby P, Cabral WA, Ledgard F, Goldberg L, Bergwitz C, Forlino A, Osdoby P, Gronowicz GA, Marini JC

J Bone Miner Res 2008;23:1983-94

The Brtl mouse, a knock-in for osteogenesis imperfecta (OI), has a G349C substitution in half of type I collagen α1(I) chains. Cortical and trabecular bone are reduced before and after puberty, with BV/TV decreased 40-45%. Brtl ObS/BS is comparable to wildtype, and Brtl and wildtype marrow generate equivalent colony forming units (CFUs). OcS/BS is increased in Brtl (36-45%), as are TRACP(+) cell numbers (57-47%). After puberty, Brtl ObS/BS decreases comparably to wildtype mice, but osteoblast matrix production (MAR) decreases to one half of wildtype values. In contrast, Brtl OcS falls moderately (16%), and Brtl TRACP staining remains elevated compared with wildtype. Consequently, Brtl BFR decreased from normal at 2 mo to one half of wildtype values at 6 mo. Increased RANK, RANKL, and osteoprotegerin (OPG) levels in Brtl is found, although RANKL/OPG ratio is normal. TRACP(+) precursors are elevated in Brtl marrow cultures and form more osteoclasts, suggesting that osteoclast increases arise from more RANK-expressing precursors. Osteoblasts and osteoclasts are unsynchronized in Brtl bone with declining BFR as Brtl ages, consistent with reduced femoral geometry. The disparity in cellular number and function results from

poorly functioning osteoblasts in addition to increased RANK-expressing precursors that respond to normal RANKL/OPG ratios to generate more bone resorbing osteoclasts.

10.2.15 An integrative genetics approach to identify candidate genes regulating BMD: Combining linkage, gene expression, and association
Farber CR, van Nas A, Ghazalpour A, Aten JE, Doss S, Sos B, Schadt EE, Ingram-Drake L, Davis RC, Horvath S, Smith DJ, Drake TA, Lusis AJ
J Bone Miner Res 2009;24:105-16

10.2.16 Gene expression profile of the bone microenvironment in human fragility fracture bone
Hopwood B, Tsykin A, Findlay DM, Fazzalari NL
Bone 2009;44:87-101

10.2.17 Replication of associations between LRP5 and ESRRA variants and bone density in premenopausal women
Giroux S, Elfassihi L, Cole DE, Rousseau F
Osteoporos Int 2008;19:1769-75

10.2.18 CLCN7 polymorphisms and bone mineral density in healthy premenopausal white women and in white men
Chu K, Koller DL, Ichikawa S, Snyder R, Curry L, Lai D, Austin A, Xuei X, Edenberg HJ, Hui SL, Foroud TM, Peacock M, Econs MJ
Bone 2008;43:995-8

10.2.19 Association of adenylate cyclase 10 (ADCY10) polymorphisms and bone mineral density in healthy adults
Ichikawa S, Koller DL, Curry LR, Lai D, Xuei X, Edenberg HJ, Hui SL, Peacock M, Foroud T, Econs MJ
Calcif Tissue Int 2009;84:97-102

10.2.20 High resolution linkage and linkage disequilibrium analyses of chromosome 1p36 SNPs identify new positional candidate genes for low bone mineral density
Zhang H, Sol-Church K, Rydbeck H, Stabley D, Spotila LD, Devoto M
Osteoporos Int 2009;20:341-6

10.2.21 Haplotypes of promoter and intron 1 polymorphisms in the COLIA1 gene are associated with increased risk of osteoporosis
Husted LB, Harslof T, Gonzalez-Bofill N, Schmitz A, Carstens M, Stenkjaer L, Langdahl BL
Calcif Tissue Int 2009;84:85-96

10.2.22 A haplotype-based analysis of the LRP5 gene in relation to osteoporosis phenotypes in Spanish postmenopausal women
Agueda L, Bustamante M, Jurado S, Garcia-Giralt N, Ciria M, Salo G, Carreras R, Nogues X, Mellibovsky L, Diez-Perez A, Grinberg D, Balcells S
J Bone Miner Res 2008;23:1954-63

10.2.23 Quantitative trait locus on chromosome 1q influences bone loss in young Mexican American adults
Shaffer JR, Kammerer CM, Bruder JM, Cole SA, Dyer TD, Almasy L, Maccluer JW, Blangero J, Bauer RL, Mitchell BD
Calcif Tissue Int 2009;84:75-84

10.2.24 Bone turnover and type I collagen C-telopeptide isomerization in adult osteogenesis imperfecta: Associations with collagen gene mutations
Garnero P, Schott AM, Prockop D, Chevrel G
Bone 2009;44:461-6

10.2.25 Characterization of a novel Alu-Alu recombination-mediated genomic deletion in the TCIRG1 gene in five osteopetrotic patients
Pangrazio A, Caldana ME, Sobacchi C, Panaroni C, Susani L, Mihci E, Cavaliere ML, Giliani S, Villa A, Frattini A
J Bone Miner Res 2009;24:162-7

10.2.26 Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with spinal BMD in 9-year-old children
Steer CD, Emmett PM, Lewis SJ, Smith GD, Tobias JH
J Bone Miner Res 2009;24:117-24

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Measurement of Bone Mass

10.2.27 Role of quantitative ultrasound to predict fracture among institutionalised older people with a history of fracture
Chen JS, March LM, Cumming RG, Cameron ID, Simpson JM, Lord SR, Sambrook PN
Osteoporos Int 2009;20:105-12

In 1982 institutionalised older people (mean age = 85.7±7.1 years) 45% reported a history of fracture. During a mean follow-up period of 1.64 years, 335 participants suffered a fracture or fractures. Fracture rates were higher in participants with a history of fracture compared with those without a history of fracture (16.0 vs. 9.2 per 100 person years, $p<0.001$). Significant associations between fracture risk and QUS parameters (broadband ultrasound attenuation and velocity of sound) were observed among participants without a history of fracture (both $p<0.01$), but not among those who had a fracture history (both $p\geq0.7$). In very frail older people, QUS measurements may be more useful for assessing fracture risk in those without a history of fracture after age 50.

10.2.28 Effect of increasing vertebral marrow fat content on BMD measurement, T-Score status and fracture risk prediction by DXA
Blake GM, Griffith JF, Yeung DK, Leung PC, Fogelman I
Bone 2009;44:495-501

185 Hong Kong Chinese (103 women, mean age 73 y; 82 men, mean age 73 y) had spine DXA scans and (1)H-MRS measurements of L3 marrow fat. The effect of varying marrow fat on BMD was modelled using vertebral body thicknesses measured in 50 men and women. A change in marrow fat from 0 to 100% produced a BMD decrease of 0.14 g/cm^2 (1.3 T-score units) in women and 0.16 g/cm^2 (1.3 T-score units) in men. Adjusting spine BMD for fat reduced the correlation, there was still a trend for marrow fat to increase with decreasing T-score with a slope of -1.2±0.7% per T-score unit ($p=0.078$) for women and -1.4±0.6% per T-score unit ($p=0.023$) for men. When the effect of marrow composition on fracture discrimination was evaluated the results showed that the higher vertebral marrow fat content found in osteoporotic subjects made a negligible contribution to the ability of spine BMD measurements to predict fracture risk.

10.2.29 Non-invasive bone competence analysis by high-resolution pQCT: An in vitro reproducibility study on structural and mechanical properties at the human radius
Mueller TL, Stauber M, Kohler T, Eckstein F, Muller R, van Lenthe GH
Bone 2009;44:364-71

Mechanical competence can be derived from HR-pQCT based microfinite element modelling (μFE). In 14 distal formalin-fixed cadaveric forearms reproducibility was best in all three regions for the full bone compartment with an average PE of 0.79%, followed by the cortical compartment (PE=1.19%) and the trabecular compartment with an average PE of 2.31%. The mechanical parameters showed similar reproducibility (PE=0.48%-2.93% for bone strength and stiffness, respectively).

10.2.30 Subpixel enhancement of nonuniform tissue (SPENT): A novel MRI technique for quantifying BMD
Yiannakas MC, Carmichael DW, Farquharson MJ, Ordidge RJ
J Bone Miner Res 2009;24:324-33

10.2.31 Generation of a 3D proximal femur shape from a single projection 2D radiographic image
Langton CM, Pisharody S, Keyak JH
Osteoporos Int 2009;20:455-61

10.2.32 Using radon transform of standard radiographs of the hip to differentiate between postmenopausal women with and without fracture of the proximal femur
Boehm HF, Lutz J, Korner M, Mutschler W, Reiser M, Pfeifer KJ
Osteoporos Int 2009;20:323-33

10.2.33 Specimen size and porosity can introduce error into microCT-based tissue mineral density measurements
Fajardo RJ, Cory E, Patel ND, Nazarian A, Laib A, Manoharan RK, Schmitz JE, Desilva JM, Maclatchy LM, Snyder BD, Bouxsein ML
Bone 2009;44:176-84

10.2.34 High resolution computed tomography of the vertebrae yields accurate information on trabecular distances if processed by 3D fuzzy segmentation approaches
Krebs A, Graeff C, Frieling I, Kurz B, Timm W, Engelke K, Gluer CC
Bone 2009;44:145-52

10.2.35 Feasibility of measuring trabecular bone structure of the proximal femur using 64-slice multidetector computed tomography in a clinical setting
Diederichs G, Link T, Marie K, Huber M, Rogalla P, Burghardt A, Majumdar S, Issever A
Calcif Tissue Int 2008;83:332-41

10.2.36 Shortcomings of DXA to assess changes in bone tissue density and microstructure induced by metabolic bone diseases in rat models

Nazarian A, Cory E, Muller R, Snyder BD

Osteoporos Int 2009;20:123-32

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Bone Material

10.2.37 Fourier transform infrared imaging microspectroscopy and tissue-level mechanical testing reveal intraspecies variation in mouse bone mineral and matrix composition
Courtland HW, Nasser P, Goldstone AB, Spevak L, Boskey AL, Jepsen KJ
Calcif Tissue Int 2008;83:342-53

16-week-old female A/J, C57BL/6J (B6), and C3H/HeJ (C3H) inbred mouse femora were analyzed using Fourier transform infrared imaging and tissue-level mechanical testing for variation in mineral composition, mineral maturity, collagen crosslink ratio, and tissue-level mechanical properties. A/J femora had an increased mineral-to-matrix ratio compared to B6. The C3H mineral-to-matrix ratio was intermediate of A/J and B6. C3H femora had reduced acid phosphate and carbonate levels and an increased collagen crosslink ratio compared to A/J and B6. Modulus values paralleled mineral-to-matrix values, with A/J femora being the most stiff, B6 being the least stiff, and C3H having intermediate stiffness. In addition, work-to-failure varied among the strains, with the highly mineralized and brittle A/J femora performing the least amount of work-to-failure. These results suggest that specific combinations of bone quality and morphological traits are genetically regulated such that mechanically functional bones can be constructed in different ways.

10.2.38 Changes in subchondral bone mineral density and collagen matrix organization in growing horses
Holopainen JT, Brama PA, Halmesmaki E, Harjula T, Tuukkanen J, van Weeren PR, Helminen HJ, Hyttinen MM
Bone 2008;43:1108-14

10.2.39 Correlation of quantitative computed tomographic subchondral bone density and ash density in horses
Drum MG, Les CM, Park RD, Norrdin RW, McIlwraith CW, Kawcak CE
Bone 2009;44:316-9

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Bone Structure

10.2.40 Site-specific deterioration of trabecular bone architecture in men and women with advancing age

Lochmuller EM, Matsuura M, Bauer J, Hitzl W, Link TM, Muller R, Eckstein F

J Bone Miner Res 2008;23:1964-73

Microstructural properties of trabecular bone were measured in vitro in 75 men and 75 age-matched women (age, 52-99 yr) using µCT. Trabecular bone samples were scanned at a 26 µm isotropic resolution at the distal radius, T10 and L2 vertebrae, iliac crest, femoral neck and trochanter, and calcaneus. DXA measurements were obtained at the distal radius and proximal femur and QCT was used at T12. No significant decrease in bone density or structure with age was found in men using µCT, DXA, or QCT at any of the anatomical sites. In women, an age-dependent decrease in BV/TV was observed at most sites, which was strongest at the iliac crest and weakest at the distal radius. The reduction in BV/TV was associated with an increase in structure model index, decrease in Tb.N, and an increase in Tb.Sp. Only in the calcaneus was it associated with a significant decrease in Tb.Th.

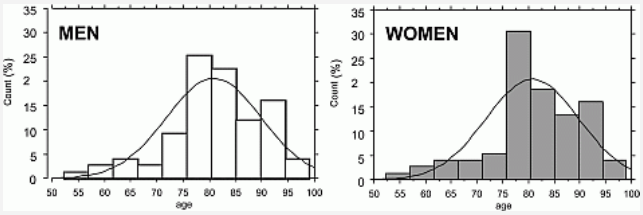

Fig. 10.2.40a Age distribution of the 150 subjects studied (75 men vs. 75 age-matched women). Reproduced from J Bone Miner Res 2008;23:1964-73 with permission of the American Society of Bone and Mineral Research.

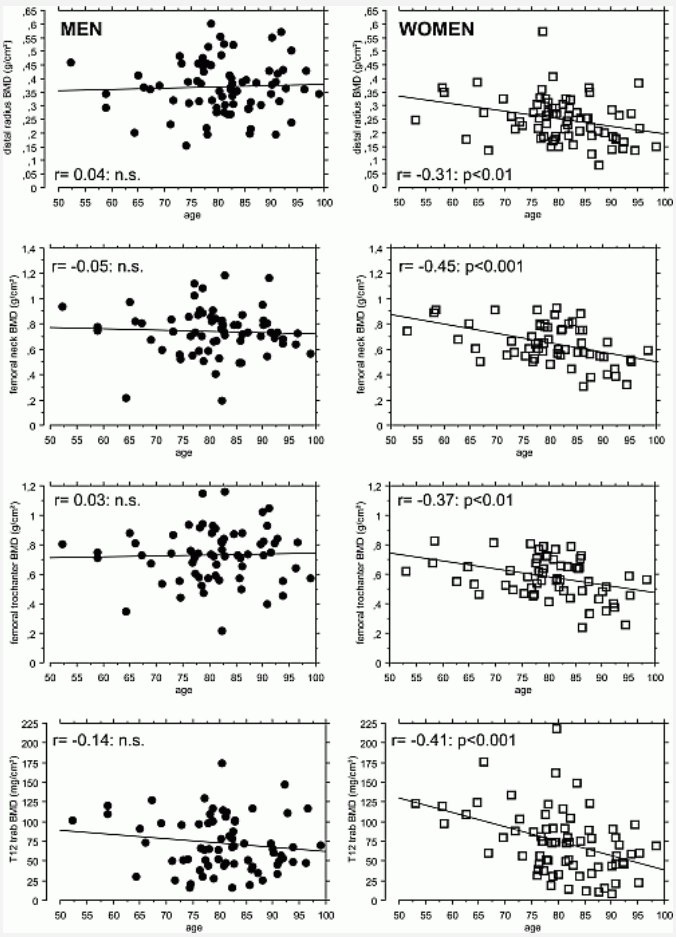

Fig. 10.2.40b Regression plots showing age-related changes in men (left column) and in women (right column) for pDXA at the forearm, DXA at the proximal femur, and for QCT at the T12 vertebra. n.s., not statistically significant at p<0.05. Reproduced from J Bone Miner Res 2008;23:1964-73 with permission of the American Society of Bone and Mineral Research.

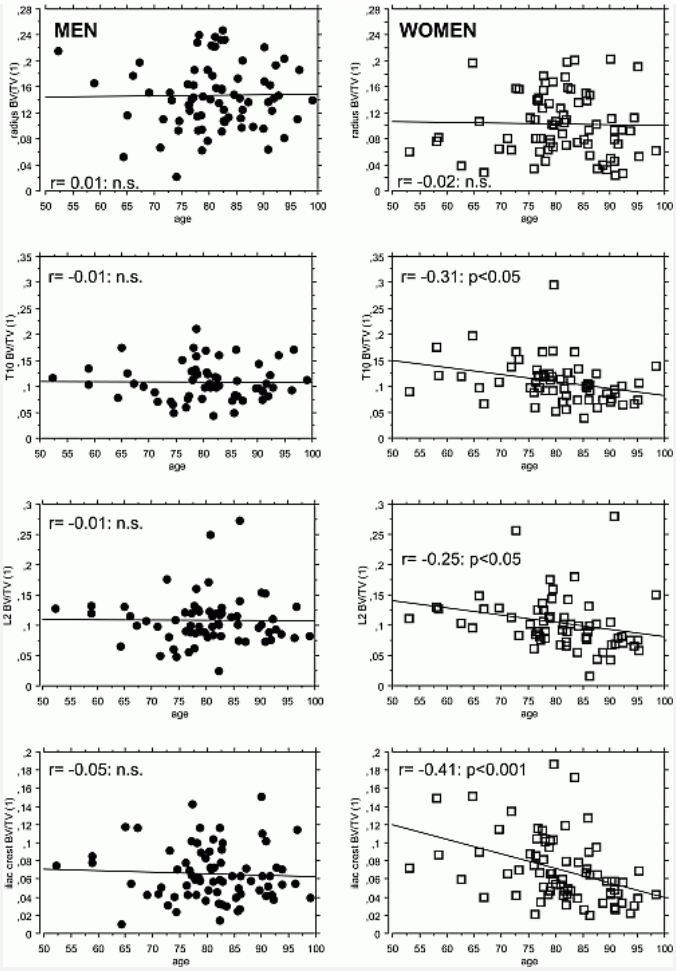

Fig. 10.2.40c Regression plots showing age-related changes in men (left column) and in women (right column) for µCT analysis of trabecular bone microstructure at the distal radius, T10 and L2 vertebrae, and the iliac crest. n.s., not statistically significant at p<0.05. Reproduced from J Bone Miner Res 2008;23:1964-73 with permission of the American Society of Bone and Mineral Research.

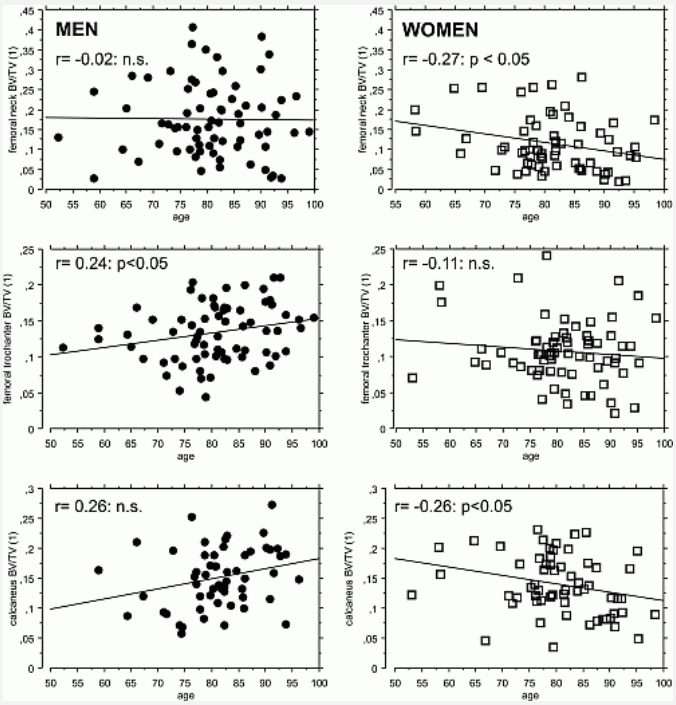

Fig. 10.2.40d Regression plots showing age-related changes in men (left column) and in women (right column) for µCT analysis of trabecular bone microstructure at the femoral neck, femoral trochanter, and the calcaneus. n.s., not statistically significant at p<0.05. Reproduced from J Bone Miner Res 2008;23:1964-73 with permission of the American Society of Bone and Mineral Research.

10.2.41 Cortical and trabecular bone in the femoral neck both contribute to proximal femur failure load prediction
Manske SL, Liu-Ambrose T, Cooper DM, Kontulainen S, Guy P, Forster BB, McKay HA
Osteoporos Int 2009;20:445-53

In 36 human cadaveric proximal femora imaged using QCT, trabecular BMD explained a significant proportion of variance in failure load after accounting for ToA and then either CoBMC or CoA, respectively. CoBMC contributed to failure load in all regions of the femoral neck except the posterior region. TbBMD contributed to failure load in all regions of the femoral neck except

the inferoanterior, superoposterior, and the posterior regions. Both cortical and trabecular bone make significant contributions to failure load in ex vivo measures of bone strength.

10.2.42 Vertebral fractures usually affect the cranial endplate because it is thinner and supported by less dense trabecular bone

Zhao FD, Pollintine P, Hole BD, Adams MA, Dolan P

Bone 2009;44:372-9

62 "motion segments" were obtained postmortem from 35 human spines (17F/18M, age 48-92 years, all spinal levels from T8-9 to L4-5). Fracture affected the cranial endplate in 55/62 specimens. Cranial endplates were thinner than caudal (p=0.003) by 14% and 11% on average in midsagittal and pedicle slices, respectively. Caudal but not cranial endplates were thicker at lower spinal levels (p=0.01). Optical density of trabecular bone adjacent to the endplates was 6% lower cranially than caudally (p=0.004), and the average optical density of trabecular bone in midsagittal slices was 10% lower in women than in men (p=0.025). Vertebral yield stress (mean 2.22 MPa, SD 0.77 MPa) was best predicted by the density of trabecular bone underlying the cranial endplate of the midsagittal slice of the fractured vertebra (r^2=0.67, p=0.0006). When vertebrae are compressed naturally by adjacent intervertebral discs, cranial endplates usually fail before caudal endplates because they are thinner and supported by less dense trabecular bone.

10.2.43 Postpubertal architectural developmental patterns differ between the L3 vertebra and proximal tibia in three inbred strains of mice

Buie HR, Moore CP, Boyd SK

J Bone Miner Res 2008;23:2048-59

In vivo µCT from 6-48 wk of age at the vertebra and tibia of C3H/HeN, C57BL/6, and BALB/C mice showed rapid longitudinal growth until 8-10 wk, slowing and fused at 8-10 mo. In the vertebrae, BV/TV increased until 12 wk. Between 12 and 32 wk, the architecture was stable but the tibial architecture changed continuously but more moderately for BV/TV and TbTh compared with the vertebra and with comparable or larger changes for TbN and TbSp. Age-related trabecular deterioration (decreased BV/TV and TbN; increased TbSp and structure model index) was evident at both sites at 32 wk. In all strains, the cortex continued to develop after trabecular values peaked. Geometric changes at the tibial diaphysis occurred rapidly until 8-10 wk, providing the C57BL/6 mice and C3H/HeN mice with the highest torsional and compressive rigidity, respectively.

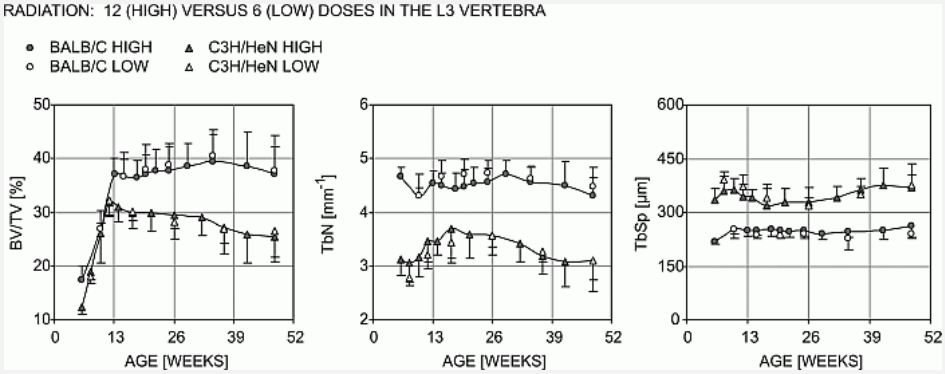

Fig. 10.2.43a Representative lack of variation in architecture between the high- and low-frequency scanning groups. Error bars represent SD. Reproduced from J Bone Miner Res 2008;23:2048-59 with permission of the American Society of Bone and Mineral Research.

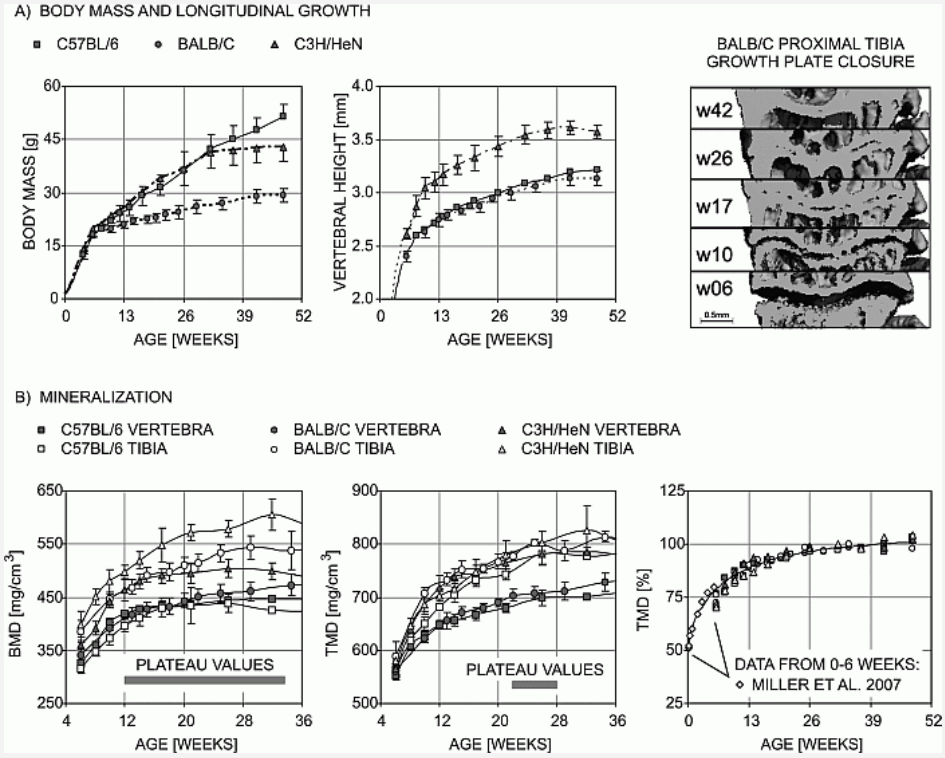

Fig. 10.2.43b (A) Temporal changes in body mass and vertebral body height along with images showing progressive bridging of

the tibial growth plate. (B) Mineralization data for all strains and sites as assessed by BMD and TMD. Data are included from Miller et al. (J Bone Miner Res 2007;22:1037) Error bars represent SD. Reproduced from J Bone Miner Res 2008;23:2048-59 with permission of the American Society of Bone and Mineral Research.

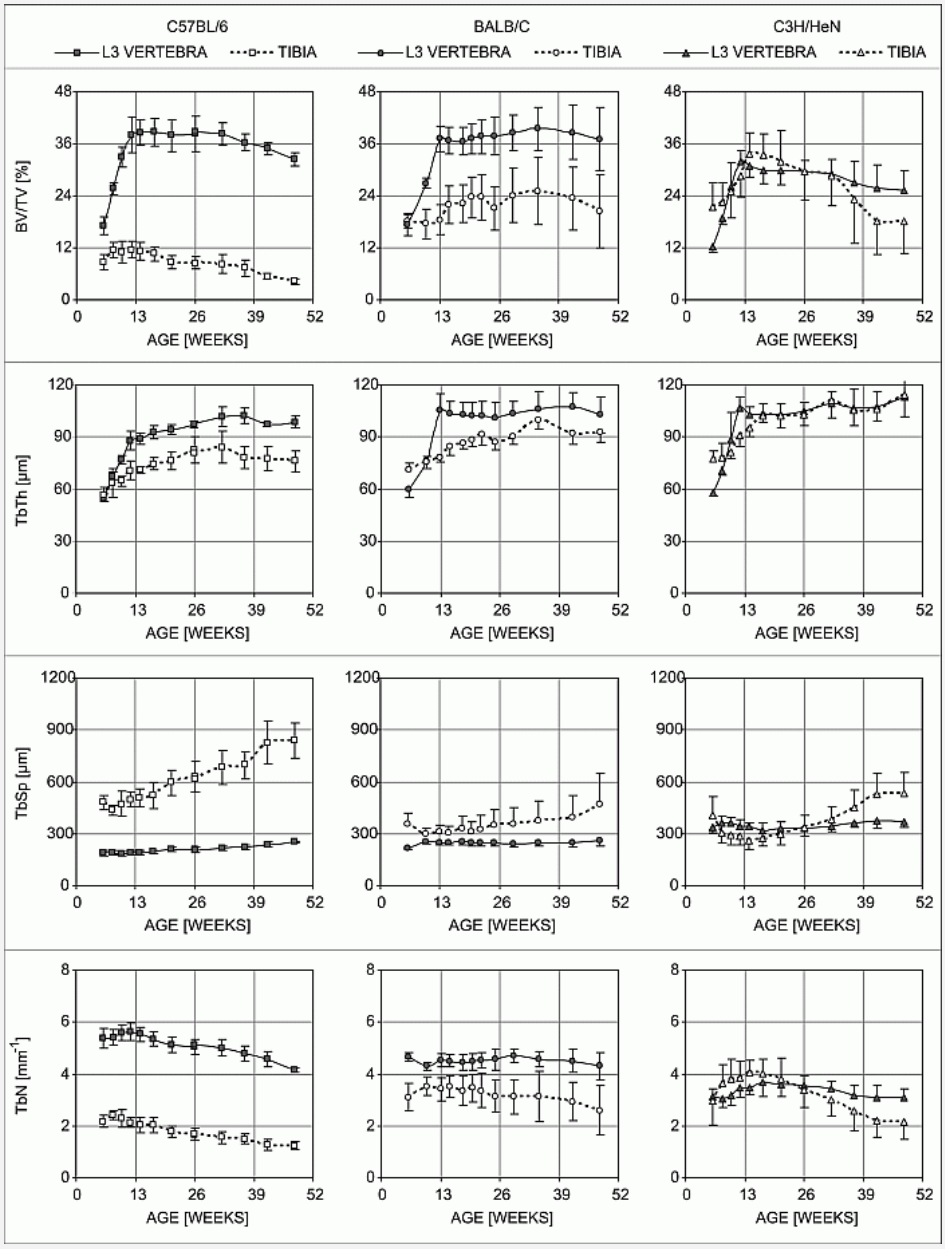

Fig. 10.2.43c Temporal changes in commonly reported architecture parameters in the high-frequency scanning group for the C57BL/6 (left column), BALB/C (center column), and C3H/HeN (right column) mice for the vertebra (solid data points) and the proximal tibial metaphysis (open data points). For the tibia, the average is reported for the left and right limbs. Because of animal euthanasia, the C57BL/6 groups were combined at 32 wk. Error bars represent SD. Reproduced from J Bone Miner Res 2008;23:2048-59 with permission of the American Society of Bone and Mineral Research.

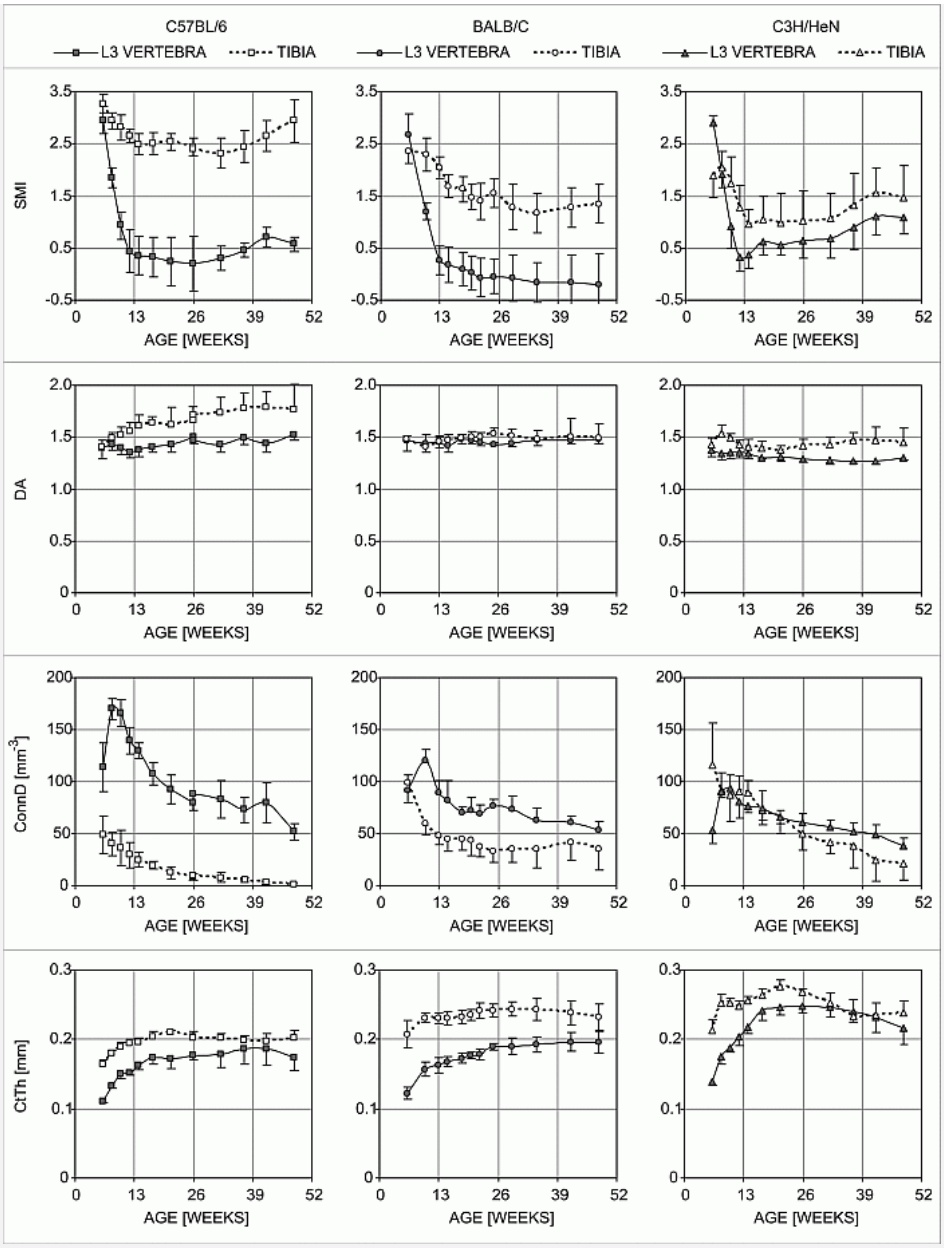

Fig. 10.2.43d Temporal changes in less commonly reported architecture parameters in the high-frequency scanning group for the C57BL/6 (left column), BALB/C (center column), and C3H/HeN (right column) mice for the vertebra (solid data points) and the proximal tibial metaphysis (open data points). For the tibia, the average is reported for the left and right limbs. Because of animal euthanasia, the C57BL/6 groups were combined at 32 wk. Error bars represent SD. Reproduced from J Bone Miner Res 2008;23:2048-59 with permission of the American Society of Bone and Mineral Research.

10.2.44 Effect of temporal changes in bone turnover on the bone mineralization density distribution: A computer simulation study
Ruffoni D, Fratzl P, Roschger P, Phipps R, Klaushofer K, Weinkamer R
J Bone Miner Res 2008;23:1905-14

10.2.45 Predicting regional variations in trabecular bone mechanical properties within the human proximal tibia using MR imaging
Lancianese SL, Kwok E, Beck CA, Lerner AL
Bone 2008;43:1039-46

10.2.46 Interpreting cortical bone adaptation and load history by quantifying osteon morphotypes in circularly polarized light images
Skedros JG, Mendenhall SD, Kiser CJ, Winet H
Bone 2009;44:392-403

10.2.47 Bone volume fraction explains the variation in strength and stiffness of cancellous bone affected by metastatic cancer and osteoporosis
Nazarian A, von Stechow D, Zurakowski D, Muller R, Snyder BD
Calcif Tissue Int 2008;83:368-79

10.2.48 Comparison of quantitative cancellous bone connectivity analyses at two- and three-dimensional levels in dialysis patients

Kazama JJ, Koda R, Yamamoto S, Narita I, Gejyo F, Tokumoto A
Calcif Tissue Int 2009;84:38-44

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editor E. Seeman

Volume 10, Issue 2, 2009

Biomechanics

10.2.49 Human cancellous bone from T12-L1 vertebrae has unique microstructural and trabecular shear stress properties
Yeni YN, Kim DG, Divine GW, Johnson EM, Cody DD
Bone 2009;44:130-6

Thoracic vertebrae from 10 human cadaver spines were examined. μCT-based large-scale finite element models were constructed and compression in the long axis of the cylindrical specimens was simulated. The maximum of trabecular shear stress amplification and minimum of bone volume fraction were found in the cancellous tissue from T12-L1. Microstructure and trabecular stresses varied with spine level, extreme being at the T12-L1 levels, for the TR specimens only. SI/TR ratio of measured parameters also had quadratic relationships with spine level, the extreme being located at T12-L1 levels for most parameters. For microstructural parameters, these ratios approached a value of one at the T12-L1 level, suggesting that T12-L1 vertebrae have most uniform cancellous properties. The mean intercept length in the secondary principal direction of trabecular orientation could account for the variation of all mechanical parameters with spine level. Cancellous tissue from T12-L1 levels is unique and may explain, in part, the higher incidence of vertebral fractures at these levels.

10.2.50 Effects of suppression of bone turnover on cortical and trabecular load sharing in the canine vertebral body
Eswaran SK, Bevill G, Nagarathnam P, Allen MR, Burr DB, Keaveny TM
J Biomech 2009;[Epub ahead of print]

T10 vertebral bodies of mature female beagle dogs were treated with saline (n=8 control) or risedronate (0.5mg/kg/day, n=9 RIS-suppressed) for one year. Suppression of bone turnover resulted in increased stiffness of the whole vertebra (20.9%, p=0.02) and the trabecular compartment (26.0%, p=0.01), while the computed stiffness of the cortical shell (difference between whole-vertebra and trabecular-compartment stiffnesses, 11.7%, p=0.15) was unaltered. Despite higher average cortical shell thickness in RIS-suppressed vertebrae (23.1%, p=0.002), the maximum load taken by the shell for a given value of shell mass fraction was lower (p=0.005) for the RIS-suppressed group, suggesting overall changes in the compressive stiffness of the vertebral body due to suppression of bone turnover were attributable more to the changes in the trabecular compartment than in the cortical shell.

10.2.51 Effects of in vivo static compressive loading on aggrecan and type II and X collagens in the rat growth plate extracellular matrix
Cancel M, Grimard G, Thuillard-Crisinel D, Moldovan F, Villemure I
Bone 2009;44:306-15

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Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 2, 2009

Growth

10.2.52 Estimated maternal ultraviolet B exposure levels in pregnancy influence skeletal development of the child
Sayers A, Tobias JH
J Clin Endocrinol Metab 2008;[Epub ahead of print]

6955 boys and girls mean age 9.9 years. Pre-specified analyses of relationships between background UVB levels in the third trimester of pregnancy, and total body less head BMC, bone area (BA), BMD and area-adjusted BMC (ABMC) as measured by DXA scans at 9.9 years. Maternal UVB exposure was positively related to BMC BA and BMD but not ABMC suggesting an effect on bone size. Both height-dependent and height-independent effects contributed to this association. Although maternal UVB exposure was also related to lean mass, a positive association between UVB and BA persisted after adjusting for both height and lean mass. Maternal UVB exposure is related to bone size at age 9.9 independently of height and lean mass, suggesting vitamin D status in pregnancy exerts direct effects on periosteal bone formation in subsequent childhood.

10.2.53 Bone structure and volumetric BMD in overweight children: A longitudinal study
Wetzsteon RJ, Petit MA, Macdonald HM, Hughes JM, Beck TJ, McKay HA
J Bone Miner Res 2008;23:1946-53

In 302 healthy weight (HW) and 143 overweight (OW) children (9-11 yr) were classified as HW (n=302) or OW (n=143) based on body mass index total (ToD) and cortical (CoD) volumetric BMD and bone area, bone strength index (BSI), stress-strain index (SSIp) and muscle cross-sectional area (CSA) at the distal (8%), midshaft (50%), and proximal (66%) tibia by pQCT. At baseline, all bone measures were greater in OW than HW children (+4-15%; p≤0.001), with the exception of CoD at the 50% and 66% sites. Over 16 mo, ToA increased more in the OW children, whereas there was no difference for change in BSI or ToD between groups at the distal tibia. At the tibial midshaft, SSIp was similar between groups at baseline when adjusted for muscle CSA, but low when adjusted for body fat in the OW group. At both sites, bone strength increased more in OW because of a greater increase in bone area. Changes in SSIp were associated with changes in lean mass (r=0.70, p<0.001) but not fat mass. OW children seem to be at an advantage in terms of absolute bone strength, bone strength did not adapt to excess body fat. Rather, bone strength was adapted to the greater muscle area in OW children.

10.2.54 Anterior-posterior bending strength at the tibial shaft increases with physical activity in boys: Evidence for non-uniform geometric adaptation
Macdonald HM, Cooper DM, McKay HA
Osteoporos Int 2009;20:61-70

202 boys (aged 9-11 years) from 10 schools were randomly assigned to control (CON, 63 boys) and intervention (INT, 139 boys) groups. INT participated in 60 min/week of classroom physical activity. The INT boys had a 3% greater gain in I_{max} than the CON boys (p=0.04) and tended to have a greater gain in second moments of area, I_{min} (approximately 2%, NS). Associated with the greater gain in I_{max} was a slightly greater (NS) gain (1-1.4%) in CoA and CTh in the anterior, medial, and posterior (but not lateral) quadrants. Regional variation in bone adaptation consistent with patterns of bone formation induced by anterior-posterior bending loads.

10.2.55 Weight-bearing bones are more sensitive to physical exercise in boys than in girls during pre- and early puberty: A cross-sectional study
Kriemler S, Zahner L, Puder JJ, Braun-Fahrlander C, Schindler C, Farpour-Lambert NJ, Kranzlin M, Rizzoli R
Osteoporos Int 2008;19:1749-58

In two hundred and sixty-nine 6- to 13-year-old children from randomly selected schools by DXA. Physical activity (PA) was measured by accelerometers and lower extremity strength by a jump-and-reach test. Boys (n=128) had higher hip and total body BMC and BMD, higher FFM, higher muscle strength and were more physically active than girls (n=141). Total hip BMC was positively associated with time spent in total and vigorous PA in boys (r=0.20-0.33, p<0.01), but not in girls (r=0.02-0.04, p=ns), even after adjusting for FFM and strength. While boys and girls in the lowest tertile of vigorous PA (22 min/day) did not differ in hip BMC (15.62 vs. 15.52 g), boys in the highest tertile (72 min/day) had higher values than the corresponding girls (16.84 vs. 15.71 g, p<0.05).

10.2.56 Quantitative CT reference values for vertebral trabecular bone density in children and young adults
Gilsanz V, Perez FJ, Campbell PP, Dorey FJ, Lee DC, Wren TA
Radiology 2009;250:222-7

QCT of trabecular bone density (TBD) obtained at the first, second, and third lumbar vertebrae in 1222 healthy white male and female subjects aged 5-21 years. TBD increased equally during growth in male and female subjects. Although the percentage increase in TBD was similar for both sexes (23.7% [57 of 241] for male subjects, 22.2% [54 of 243] for female subjects), the rise began and reached peak values at an earlier age in female subjects; increases in TBD occurred from 10-15 years of age in female subjects, whereas in male subjects, these increases were not observed until age 12 years and were completed at 17 years.

10.2.57 Deleterious effect of late menarche on distal tibia microstructure in healthy 20-year-old and premenopausal middle-aged women
Chevalley T, Bonjour JP, Ferrari S, Rizzoli R
J Bone Miner Res 2009;24:144-52

The influence of menarcheal age (MENA) on FN aBMD and microstructure of distal tibia by HR-pQCT in healthy young adult (YAD; 20.4±0.6 [SD] years, n=124) and premenopausal middle-aged (PREMENO; 45.8±3.4 years, n=120) women was studied. In YAD and PREMENO (n=244), FN aBMD (R=–0.29, p=0.013), as well as total volumetric BMD (Dtot; R=–0.23, p=0.006) and cortical thickness (Ct.Th; R=–0.18, p=0.011) of distal tibia were inversely correlated to MENA. After segregation by the median of MENA in EARLY and LATE subgroups, the influences of both MENA (p=0.004) and age (p<0.0001) were observed for FN aBMD and trabecular bone volume fraction of the distal tibia with similar differences in T-scores between LATE and EARLY subgroups in YAD (-0.36 and -0.31 T-scores) and PREMENO (-0.35 and -0.42 T-scores) women. Ct.Th was negatively influenced by MENA, whereas trabecular thickness (Tb.Th) was negatively influenced by chronological age. There was an inverse relationship between cross-sectional area and Ct.Th (R=–0.57, p<0.001).

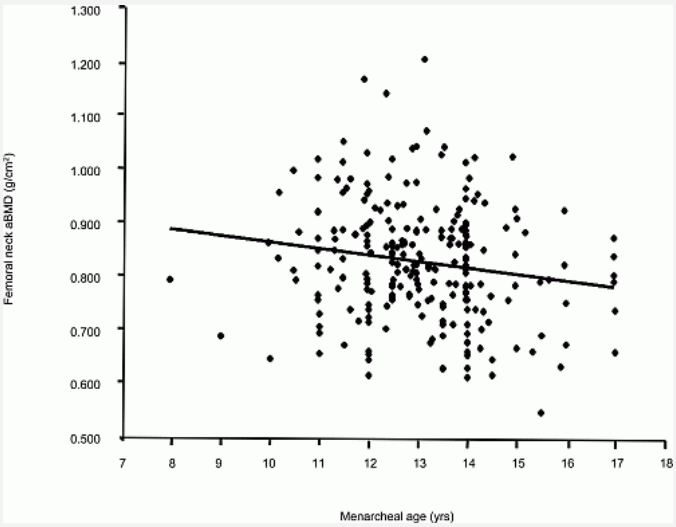


Fig. 10.2.57a Relationship between menarcheal age and areal BMD of the femoral neck in 244 healthy young adult and middle-aged premenopausal women. The regression line is Y = −0.012X + 0.992, R=−0.16, p=0.012. Reproduced from J Bone Miner Res 2009;24:144-52 with permission of the American Society of Bone and Mineral Research.

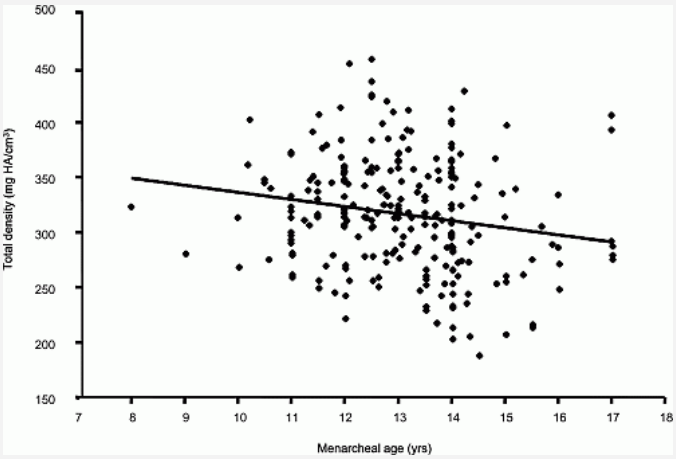
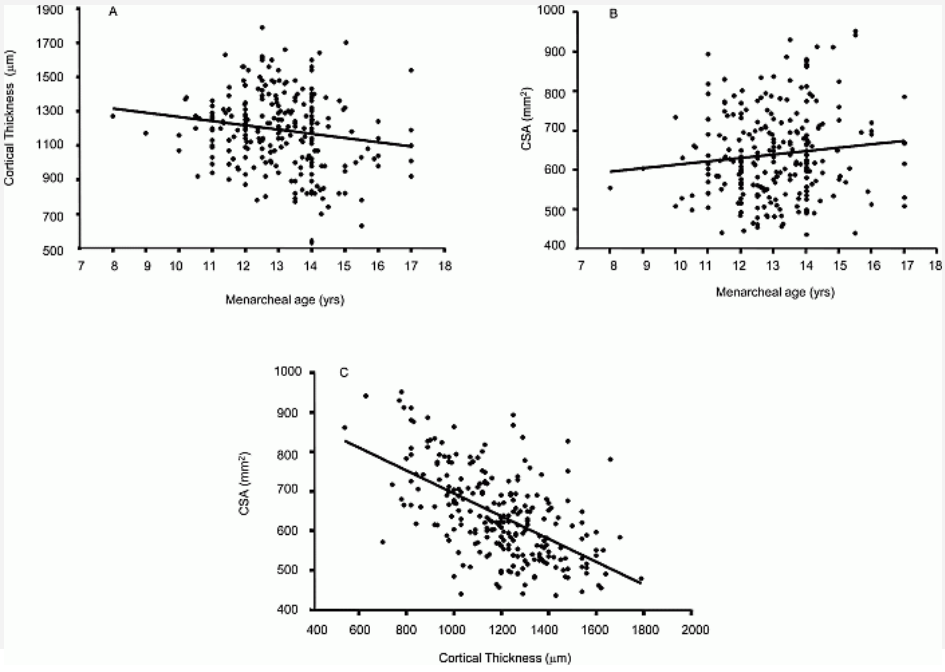


Fig. 10.2.57b Relationship between menarcheal age and total volumetric BMD of the distal tibia in 244 healthy young adult and middle-aged premenopausal women. The regression line is Y = −6.45X + 401, R=−0.18, p=0.006. Reproduced from J Bone Miner Res 2009;24:144-52 with permission of the American Society of Bone and Mineral Research.



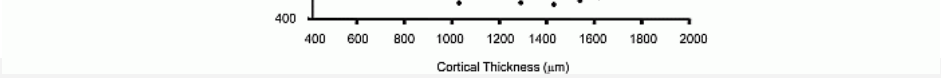


Fig. 10.2.57c Relationships between menarcheal age, cortical thickness, and cross-sectional area (CSA) of the distal tibia in 244 healthy young adult and middle-aged premenopausal women. The regression lines of cortical thickness (A) and CSA (B) on menarcheal age are Y = −24.7X + 1513, R=−0.16, p=0.011, and Y = 8.69X + 526, R=0.11, p=0.077, respectively. The regression line of CSA (C) on cortical thickness was Y = −0.289X + 984, R=−0.57, p<0.001. Reproduced from J Bone Miner Res 2009;24:144-52 with permission of the American Society of Bone and Mineral Research.

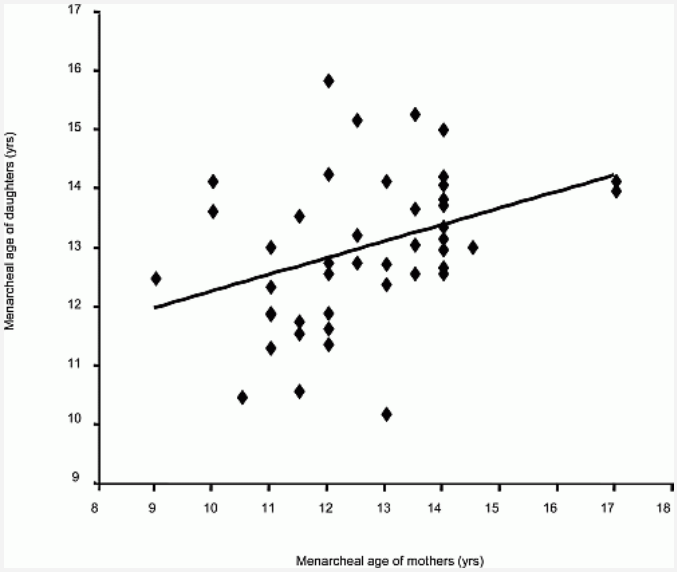


Fig. 10.2.57d Menarcheal age relationship between mother-daughter pairs. The regression line equation was Y = 0.282X + 9.435, R=0.39, N=46, p<0.01. The 46 mother-daughter pairs belong to a subgroup of the cohort presented in Table 1 (of this paper). Reproduced from J Bone Miner Res 2009;24:144-52 with permission of the American Society of Bone and Mineral Research.

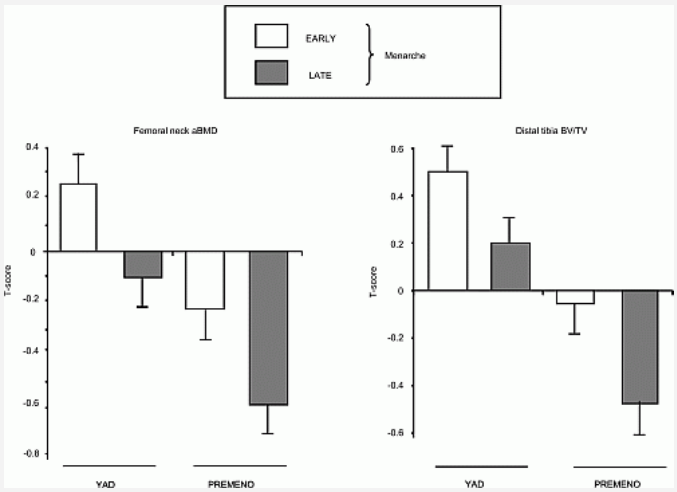


Fig. 10.2.57e T-score of femoral neck aBMD and trabecular bone volume fraction (BV/TV) of distal tibia in relation with menarcheal age in young and middle-aged premenopausal healthy women. The two cohorts of young adult (YAD, 20.4 yr, n=124) and middle-aged premenopausal (PREMENO, 45.8 yr, n=120) women were segregated by the median in EARLY and LATE menarcheal age. The mean menarcheal age (years±SD) were as follows: YAD EARLY, 12.1±0.7; YAD LATE, 14.0 ±0.7; PREMENO EARLY, 11.8±1.0; PREMENO LATE, 14.4±1.1. The T-scores (±SE) were obtained from the values of femoral neck aBMD (mg/cm^2) and BV/TV (%) detailed in Table 5 (of this paper). Reproduced from J Bone Miner Res 2009;24:144-52 with permission of the American Society of Bone and Mineral Research.

10.2.58 Vitamin D status and muscle function in post-menarchal adolescent girls
Ward KA, Das G, Berry JL, Roberts SA, Rawer R, Adams JE, Mughal Z
J Clin Endocrinol Metab 2009;94:559-63

In 99 post-menarchal 12- to 14-yr-old females median serum 25(OH)D was 21.3 nmol/liter (range 2.5-88.5) and PTH 3.7 pmol/liter (range 0.47-26.2). After correction for weight using a quadratic function, there was a positive relationship between 25(OH)D and jump velocity (P=0.002), jump height (P=0.005), power (P=0.003), Esslinger Fitness Index (P=0.003), and force (P=0.05). There was a negative effect of PTH upon jump velocity (P=0.04). From these data we conclude that vitamin D was significantly associated with muscle power and force in adolescent girls.

10.2.59 Vitamin D status and its relationship to body fat, final height, and peak bone mass in young women
Kremer R, Campbell PP, Reinhardt T, Gilsanz V
J Clin Endocrinol Metab 2009;94:67-73

Of 90 postpubertal females, aged 16-22 yr, approximately 59% of subjects were 25OHD insufficient (≤29 ng/ml), and 41% were sufficient (≥30 ng/ml). Strong negative relationships were present between serum 25OHD and computed tomography measures of visceral and sc fat and DXA values of BF. In addition, weight, body mass, and imaging measures of adiposity at all sites were lower in women with normal serum 25OHD than women with insufficient levels. In contrast, no relationship was observed between circulating 25OHD concentrations and measures of bone mineral density at any site. Unexpectedly, there was a positive correlation between 25OHD levels and height.

10.2.60 Lumbar spine peak bone mass and bone turnover in men and women: A longitudinal study
Walsh JS, Henry YM, Fatayerji D, Eastell R
Osteoporos Int 2009;20:355-62

In 116 healthy males and females ages 11-40, followed up at an interval of 5-9 years. Most peak bone mass was attained by the mid-twenties. Increases in BMC in adolescents and young adults were mostly due to increases in bone size. Bone turnover markers decreased through adolescence and the third decade and the decreasing rate of change in bone turnover corresponded with the decreasing rate of change in lumbar spine measurements.

10.2.61 Previous sport activity during childhood and adolescence is associated with increased cortical bone size in young adult men
Nilsson M, Ohlsson C, Mellstrom D, Lorentzon M
J Bone Miner Res 2009;24:125-33

1068 men (18.9±0.6 [SD] years) were included. Subjects who continued to be active (n=678) and who had been previously active (n=285) in sports had a wider cortical bone (periosteal circumference [PC], 4.5% and 3.2%, respectively) with increased cross-sectional area (CSA; 12.5% and 6.9%) of the tibia than the always inactive subjects (n=82). Previous sport activity was associated with cortical bone size of the tibia (CSA and PC). Amount of previous sport activity explained 7.3% of the total variation in cortical CSA. Subjects, who ceased their sport activity for up to 6.5 years previously, still had greater cortical PC and CSA of the tibia than always inactive subjects.

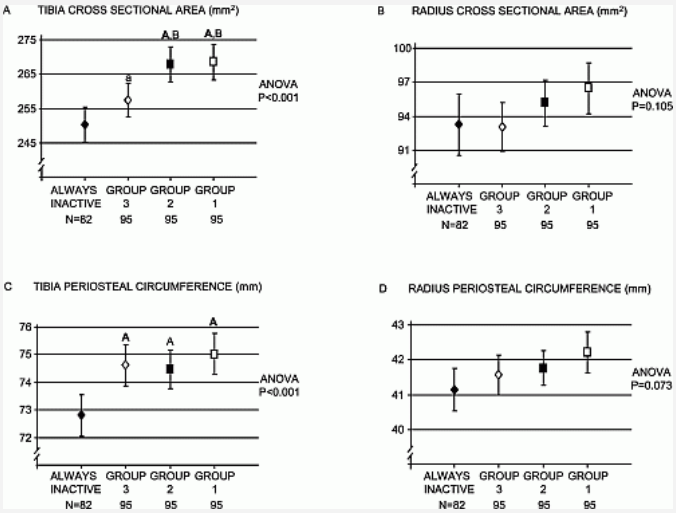


Fig. 10.2.61 Subjects previously engaged in sport activity have greater cortical cross-sectional area (A) and periosteal circumference (C) of the tibia than always inactive subjects. No differences were seen for the corresponding bone parameters of the radius (B and D). Subjects were divided into always inactive and three equal groups (previously sports active), according to the duration of inactivity: group 1, >0 and ≤2.24 yr (n=95); group 2, >2.24 and ≤4.26 yr (n=95); group 3, >4.26 yr (n=95). A>always inactive, B>group 3. Capital and lowercase letters represent p<0.01 and p<0.05, respectively. Capital bold letters represent p<0.001. Mean and 95% CIs of cortical bone size parameters adjusted for age, height, weight, calcium intake, and smoking status are presented. Reproduced from J Bone Miner Res 2009;24:125-33 with permission of the American Society of Bone and Mineral Research.

10.2.62 Fracture rates in urban South African children of different ethnic origins: The Birth to Twenty cohort
Thandrayen K, Norris SA, Pettifor JM
Osteoporos Int 2009;20:47-52

Using the Birth to Twenty longitudinal cohort of children, information on fractures and their sites from birth to 14.9 years of age were obtained in 2031 participants. The ethnic breakdown of the children was black (B) 78%, white (W) 9%, mixed ancestry (MA) 10.5% and Indian (I) 1.5%. 441 (22%) children sustained a fracture one or more times during their lifetime (males 27.5% and females 16.3%; p<0.001). The percentage of children fracturing differed between the ethnic groups (W 41.5%, B 19%, MA 21%, I 30%; p<0.001). Of the 441 children reporting fractures, 89 (20%) sustained multiple fractures. The most common site of fracture was the upper limb (57%).

10.2.63 Accounting for body size deviations when reporting bone mineral density variables in children
Webber CE, Sala A, Barr RD
Osteoporos Int 2009;20:113-21

10.2.64 Carboxypeptidase Z (CPZ) links thyroid hormone and Wnt signaling pathways in growth plate chondrocytes
Wang L, Shao YY, Ballock RT
J Bone Miner Res 2009;24:265-73

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Bone Formation

10.2.65 Critical interplay between neuropeptide Y and sex steroid pathways in bone and adipose tissue homeostasis
Allison SJ, Baldock PA, Enriquez RF, Lin E, During M, Gardiner EM, Eisman JA, Sainsbury A, Herzog H
J Bone Miner Res 2009;24:294-304

Y2 receptor-mediated anabolic response on bone formation is mediated by a hypothalamic relay while the Y1-mediated response is likely mediated by osteoblastic Y1 receptors. The presence of Y1 receptors on osteoblasts suggests that circulating factors may also interact with the Y1-mediated pathways. The skeletal and adipose tissue (peripheral and marrow) responses to Y1 receptor deficiency were examined after (1) leptin deficiency, (2) gonadectomy, and (3) hypothalamic NPY overexpression. Bone formation was increased in intact Y1-/- mice. However, the hypogonadism of gonadectomy or leptin deficiency blocked this anabolism in male Y1-/- mice, whereas females remained unchanged. Y1 deficiency also led to increased weight and/or adiposity with the exception of male ob/ob, showing a general adipogenic effect of Y1 deficiency that is not dependent on androgens. Marrow adipocytes were regulated differently than general adipose depots in these models. This interaction represents a mechanism for the integration of endocrine and neural signals initiated in the hypothalamus.

10.2.66 Periostin-like-factor and Periostin in an animal model of work-related musculoskeletal disorder
Rani S, Barbe MF, Barr AE, Litvin J
Bone 2009;44:502-12

Periostin-like-factor (PLF) and Periostin were examined. Both belong to a family of vitamin K-dependent gamma carboxylated proteins characterized by the presence of conserved Fasciclin domains and not detected in adult tissues except under conditions of chronic overload, injury, stress or pathology. PLF was present primarily in the cellular periosteum, articular cartilage, osteoblasts, osteocytes and osteoclasts at weeks 3 and 6 in all distal bone sites examined. This increase coincided with a transient increase in serum osteocalcin in week 6, indicative of adaptive bone formation at this time point. PLF immunoexpression decreased in the distal periosteum and metaphysis by week 12, coincided temporally with an increase in serum TRAP5b, thinning of the growth plate and reduced cortical thickness. In contrast to PLF, once Periostin was induced by task performance, it continued to be present at a uniformly high level between 3 and 12 weeks in the trabeculae, fibrous and cellular periosteum, osteoblasts and osteocytes. PLF is located in tissues during the early adaptive stage of remodeling but not during the pathological phase and therefore might be a marker of early adaptive remodelling.

10.2.67 Cardiotrophin-1 is an osteoclast-derived stimulus of bone formation required for normal bone remodelling
Walker EC, McGregor NE, Poulton IJ, Pompolo S, Allan EH, Quinn JM, Gillespie MT, Martin TJ, Sims NA
J Bone Miner Res 2008;23:2025-32

Cardiotrophin (CT-1) signals through gp130 and the LIF receptor and plays a major role in cardiac, neurological, and liver biology. CT-1 is also expressed in osteoclasts and increases osteoblast activity and mineralization in vitro and in vivo. CT-1 stimulated CAAT/enhancer-binding protein-delta (C/EBPdelta) expression and Runx2 activation. In neonate CT-1(-/-) mice, low bone mass associated with reduced osteoblasts and many large osteoclasts was found, but increased cartilage remnants within the bone suggest impaired resorption. Cultured marrow from CT-1(-/-) mice generated many oversized osteoclasts and mineralized poorly compared with wildtype marrow. As the CT-1(-/-) mice aged, the reduced osteoblast surface (ObS/BS) was no longer detected, but impaired bone resorption continued resulting in an osteopetrotic phenotype in adult bone. CT-1 is an osteoclast-derived stimulus of bone formation and resorption.

10.2.68 Mechanical stimulation of mesenchymal stem cell proliferation and differentiation promotes osteogenesis while preventing dietary-induced obesity
Luu YK, Capilla E, Rosen CJ, Gilsanz V, Pessin JE, Judex S, Rubin CT
J Bone Miner Res 2009;24:50-61

Low magnitude mechanical signals (LMMS) are anabolic and suppress the development of fat in normal animals. Using male C57BL/6J mice, the ability of LMMS (0.2 g, 90 Hz signal applied for 15 min/d, 5 d/wk) to promote bone formation and prevent diet-induced obesity was correlated to mechanical influences. Six weeks of LMMS increased the overall marrow-based stem cell population by 37% and the number of mesenchymal stem cells (MSCs) by 46%. MSCs Runx2 by 72% was upregulated and PPARγ downregulation by 27%. Visceral adipose tissue formation was suppressed by 28%, whereas trabecular bone volume fraction in the tibia was increased by 11%.

10.2.69 Dspp effects on in vivo bone mineralization
Verdelis K, Ling Y, Sreenath T, Haruyama N, Macdougall M, van der Meulen MC, Lukashova L, Spevak L, Kulkarni AB, Boskey AL
Bone 2008;43:983-90

Dentin sialophosphoprotein is implicated in mineralization based on the defective dentin formation in Dspp null mice (Dspp-/-). Dspp is expressed at low levels in bone and Dspp-/- femurs exhibit mineral and matrix property differences from wildtype femurs in mice. Compared to wildtype, Dspp-/- mice initially (5 weeks) and at 7 months had higher trabecular bone volume and lower trabecular separation, while at 9 months, bone volume fraction and trabecular number were lower. Cortical bone mineral density, area, and moments of inertia in Dspp-/- were reduced at 9 months. By FTIRI, Dspp-/- animals initially (5 months) contained more stoichiometric bone apatite with higher crystallinity (crystal size/perfection) and lower carbonate substitution. This difference progressively reversed with age (decreased crystallinity and increased acid phosphate content in Dspp-/- cortical bone by 9 months of age). Mineral density in individual cortical and trabecular bones correlated (r^2=0.6, $p<0.04$). From the matrix analysis, the collagen maturity of both cortical and trabecular bones was greater in Dspp-/- than controls at 5 weeks; by 9 months this difference in crosslinking pattern did not exist.

10.2.70 Inhibition of lamin A/C attenuates osteoblast differentiation and enhances RANKL-dependent osteoclastogenesis
Rauner M, Sipos W, Goettsch C, Wutzl A, Foisner R, Pietschmann P, Hofbauer LC
J Bone Miner Res 2009;24:78-86

Hutchinson-Gilford progeria syndrome of accelerated aging is linked to mutations in the gene encoding for the nuclear lamina protein lamin A/C. Lamin A/C was knocked-down in human bone marrow stromal cells (BMSCs) led to an inhibition of osteoblast proliferation by 26% and impaired osteoblast differentiation by 48%. In mature osteoblasts, expression levels of Runx2 and osteocalcin mRNA were decreased by lamin A/C knockdown by 44% and 78%, respectively. Osteoblasts with diminished levels of lamin A/C also secreted less osteocalcin and expressed a lower alkaline phosphatase activity (-50%). Lamin A/C inhibition increased RANKL mRNA and protein levels, whereas osteoprotegerin (OPG) expression was decreased, resulting in an increased RANKL/OPG ratio and an enhanced ability to support osteoclastogenesis, as reflected by a 34% increase of TRACP (+) multinucleated cells. Lamin A/C is essential for proper osteoblastogenesis. Moreover, lack of lamin A/C favors an osteoclastogenic milieu and contributes to enhanced osteoclastogenesis.

10.2.71 Disruption of BMP signaling in osteoblasts through type IA receptor (BMPRIA) increases bone mass
Kamiya N, Ye L, Kobayashi T, Lucas DJ, Mochida Y, Yamauchi M, Kronenberg HM, Feng JQ, Mishina Y
J Bone Miner Res 2008;23:2007-17

10.2.72 COX-2 from the injury milieu is critical for the initiation of periosteal progenitor cell mediated bone healing
Xie C, Ming X, Wang Q, Schwarz EM, Guldberg RE, O'Keefe RJ, Zhang X
Bone 2008;43:1075-83

10.2.73 Micro-computed tomography assessment of fracture healing: Relationships among callus structure, composition, and mechanical function
Morgan EF, Mason ZD, Chien KB, Pfeiffer AJ, Barnes GL, Einhorn TA, Gerstenfeld LC
Bone 2009;44:335-44

10.2.74 Stress fracture healing: Fatigue loading of the rat ulna induces upregulation in expression of osteogenic and angiogenic genes that mimic the intramembranous portion of fracture repair
Wohl GR, Towler DA, Silva MJ
Bone 2009;44:320-30

10.2.75 The effect of antiresorptive therapies on bone graft healing in an ovariectomized rat spinal arthrodesis model
Takahata M, Ito M, Abe Y, Abumi K, Minami A
Bone 2008;43:1057-66

10.2.76 Congenital pseudarthrosis of neurofibromatosis type 1: Impaired osteoblast differentiation and function and altered NF1 gene expression
Leskela HV, Kuorilehto T, Risteli J, Koivunen J, Nissinen M, Peltonen S, Kinnunen P, Messiaen L, Lehenkari P, Peltonen J
Bone 2009;44:243-50

10.2.77 Altered fracture callus formation in chondromodulin-I deficient mice
Yukata K, Matsui Y, Shukunami C, Takimoto A, Goto T, Nishizaki Y, Nakamichi Y, Kubo T, Sano T, Kato S, Hiraki Y, Yasui N
Bone 2008;43:1047-56

10.2.78 Skeletal cell fate decisions within periosteum and bone marrow during bone regeneration
Colnot CI
J Bone Miner Res 2009;24:274-82

10.2.79 Comparison of multipotent differentiation potentials of murine primary bone marrow stromal cells and mesenchymal stem cell line C3H10T1/2
Zhao L, Li G, Chan KM, Wang Y, Tang PF
Calcif Tissue Int 2009;84:56-64

10.2.80 Gene expression analysis in osteoblastic differentiation from peripheral blood mesenchymal stem cells
Valenti MT, Carbonare LD, Donatelli L, Bertoldo F, Zanatta M, Lo Cascio V
Bone 2008;43:1084-92

10.2.81 Gene expression signatures of a fibroblastoid preosteoblast and cuboidal osteoblast cell model compared to the MLO-Y4 osteocyte cell model
Yang W, Harris MA, Heinrich JG, Guo D, Bonewald LF, Harris SE
Bone 2009;44:32-45

10.2.82 Role of MT1-MMP in the osteogenic differentiation
Manduca P, Castagnino A, Lombardini D, Marchisio S, Soldano S, Ulivi V, Zanotti S, Garbi C, Ferrari N, Palmieri D
Bone 2009;44:251-65

10.2.83 The role of gap junctions in megakaryocyte-mediated osteoblast proliferation and differentiation

Ciovacco WA, Goldberg CG, Taylor AF, Lemieux JM, Horowitz MC, Donahue HJ, Kacena MA
Bone 2009;44:80-6

10.2.84 Effect of lamin A/C knockdown on osteoblast differentiation and function
Akter R, Rivas D, Geneau G, Drissi H, Duque G
J Bone Miner Res 2009;24:283-93

10.2.85 Functional characterization of genetic variation in the Frizzled 1 (FZD1) promoter and association with bone phenotypes: More to the LRP5 story?
Yerges LM, Zhang Y, Cauley JA, Kammerer CM, Nestlerode CS, Wheeler VW, Patrick AL, Bunker CH, Moffett SP, Ferrell RE, Zmuda JM
J Bone Miner Res 2009;24:87-96

10.2.86 Damaging effects of chronic low-dose methotrexate usage on primary bone formation in young rats and potential protective effects of folinic acid supplementary treatment
Fan C, Cool JC, Scherer MA, Foster BK, Shandala T, Tapp H, Xian CJ
Bone 2009;44:61-70

10.2.87 CCN family 2/connective tissue growth factor (CCN2/CTGF) regulates the expression of VEGF through Hif-1alpha expression in a chondrocytic cell line, HCS-2/8, under hypoxic condition
Nishida T, Kondo S, Maeda A, Kubota S, Lyons KM, Takigawa M
Bone 2009;44:24-31

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Bone Resorption

10.2.88 Bone density, strength, and formation in adult cathepsin K (-/-) mice
Pennypacker B, Shea M, Liu Q, Masarachia P, Saftig P, Rodan S, Rodan G, Kimmel D
Bone 2009;44:199-207

Cathepsin K (CatK) is a cysteine protease expressed in osteoclasts which degrades type I collagen. Growing CatK null mice have osteopetrosis. Central femur ultimate load was positively influenced by genotype and correlated with cortical area and BMC. Lumbar vertebral body ultimate load also correlated with BMC. Genotype did not influence the relationship of ultimate load to BMC in either the central femur or vertebral body. CatK (-/-) mice had less lamellar cortical bone than WT. Higher bone volume, trabecular thickness, and trabecular number were observed at the distal femur in CatK (-/-) mice. Smaller marrow cavities were also present at the central femur of CatK (-/-) mice. CatK (-/-) mice exhibited greater trabecular mineralizing surface, associated with normal volume-based formation of trabecular bone. Adult CatK (-/-) mice have higher bone mass in both cortical and cancellous regions than WT mice. Though no direct measures of bone resorption rate were made, the higher cortical bone quantity is associated with a smaller marrow cavity and increased retention of nonlamellar bone, signs of decreased endocortical resorption.

10.2.89 CD33+ CD14- phenotype is characteristic of multinuclear osteoclast-like cells in giant cell tumor of bone
Forsyth RG, De Boeck G, Baelde JJ, Taminiau AH, Uyttendaele D, Roels H, Praet MM, Hogendoorn PC
J Bone Miner Res 2009;24:70-7

10.2.90 The endovanilloid/endocannabinoid system in human osteoclasts: Possible involvement in bone formation and resorption
Rossi F, Siniscalco D, Luongo L, De Petrocellis L, Bellini G, Petrosino S, Torella M, Santoro C, Nobili B, Perrotta S, Di Marzo V, Maione S
Bone 2009;44:476-84

10.2.91 High oxygen tension prolongs the survival of osteoclast precursors via macrophage colony-stimulating factor
Yamasaki N, Tsuboi H, Hirao M, Nampei A, Yoshikawa H, Hashimoto J
Bone 2009;44:71-9

10.2.92 Non-invasive optical detection of cathepsin K-mediated fluorescence reveals osteoclast activity in vitro and in vivo
Kozloff KM, Quinti L, Patntirapong S, Hauschka PV, Tung CH, Weissleder R, Mahmood U
Bone 2009;44:190-8

10.2.93 Water solution of onion crude powder inhibits RANKL-induced osteoclastogenesis through ERK, p38 and NF-kappaB pathways
Tang CH, Huang TH, Chang CS, Fu WM, Yang RS
Osteoporos Int 2009;20:93-103

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Risk Factors

10.2.94 Activation of renin-angiotensin system induces osteoporosis independently of hypertension
Asaba Y, Ito M, Fumoto T, Watanabe K, Fukuhara R, Takeshita S, Nimura Y, Ishida J, Fukamizu A, Ikeda K
J Bone Miner Res 2009;24:241-50

The renin-angiotensin system (RAS) plays a role in the control of blood pressure. Using a chimeric RAS model of transgenic THM (Tsukuba hypertensive mouse) expressing the human renin and angiotensinogen genes, activation of RAS induces high turnover osteoporosis with accelerated bone resorption. Transgenic mice that express only the human renin gene were normotensive and yet exhibited a low bone mass, suggesting that osteoporosis occurs independently of hypertension. Ex vivo cultures showed that angiotensin II (AngII) acted on osteoblasts and increased RANKL and vascular endothelial growth factor, thereby stimulating the formation of osteoclasts. Knockdown of AT2 receptor inhibited the AngII activity, whereas silencing of the AT1 receptor paradoxically enhanced it, suggesting a functional interaction between the two AngII receptors on the osteoblastic cell surface. ACE inhibitor, enalapril, improved osteoporosis and hypertension, whereas treatment with losartan, an angiotensin receptor blockers specific for AT1, resulted in exacerbation of the low bone mass phenotype. Thus, blocking the synthesis of AngII may be an effective treatment of osteoporosis and hypertension, especially for those afflicted with both conditions.

10.2.95 Body mass influences cortical bone mass independent of leptin signaling
Iwaniec UT, Dube MG, Boghossian S, Song H, Helferich WG, Turner RT, Kalra SP
Bone 2009;44:404-12

Male C57Bl/6 wildtype (WT) and leptin-deficient ob/ob mice were studied to determine whether body mass gain by high fat intake increases bone mass and whether this requires central leptin signaling. Slowly and rapidly growing ob/ob mice were injected in the hypothalamus with a recombinant adeno-associated virus containing the leptin gene (rAAV-lep) or a control vector, rAAV-GFP (green fluorescent protein). In the WT, femoral and vertebral bone mass correlated with body mass (r=0.65-0.88). rAAV-lep therapy decreased body mass (-61%) but increased femur length. However, in the distal femur and lumbar vertebra, rAAV-lep therapy reduced cancellous bone volume/tissue volume. The high fat diet increased body mass, irrespective of vector treatment. Total femur bone volume, length, cross-sectional volume, and cortical volume and thickness were increased in mice with increased body mass, independent of rAAV treatment. In the distal femur, increased body mass had no effect on cancellous architecture and there were no vector x body mass interactions. In WT, increased body mass increased (+33%) vertebral cancellous bone volume/tissue volume. Increased body mass had minimal independent effect on cancellous vertebral bone mass in ob/ob mice. Increased body mass has a positive effect on femur cortical bone mass independent of leptin signaling.

10.2.96 Association between change in BMD and fragility fracture in women and men
Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse RG, Prior JC, Kreiger N, Tenenhouse A, Goltzman D
J Bone Miner Res 2009;24:361-70

In 3635 women and 1417 men 50-85 years of age, independent of baseline BMD, a decrease of 0.01 g/cm^2/yr in total hip BMD was associated with an increased risk of fragility fracture with ORs of 1.15 (95% CI: 1.01; 1.32) in women and 1.34 (95% CI: 1.02; 1.78) in men. The risk of fragility fractures in subgroups such as fast losers and those with osteopenia was better estimated by models that included BMD change than by models that included baseline BMD but excluded BMD change. Although the association between baseline BMD and fragility fractures was similar in users and nonusers of antiresorptives, the association was stronger in nonusers compared with users. These results show that BMD change in both men and women is an independent risk factor for fragility fractures and also predicts fracture risk in those with osteopenia.

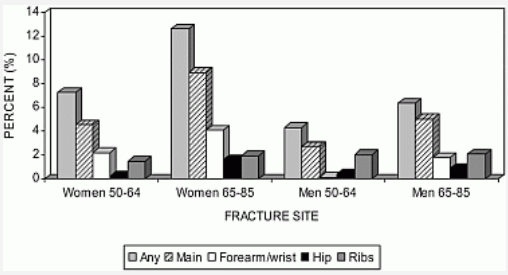

Fig. 10.2.96a Cumulative incidence of fragility fractures over 7 yr in women and men who are taking and not taking antiresorptive agents. Reproduced from J Bone Miner Res 2009;24:361-70 with permission of the American Society of Bone and Mineral Research.

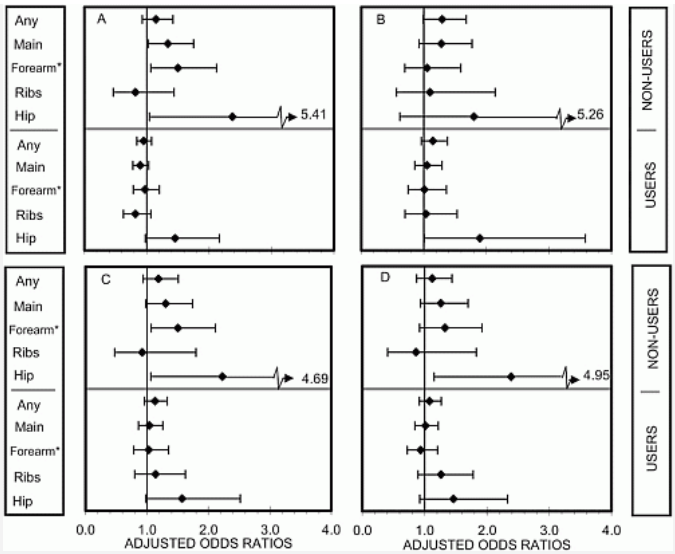

Fig. 10.2.96b Adjusted ORs and 95% CIs for a BMD decrease of 0.01 g/cm^2/yr in women using or not using antiresorptive therapies in estimating fragility fracture. (A) Lumbar spine. (B) Femoral neck. (C) Total hip. (D) Trochanter. Forearm includes forearm and wrist fractures. Reproduced from J Bone Miner Res 2009;24:361-70 with permission of the American Society of Bone and Mineral Research.

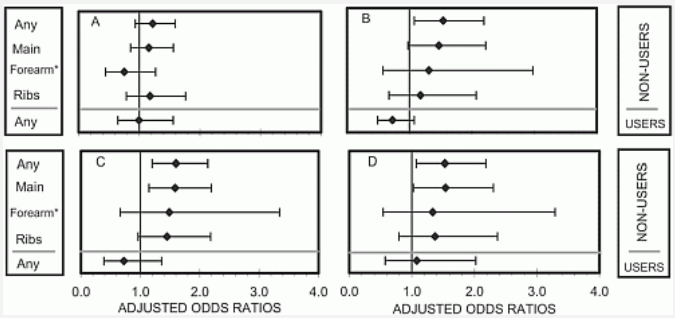

Fig. 10.2.96c Adjusted ORs and 95% CIs for a BMD decrease of 0.01 g/cm^2/yr in men using or not using antiresorptive therapies in estimating fragility fracture. (A) Lumbar spine. (B) Femoral neck. (C) Total hip. (D) Trochanter. Forearm includes forearm and wrist fractures. Reproduced from J Bone Miner Res 2009;24:361-70 with permission of the American Society of Bone and Mineral Research.

10.2.97 Simplified system for absolute fracture risk assessment: Clinical validation in Canadian women
Leslie WD, Tsang JF, Lix LM
J Bone Miner Res 2009;24:353-60

16,205 women ≥50 years of age at the time of baseline BMD (1998-2002) were identified. Basal 10-year fracture risk from age and minimum T-score (lumbar spine, femur neck, trochanter, total hip) was categorized as low (<10%), moderate (10-20%), or high (>20%). Health service records since 1987 were assessed for prior fracture codes (N=5224), recent major corticosteroid use (N=616), and fracture codes after BMD testing (mean, 3.1 years of follow-up) for the hip, vertebrae, forearm, or humerus (designated osteoporotic, N=757). Fracture risk predicted from age and minimum T-score alone showed a gradient in fracture rates (low 5.1 [95% CI 4.1-6.4], moderate 11.5 [95% CI 10.1-13.0], high 25.4 [95% CI 23.2-27.9] per 1000 person-years; p-for-trend<0.0001). There was an incremental increase in incident fracture rates from a prior fracture (13.9 [95% CI 11.3-16.4] per 1000 person-years) or major CS use (11.2 [95% CI 4.1-18.2] per 1000 person-years).

10.2.98 Successful skeletal aging: A marker of low fracture risk and longevity. The Study of Osteoporotic Fractures (SOF)
Cauley JA, Lui LY, Barnes D, Ensrud KE, Zmuda JM, Hillier TA, Hochberg MC, Schwartz AV, Yaffe K, Cummings SR, Newman AB
J Bone Miner Res 2009;24:134-43

8224 measured a maximum of five times over 15 years showed three groups "maintained" BMD: slope≥0, n=724 (9%); "expected" BMD loss: slope <0 to <1 SD below mean, n=6478 (79%); and "accelerated" BMD loss: slope≥1 SD below mean, n=1022 (12%). RH of nonspine fracture was 0.81 (0.71-0.93) and of hip fracture was 0.36 (0.25-0.53) for women in the maintained compared with the expected group. Women with accelerated bone loss were more likely to develop disability (RH=1.56; 95% CI 1.33-1.84). Mortality risks were lower in the maintained compared with the expected group (RH=0.49; 95% CI 0.42-0.58). In older women maintaining BMD up to 15 years, suggesting that bone loss is not an inevitable consequence of aging. These women experienced a lower risk of fractures, disability, and mortality.

10.2.99 Muscle power is related to tibial bone strength in older women
Ashe MC, Liu-Ambrose TY, Cooper DM, Khan KM, McKay HA
Osteoporos Int 2008;19:1725-32

In 74 community-dwelling women aged 65-75 years muscle power contributed 6.6% of the variance in the bone strength-strain index and 8.9% the variance in the section modulus in older women after accounting for age, height, weight, and physical activity. Moderate to vigorous physical activity was related to muscle power in the lower extremity (r=0.260; p=0.041).

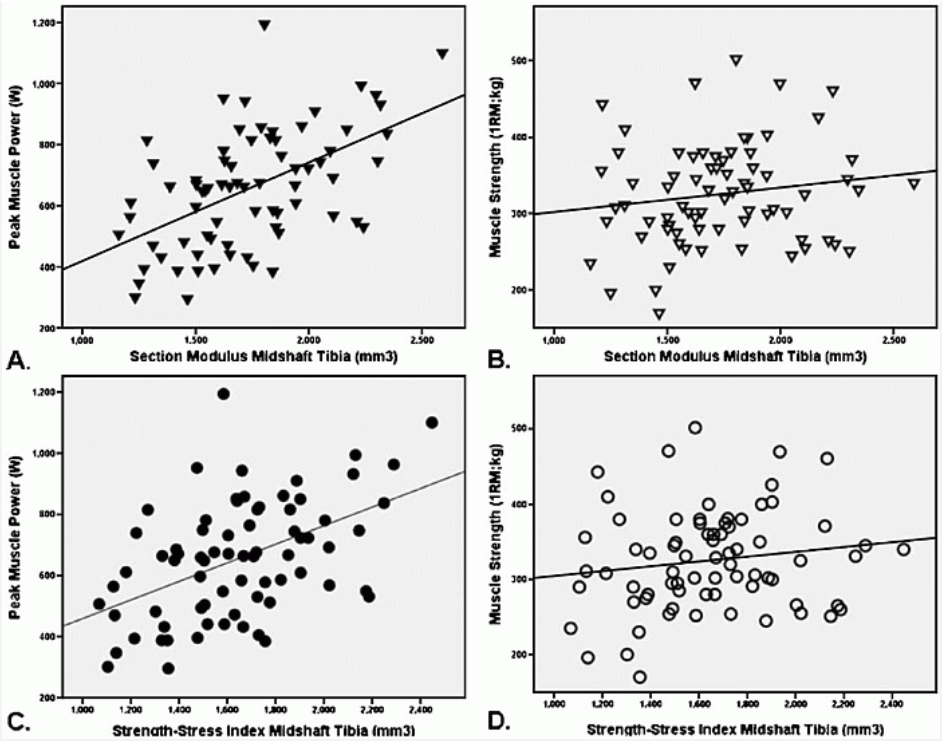

Fig. 10.2.99 Relation between muscle performance (muscle strength [one repetition maximum; 1RM] and muscle power) and bone strength measures. a, b represent muscle measures and section modulus; c, d illustrate the relation between muscle measures and the strength-stress index. The line fit is based on linear regression: a: R^2=0.279; b: R^2=0.023; c: R^2=0.238; d: R^2=0.022. Reproduced from Osteoporos Int 2008;19:1725-32 with permission from Springer.

10.2.100 Prediction of incident hip fracture risk by femur geometry variables measured by hip structural analysis in the study of osteoporotic fractures
Kaptoge S, Beck TJ, Reeve J, Stone KL, Hillier TA, Cauley JA, Cummings SR
J Bone Miner Res 2008;23:1892-904

Among 7474 women with hip DXA scans at baseline, there were 635 incident hip fractures over 13 years. Hip structural analysis software reported that cases had larger neck-shaft angles, larger subperiosteal and estimated endosteal diameters, greater distances from lateral cortical margin to center of mass (lateral distance), and higher buckling ratios. aBMD, cross-sectional area, cross-sectional moment of inertia, section modulus, estimated cortical thickness, and centroid position were lower in cases. In hip fracture prediction using NN parameters, estimated cortical thickness, aBMD, and buckling ratio were equivalent (C-index=0.72; 95% CI 0.70, 0.74), but section modulus performed less well (C-index=0.61; 95% CI 0.58, 0.63; p<0.0001). In multivariable models were interchangeable, whereas age and neck-shaft angle were independent predictors. Several parsimonious multivariable models that were prognostically equivalent for the NN region were obtained combining a measure of width, a measure of mass, age, and neck-shaft angle (BMD is a ratio of mass to width in the NN region; C-index=0.77; 95% CI 0.75, 0.79). Trochanteric fractures were best predicted by analysis of the IT region.

10.2.101 Use of DXA-based structural engineering models of the proximal femur to discriminate hip fracture
Yang L, Peel N, Clowes JA, McCloskey EV, Eastell R
J Bone Miner Res 2009;24:33-42

The hip DXA scans of 51 postmenopausal women with hip fracture (30 femoral neck, 17 trochanteric, and 4 unspecified) and 153 controls were reanalyzed using a special version of Hologic's software that produced a pixel-by-pixel BMD map. For each map, a curved-beam, a curved composite-beam, and a finite element model were generated to calculate stress within the bone when falling sideways. An index of fracture risk (IFR) was defined as the stress/yield stress at each pixel and averaged over the regions of interest. Hip structure analysis (HSA) was also performed using Hologic APEX analysis software. Hip BMD and almost all parameters derived from HSA and SEM were discriminators of hip fracture on their own but only the bone width discriminated hip fracture independently from total hip BMD. Judged by the ROC analysis, the trochanteric IFR derived from the finite element model was better than total hip BMD and similar to the total hip BMD plus bone width in discriminating all hip fracture and femoral neck fracture. No index was better than total hip BMD for discriminating trochanteric fractures.

10.2.102 Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons
Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P
J Clin Endocrinol Metab 2009;[Epub ahead of print]

In men (n=643) and women (n=676), aged 65-88 years serum 25(OH)D was <25 nmol/l in 11.5%, <50 nmol/l in 48.4%, <75 nmol/l in 82.4% and >75 nmol/l in 17.6% of the respondents. Mean serum PTH decreased gradually from 5.1 pmol/l when serum 25(OH)D <25 nmol/l to 3.1 pmol/l when serum 25(OH)D >75 nmol/l (p<0.001) without reaching a plateau. All BMD values were higher in the higher serum 25(OH)D groups, although only significantly for total hip (p=0.01), trochanter (p=0.001) and total body BMC (p=0.005). A threshold of about 40 nmol/l existed for OC and DPD/Cr, 50 nmol/l for BMD and 60 nmol/l for physical performance. Low serum 25(OH)D concentrations are common in the elderly.

10.2.103 Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women
Kuroda T, Shiraki M, Tanaka S, Ohta H
Bone 2009;44:168-72

In 1232 postmenopausal female volunteers were observed for 6.9±3.6 years (mean±SD) and a total of 107 participants (8.7%) died. Age (hazard ratio 1.73, 95% CI 1.51-1.98, P<0.01), 25-OH vitamin D level <50 nmol/l (HR 2.17, 1.27-3.72, P=0.01), prevalent malignancies (HR 5.60, 3.36-9.31, P<0.01) and osteoporosis (HR 2.14, 1.22-3.75, P=0.01) were independent risk factors for all-cause mortality.

10.2.104 Positive association between the course of vitamin D intake and bone mineral density at 36 years in men
van Dijk CE, de Boer MR, Koppes LL, Roos JC, Lips P, Twisk JW
Bone 2009;44:437-41

Vitamin D intake was assessed 3-8 times between the age of 13 and 36 years in 152 men and 168 women from the Amsterdam Growth and Health Longitudinal Study. Mean baseline vitamin D was 6.86 (SD: 2.18) µg/day for men and 4.90 (1.19) µg/day for women. Mean course of vitamin D was -0.10 (0.12) µg/day/year and -0.05 (0.18) µg/day/year for men and women, respectively. The associations between baseline vitamin D intake and BMD were significant in the total hip (0.018 g/cm^2 per -1 µg/day; 95% CI 0.001-0.035) and total body (0.015 per -1 µg/day; 0.001-0.029). The course of vitamin D intake was associated with BMD in the lumbar spine (0.50 g/cm^2 per -1 µg/day/year; 0.130-0.867), femoral neck (0.42 g/cm^2 per -1 µg/day/year; 0.10-0.743), total body (0.34 g/cm^2 per -1 µg/day/year; 0.09-0.59) and total hip (0.44 g/cm^2 per -1 µg/day/year; 0.11-0.77) in men. In men, the level of vitamin D intake in adolescence and the course of vitamin D intake from adolescence into adulthood are positively related with BMD in adulthood. In women, however, no significant associations are found.

10.2.105 Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2009;84:45-55

In 124,655 fracture cases and 373,962 age- and sex-matched controls, diabetes and all complications were associated with increased risk of fractures. The increase in risk of fractures was higher in type 1 diabetes (T1D) than in type 2 diabetes (T2D). However, after adjustment for confounders, the difference between T1D and T2D disappeared, and only diabetic kidney disease in T1D retainedincreased risk of fractures. There was a time dependency in the risk of fractures with an early increase at <2.5 years after diagnosis, followed by a decrease to the level of the background population from 2.5 to 5 years after diagnosis, and a limited increase in T1D but not T2D at >5 years after diagnosis.

10.2.106 IGF-1 and IGF-binding proteins and bone mass, geometry, and strength: Relation to metabolic control in adolescent girls with type 1 diabetes
Moyer-Mileur LJ, Slater H, Jordan KC, Murray MA
J Bone Miner Res 2008;23:1884-91

In adolescent girls 12-15 years of age with T1DM (n=11) and matched controls (n=10) serum GH, IGFBP-1 and -5, glycosylated hemoglobin (HbA(1c)), glucose, and urine magnesium levels were higher and IGF-1 were lower than controls (p<0.05). Whole body BMC/bone area (BA), femoral neck aBMD and BMAD, and tibia cortical BMC were lower in T1DM (p<0.05). Poor diabetes control predicted lower IGF-1 (r^2=0.21) and greater IGFBP-1 (r^2=0.39), IGFBP-5 (r^2=0.38), and BALP (r^2=0.41, p<0.05). Higher urine magnesium excretion predicted an overall shorter, lighter skeleton, and lower tibia cortical bone size, mineral, and density (r^2=0.44-0.75, p<0.05). In the T1DM cohort, earlier age at diagnosis was predictive of lower IGF-1, higher urine magnesium excretion, and lighter, thinner cortical bone (r^2=0.45, p<0.01).

10.2.107 Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus
Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Kurioka S, Yano S, Sugimoto T
J Clin Endocrinol Metab 2009;94:45-9

In 179 men and 149 postmenopausal women, osteocalcin negatively correlated with fasting plasma glucose and hemoglobin A(1c) in both men and postmenopausal women (P<0.05) and with percent fat, baPWV, and IMT in men (P<0.05). Osteocalcin positively correlated with total adiponectin in postmenopausal women (P<0.001). After additional adjustments for systolic blood pressure, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, hemoglobin A(1c), and Brinkmann index, osteocalcin still significantly and negatively correlated with baPWV and IMT in men. In contrast, osteocalcin did not correlate with fasting C-peptide, and bone-specific alkaline phosphatase did not correlate with any variable in either men or postmenopausal women. Serum osteocalcin is associated with glucose and total adiponectin levels, fat mass, and atherosclerosis parameters in patients with type 2 diabetes, suggesting that osteocalcin is important for not only bone metabolism but also glucose and fat metabolism.

10.2.108 Proteins, dietary acid load, and calcium and risk of postmenopausal fractures in the E3N French women prospective study
Dargent-Molina P, Sabia S, Touvier M, Kesse E, Breart G, Clavel-Chapelon F, Boutron-Ruault MC
J Bone Miner Res 2008;23:1915-22

During an average of 8.37±1.73 years of follow-up, 2408 women reported a fracture (excluding high-impact trauma) among 36,217 postmenopausal women. There was no association between fracture risk and total protein or RNAE. However, in the lowest quartile of calcium (<400 mg/1000 kcal), high protein intake was associated with a significant increased fracture risk (RR=1.51 for highest vs. lowest quartile; 95% CI 1.17-1.94). An increasing fracture risk with increasing animal protein intake was also observed (trend, p<0.0001).

10.2.109 Dynamic and structural properties of the skeleton in hypoparathyroidism
Rubin MR, Dempster DW, Zhou H, Shane E, Nickolas T, Sliney J, Silverberg SJ, Bilezikian JP
J Bone Miner Res 2008;23:2018-24

33 subjects with hypoparathyroidism and 33 controls had iliac crest bone biopsies. Cases had greater cancellous bone volume (23.5 ±8 vs. 19.7±5%, p=0.02), trabecular width (Tb.Wi: 136.1±37 vs. 119.3±21 µm, p=0.03), and cortical width (Ct.Wi: 923.4±420 vs. 753.5±246 µm, p=0.05) than controls. Mineralizing surface (MS: 0.85±1.58 vs. 4.27±3.32%, p<0.0001) and bone formation rate (BFR/BS: 0.006±0.014 vs. 0.032±0.028 µm^3/µm^2/d, p<0.0001), were suppressed.

10.2.110 Increase in vertebral fracture risk in postmenopausal women using omeprazole
Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D, Reid DM, Eastell R, Gluer CC
Calcif Tissue Int 2009;84:13-9

5% of 1211 postmenopausal women were using omeprazole. Age-adjusted rates for vertebral fractures were 1.89 and 0.60 for 100 person-years for omeprazole users and nonusers, respectively (P=0.009). Omeprazole use was a significant and independent predictor of vertebral fractures (RR=3.50, 95% CI 1.14-8.44). The other predictors were age higher than 65 years (RR=2.34, 95% CI 1.02-5.34), prevalent vertebral fractures (RR=3.62, 95% CI 1.63-8.08), and lumbar spine T-score≤–2.5 (RR=2.38, 95% CI 1.03-5.49).

10.2.111 Vitamin A and retinol intakes and the risk of fractures among participants of the Women's Health Initiative Observational Study
Caire-Juvera G, Ritenbaugh C, Wactawski-Wende J, Snetselaar LG, Chen Z
Am J Clin Nutr 2009;89:323-30

A total of 75,747 women from the Women's Health Initiative Observational Study participated. In the analysis adjusted for some covariates the association between vitamin A intake and the risk of fracture was not statistically significant. Analyses for retinol showed similar trends.

10.2.112 Poverty is a risk factor for osteoporotic fractures
Navarro MC, Sosa M, Saavedra P, Lainez P, Marrero M, Torres M, Medina CD
Osteoporos Int 2009;20:393-8

Compared to women with a medium and high socioeconomic status (n=665), those who were classified into poverty (annual family income lower than 6,346.80 Euros, in a one-member family, n=474), were older and heavier and had lower height, lower prevalence of tobacco and alcohol consumption, lower use of HRT and higher use of thiazides. After correcting for age and BMI, women in poverty had lower spine BMD values than women with a medium and high socioeconomic status (0.840 g/cm^2 vs. 0.867 g/cm^2, p=0.005), but there were no statistical differences in femoral neck BMD between groups. The prevalence of osteoporosis was also higher in women in poverty [40.6% vs. 35.6%, (OR 1.35l; 95% CI 1.03, 1.76)] after adjusting by age and BMI. Moreover, 37.8% of women in poverty had a history of at least one fragility fracture compared to 27.7% of women not in poverty (OR: 1.45; 95% CI 1.11, 1.90). The prevalence of vertebral fractures was also higher in women in poverty 24.7% vs. 13.4%, (OR 2.01; 95% CI 1.44, 2.81).

10.2.113 Recovery of muscle atrophy and bone loss from 90 days bed rest: Results from a one-year follow-up
Rittweger J, Felsenberg D
Bone 2009;44:214-24

25 men (mean age 32 years, SD 4.2) were randomly assigned to bed rest (Ctrl), resistive flywheel exercise (FW), or 60 mg. i. v pamidronate prior to bed rest (Pam). In Pam and FW, diaphyseal bone losses recovered at a 180-day follow-up with a small surplus after one year. Epiphyseal bone losses were largely recovered after one year. Recovery of calf muscle cross-section and resumption of impact sport activities seemed to precede bone recovery, and bone accrual was closely matching the prior losses on an individual basis.

10.2.114 Reduction in proximal femoral strength due to long-duration spaceflight
Keyak JH, Koyama AK, Leblanc A, Lu Y, Lang TF
Bone 2009;44:449-53

Pre-and post-flight CT scan-based patient-specific finite element models of the left proximal femur of 13 astronauts who spent 4.3 to 6.5 months on the International Space Station were generated. Loading conditions representing single-limb stance and a fall onto the posterolateral aspect of the greater trochanter were modelled, and proximal femoral strength (F(FE)) was computed. Mean F(FE) decreased from 18.2 times body weight (BW) pre-flight to 15.6 BW postflight for stance loading and from 3.5 BW preflight to 3.1 BW postflight for fall loading. When normalized for flight duration, F(FE) under stance and fall loading decreased at mean rates of 2.6% (0.6% to 5.0%) per month and 2.0% (0.6% to 3.9%) per month, respectively. These values are greater than reported reductions in femoral BMD (0.4 to 1.8% per month). In some subjects, the magnitudes of the reductions in proximal femoral strength were comparable to estimated lifetime losses associated with aging.

10.2.115 Hyperhomocysteinemia induces a tissue specific accumulation of homocysteine in bone by collagen binding and adversely affects bone
Herrmann M, Tami A, Wildemann B, Wolny M, Wagner A, Schorr H, Taban-Shomal O, Umanskaya N, Ross S, Garcia P, Hubner U, Herrmann W
Bone 2009;44:467-75

Hyperhomocysteinemia (HHCY) has been suggested to have adverse effects on bone. This study investigated if HHCY in rats induces an accumulation of homocysteine (HCY) in bone tissue that is accompanied by bone loss and reduced bone strength. HHCY was induced in healthy rats by either a methionine (Meth)- or a homocystine (Homo)-enriched diet. Homocystine is the product of two disulfide linked HCY molecules. Tissue and plasma concentrations of HCY, S-adenosylhomocysteine (SAH) and S-adenosylmethionine (SAM) were measured. Meth and Homo animals developed HHCY accompanied by a tissue specific accumulation of HCY (1300 to 2000% vs. controls). 65% of HCY in bone was bound to collagen of the extracellular matrix. The SAH / SAM-ratio in bone and plasma of Meth and Homo animals exhibited a tissue specific increase indicating a reduced methylation capacity. Accumulation of HCY in bone was characterized by a reduction of cancellous bone (proximal femur: -25 to -35%; distal femur -56 to -58%, proximal tibia: -28 to -43%). Bone strength was reduced (-9 to -12%). A tissue specific accumulation of HCY in bone may explain adverse effects of HHCY on bone.

10.2.116 Impaired energetic metabolism after central leptin signaling leads to massive appendicular bone loss in hindlimb-suspended rats
Martin A, David V, Vico L, Thomas T
J Bone Miner Res 2008;23:2040-7

Female rats were hindlimb unloaded or not and treated with intracerebroventricular infusion of leptin which reduced food

intake, weight, abdominal fat, and lean mass. Leptin infusion inhibited bone elongation and blunted cortical thickening at the femoral diaphysis site. Interestingly, leptin effects were site dependent in the cancellous bone envelopes because tibia metaphysis BMD was lower and lumbar spine BMD was higher under intracerebroventricular leptin. Treated groups showed reduced bone remodeling independently of hindlimb unloading. Therefore, the intracerebroventricular leptin-induced bone loss could be largely related to the alteration of energetic and metabolic status.

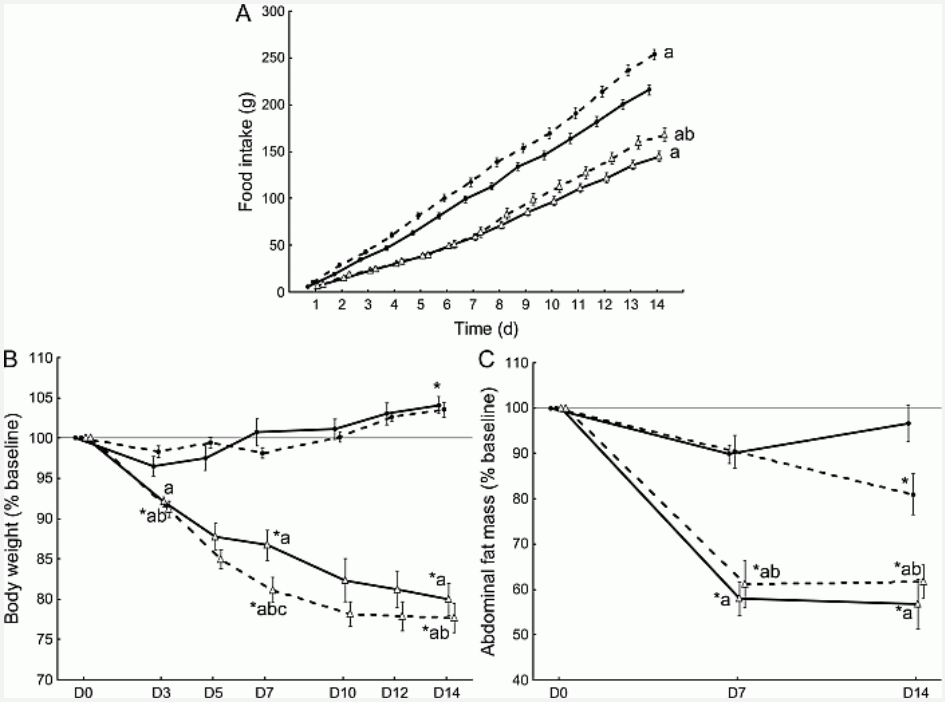

*Fig. 10.2.116a Evolution of cumulative food intake (A), body weight (B), and abdominal fat mass (C) over a 2-wk period in hindlimb-suspended (doted lines) or nonsuspended (solid lines) female rats, treated with 10 μg/kg/d of intracerebroventricular murine leptin (△) or vehicle (●). Values are mean±SE of 10 female rats per group. Comparisons were performed using one-way and repeated-measures ANOVA and posthoc Scheffe test. For reading convenience, significant differences are given only at D3, D7, and/or D14. p<0.05 vs. *D0 or baseline, [a]nonsuspended vehicle, [b]suspended vehicle, or [c]nonsuspended leptin. Reproduced from J Bone Miner Res 2008;23:2040-7 with permission of the American Society of Bone and Mineral Research.*

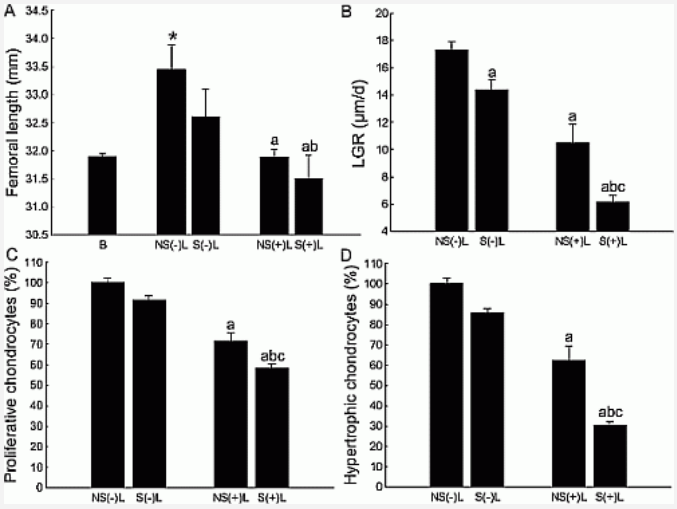

*Fig. 10.2.116b Effect of intracerebroventricular leptin treatment at 10 μg/kg/d [(+)L] or vehicle [(−)L] on (A) bone length, (B) longitudinal growth rate (LGR), (C) proliferative, and (D) hypertrophic chondrocytes over 14 days in hindlimb-suspended (S) or nonsuspended (NS) female rats. Values are mean±SE of five female rats per group. Comparisons were performed using one-way ANOVA and posthoc Scheffe test. p<0.05 vs. *baseline, [a]nonsuspended vehicle, [b]suspended vehicle, or [c]nonsuspended leptin. Reproduced from J Bone Miner Res 2008;23:2040-7 with permission of the American Society of Bone and Mineral Research.*

10.2.117 Differential mRNA expression profiles in proximal tibia of aged rats in response to ovariectomy and low-Ca diet
Zhang Y, Dong XL, Leung PC, Wong MS
Bone 2009;44:46-52

Both ovariectomized animals and animals fed with Ca-depleted diets. Ovariectomy increased serum N-telopeptides of bone type I collagen (NTx) levels in aged rats fed with HCD (P<0.05). In addition, ovariectomy reduced BMD and predicted bone strength of tibial proximal metaphysis in aged rats fed with either LCD or HCD. Dietary Ca deficiency did not alter serum bone-specific alkaline phosphatase (BAP) or NTx levels, but induced a loss of BMD at tibia proximal metaphysis in aged rats. Ovariectomy promoted the mRNA expression of α1 type I collagen (COL), OPG and RANKL; and inhibited the mRNA expression of cathepsin K and MMP-9 in the proximal tibia of aged rats. Low-Ca diet upregulated the mRNA expression of COL, Cbfa1, OPG and carbonic anhydrase II (CAII) in proximal tibia of aged rats. The genomic responses of bone in proximal tibia to ovariectomy and dietary Ca deficiency were different. The bone loss induced by ovariectomy appears to be mediated primarily by an increase in RANKL mRNA expression; whereas the induction by dietary Ca restriction might be mediated by the induction of CAII expression.

10.2.118 Vitamin D-independent therapeutic effects of extracellular calcium in a mouse model of adult-onset secondary hyperparathyroidism
Weber K, Bergow C, Hirmer S, Schuler C, Erben RG
J Bone Miner Res 2009;24:22-32

Correction of extracellular calcium in secondary hyperparathyroidism (sHPT) was assessed in mice with a nonfunctioning vitamin D receptor (VDR). Wildtype and homozygous VDR mutant mice were kept on a 2% calcium (Ca), 1.25% phosphorus (P), and 20% lactose until they were 4 mo or 1 yr of age. 4-mo-old mice were switched to a challenge diet (CD) containing 0.5% Ca, 0.4% P, and 0% lactose. After 2 mo on the CD, groups of VDR mutant mice were either fed CD, a normal mouse chow with 0.9% Ca, 0.7% P, and 0% lactose, or the RD for another 3 mo. Feeding the RD protected VDR mutants against sHPT over 1 yr, showing that vitamin D is not essential for the function of parathyroid cells. When 4-mo-old VDR mutants were switched to the CD for 2 mo, they developed severe sHPT associated with hypertrophy and hyperplasia of parathyroids and bone loss. Subsequent feeding of the RD during a 3-mo therapy phase fully corrected sHPT, reduced chief cell proliferation, and reduced maximum parathyroid gland area by 25% by cell atrophy. There was no evidence of RD-induced chief cell apoptosis. Signaling by the calcium-sensing receptor regulates chief cell function and size in the absence of VDR.

10.2.119 Reduced COX-2 expression in aged mice is associated with impaired fracture healing
Naik AA, Xie C, Zuscik MJ, Kingsley P, Schwarz EM, Awad H, Guldberg R, Drissi H, Puzas JE, Boyce B, Zhang X, O'Keefe RJ
J Bone Miner Res 2009;24:251-64

Cyclooxygenase 2 (COX-2), the inducible regulator of prostaglandin E2 (PGE2) synthesis, is critical for bone repair. A femoral fracture repair model was used in mice at either 7-9 or 52-56 weeks of age, and healing evaluated. Aging was associated with a decreased rate of chondrogenesis, decreased bone formation, reduced callus vascularization, delayed remodelling, and altered expression of genes involved in repair and remodelling. COX-2 expression in young mice peaked at 5 days, coinciding with the transition of mesenchymal progenitors to cartilage and the onset of expression of early cartilage markers. COX-2 is expressed primarily in early cartilage precursors that coexpress col-2 and expression was reduced by 75% and 65% in fractures from aged mice compared with young mice on days 5 and 7, respectively. Local administration of an EP4 agonist to the fracture repair site in aged mice enhanced the rate of chondrogenesis and bone formation to levels in young mice, suggesting that the expression of COX-2 during the early inflammatory phase of repair regulates critical subsequent events including chondrogenesis, bone formation, and remodelling. COX-2/EP4 agonists may compensate for deficient molecular signals that result in the reduced fracture healing associated with aging.

10.2.120 Bone mass and microarchitecture of irradiated and bone marrow-transplanted mice: Influences of the donor strain
Dumas A, Brigitte M, Moreau MF, Chretien F, Basle MF, Chappard D
Osteoporos Int 2009;20:435-43

Osteoporosis complicates of bone marrow transplants (BMT). The influence of total body irradiation (TBI) is unknown. Eighteen C57Bl/6 (B6) mice receiving lethal TBI had a BMT with marrow cells from green fluorescent protein-transgenic-C57Bl/6 (GFP) mice. Transplanted (T(GFP)B6), B6, and GFP mice were euthanized after BMT. T(GFP)B6 presented a dramatic bone loss compared with B6 and did not restore their trabecular bone mass over time, despite a cortical thickening 6 months after BMT. GFP mice have less trabeculae, thicker cortices, but a narrower femoral shaft than B6 mice. From 3 months after BMT, cortical characteristics of T(GFP)B6 mice differed statistically from B6 mice and were identical to those of GFP mice. GFP (+) cells were located along trabecular surfaces and in periosteal and endosteal envelopes, but none of the osteocytes expressed GFP. Engrafted cells did not restore the irradiation-induced trabecular bone loss, but reconstituted a marrow microenvironment and bone remodeling similar to those of the donor.

10.2.121 Weight and body mass index predict bone mineral density and fractures in women aged 40 to 59 years
Morin S, Tsang JF, Leslie WD
Osteoporos Int 2009;20:363-70

10.2.122 Dietary Reference Intakes for vitamin D: justification for a review of the 1997 values
Yetley EA, Brule D, Cheney MC, Davis CD, Esslinger KA, Fischer PW, Friedl KE, Greene-Finestone LS, Guenther PM, Klurfeld DM, L'Abbe M R, McMurry KY, Starke-Reed PE, Trumbo PR
Am J Clin Nutr 2009;89:719-27

10.2.123 Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: An ecologic meta-regression analysis
Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, Vestergaard P
Osteoporos Int 2009;20:133-40

10.2.124 Development of a tool for the assessment of calcium and vitamin D intakes in clinical settings
Severo M, Lopes C, Lucas R, Barros H
Osteoporos Int 2009;20:231-7

10.2.125 Activation of the calcium sensing receptor stimulates gastrin and gastric acid secretion in healthy participants
Ceglia L, Harris SS, Rasmussen HM, Dawson-Hughes B
Osteoporos Int 2009;20:71-8

10.2.126 Alkaline mineral water lowers bone resorption even in calcium sufficiency: Alkaline mineral water and bone metabolism
Wynn E, Krieg MA, Aeschlimann JM, Burckhardt P
Bone 2009;44:120-4

10.2.127 Role of iron metabolism and oxidative damage in postmenopausal bone loss
D'Amelio P, Cristofaro MA, Tamone C, Morra E, Di Bella S, Isaia G, Grimaldi A, Gennero L, Gariboldi A, Ponzetto A, Pescarmona

GP, Isaia GC
Bone 2008;43:1010-5

10.2.128 The effects of high potassium consumption on bone mineral density in a prospective cohort study of elderly postmenopausal women
Zhu K, Devine A, Prince RL
Osteoporos Int 2009;20:335-40

10.2.129 Inverse association of carotenoid intakes with 4-y change in bone mineral density in elderly men and women: The Framingham Osteoporosis Study
Sahni S, Hannan MT, Blumberg J, Cupples LA, Kiel DP, Tucker KL
Am J Clin Nutr 2009;89:416-24

10.2.130 Hypertension is a risk factor for fractures
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2009;84:103-11

10.2.131 Association between serum cholesterol and bone mineral density
Makovey J, Chen JS, Hayward C, Williams FM, Sambrook PN
Bone 2009;44:208-13

10.2.132 Changes in soft tissue composition are the primary predictors of 4-year bone mineral density changes in postmenopausal women
Milliken LA, Cussler E, Zeller RA, Choi JE, Metcalfe L, Going SB, Lohman TG
Osteoporos Int 2009;20:347-54

10.2.133 Factors influencing changes in bone mineral density in patients with anorexia nervosa-related osteoporosis: The effect of hormone replacement therapy
Legroux-Gerot I, Vignau J, Collier F, Cortet B
Calcif Tissue Int 2008;83:315-23

10.2.134 Body composition, volumetric and areal bone parameters in male-to-female transsexual persons
Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman JM, T'Sjoen G G
Bone 2008;43:1016-21

10.2.135 Diabetes causes the accelerated loss of cartilage during fracture repair which is reversed by insulin treatment
Kayal RA, Alblowi J, McKenzie E, Krothapalli N, Silkman L, Gerstenfeld L, Einhorn TA, Graves DT
Bone 2009;44:357-63

10.2.136 Combination of obesity with hyperglycemia is a risk factor for the presence of vertebral fractures in type 2 diabetic men
Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Yano S, Sugimoto T
Calcif Tissue Int 2008;83:324-31

10.2.137 Osteoporotic fractures and hospitalization risk in chronic spinal cord injury
Morse LR, Battaglino RA, Stolzmann KL, Hallett LD, Waddimba A, Gagnon D, Lazzari AA, Garshick E
Osteoporos Int 2009;20:385-92

10.2.138 Bone density and fragility fractures in patients with developmental disabilities
Leslie WD, Pahlavan PS, Roe EB, Dittberner K
Osteoporos Int 2009;20:379-83

10.2.139 Bone resorption in stroke and institutionalized subjects
Haddaway MJ, Bainbridge NJ, Powell DE, Davie MW
Calcif Tissue Int 2009;84:118-25

10.2.140 Low bone mass is associated with carotid atherosclerosis in postmenopausal women: The Japanese Population-based Osteoporosis (JPOS) cohort study
Tamaki J, Iki M, Hirano Y, Sato Y, Kajita E, Kagamimori S, Kagawa Y, Yoneshima H
Osteoporos Int 2009;20:53-60

10.2.141 Physical activity and dietary calcium interactions in bone mass in Scottish postmenopausal women
Mavroeidi A, Stewart AD, Reid DM, Macdonald HM
Osteoporos Int 2009;20:409-16

10.2.142 Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women
Hiligsmann M, Bruyere O, Ethgen O, Gathon HJ, Reginster JY
Bone 2008;43:991-4

10.2.143 Assessment of clinical risk factors to validate the probability of osteoporosis and subsequent fractures in Korean women
Kim YM, Hyun NR, Shon HS, Kim HS, Park SY, Park IH, Chung YS, Jung HG, Kim DH, Lim SK
Calcif Tissue Int 2008;83:380-7

10.2.144 Change in bone mineral density and its determinants in pre- and perimenopausal Chinese women: The Hong Kong Perimenopausal Women Osteoporosis Study
Ho SC, Chan SG, Yip YB, Chan CS, Woo JL, Sham A
Osteoporos Int 2008;19:1785-96

10.2.145 Relationship between vitamin D status, body composition and physical exercise of adolescent girls in Beijing
Foo LH, Zhang Q, Zhu K, Ma G, Trube A, Greenfield H, Fraser DR
Osteoporos Int 2009;20:417-25

10.2.146 Clinical risk factors for osteoporotic fractures in Brazilian women and men: The Brazilian Osteoporosis Study (BRAZOS)
Pinheiro MM, Ciconelli RM, Martini LA, Ferraz MB
Osteoporos Int 2009;20:399-408

10.2.147 High bone density in young Hutterite children
Wey CL, Beare T, Biskeborn K, Binkley T, Arneson L, Specker B
Bone 2009;44:454-60

10.2.148 Pregnancy outcome following in utero exposure to bisphosphonates
Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, Moretti M, Koren G, Ito S
Bone 2009;44:428-30

10.2.149 Vitamin D deficiency in patients with active systemic lupus erythematosus
Borba VZ, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M
Osteoporos Int 2009;20:427-33

10.2.150 Well-nourished cystic fibrosis patients have normal mineral density, but reduced cortical thickness at the forearm
Louis O, Clerinx P, Gies I, De Wachter E, De Schepper J
Osteoporos Int 2009;20:309-14

10.2.151 Lithium's effect on bone mineral density
Zamani A, Omrani GR, Nasab MM
Bone 2009;44:331-4

10.2.152 Myostatin (GDF-8) deficiency increases fracture callus size, Sox-5 expression, and callus bone volume
Kellum E, Starr H, Arounleut P, Immel D, Fulzele S, Wenger K, Hamrick MW
Bone 2009;44:17-23

10.2.153 Ethanol impairs estrogen receptor signaling resulting in accelerated activation of senescence pathways, whereas estradiol attenuates the effects of ethanol in osteoblasts
Chen J-R, Lazarenko OP, Haley RL, Blackburn ML, Badger TM, Ronis MJ
J Bone Miner Res 2009;24:221-30

10.2.154 Metabolic acidosis increases intracellular calcium in bone cells through activation of the proton receptor OGR1
Frick KK, Krieger NS, Nehrke K, Bushinsky DA
J Bone Miner Res 2009;24:305-13

10.2.155 Diaminobutane (DAB) dendrimers are potent binders of oral phosphate
Williams KB, Barycka K, Zella JB, Deluca HF
J Bone Miner Res 2009;24:97-101

10.2.156 Skeletal unloading induces a full-thickness patellar cartilage defect with increase of urinary collagen II CTx degradation marker in growing rats
Tomiya M, Fujikawa K, Ichimura S, Kikuchi T, Yoshihara Y, Nemoto K
Bone 2009;44:295-305

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 2, 2009

Corticosteroid Therapy

10.2.157 A novel semisynthesized small molecule icaritin reduces incidence of steroid-associated osteonecrosis with inhibition of both thrombosis and lipid-deposition in a dose-dependent manner

Zhang G, Qin L, Sheng H, Wang XL, Wang YX, Yeung DK, Griffith JF, Yao XS, Xie XH, Li ZR, Lee KM, Leung KS

Bone 2009;44:345-56

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 2, 2009

Treatment

10.2.158 Effectiveness of antiresorptives for the prevention of nonvertebral low-trauma fractures in a population-based cohort of women
Langsetmo LA, Morin S, Richards JB, Davison KS, Olszynski WP, Prior JC, Josse R, Goltzman D
Osteoporos Int 2009;20:283-90

In a retrospective nested case-control study (density-based sampling) within the Canadian Multicentre Osteoporosis Study, 5979 women (453 cases, 1304 controls), current use of antiresorptives was associated with a lower risk of fracture (OR=0.68, 95% CI 0.52-0.91). Subgroup analysis yielded OR=0.61, 95% CI 0.42-0.89 for ages 50-74; OR=0.76, 95% CI 0.50-1.17 for ages 75 +; OR=0.58, 95% CI 0.40-0.83 for those with a major risk factor; and OR=0.92; 95% CI 0.59-1.42 for those without a major risk factor. Major risk factors were prevalent low-trauma fracture, vertebral deformity (grade 2+), and BMD T-score≤–2.5.

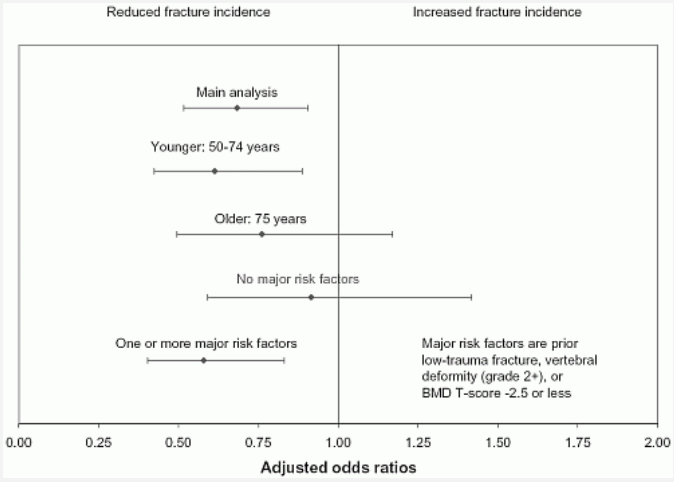

Fig. 10.2.158a Association between antiresorptive use and low trauma nonvertebral fracture analyzed according to age and risk subgroups. Reproduced from Osteoporos Int 2009;20:283-90 with permission from Springer.

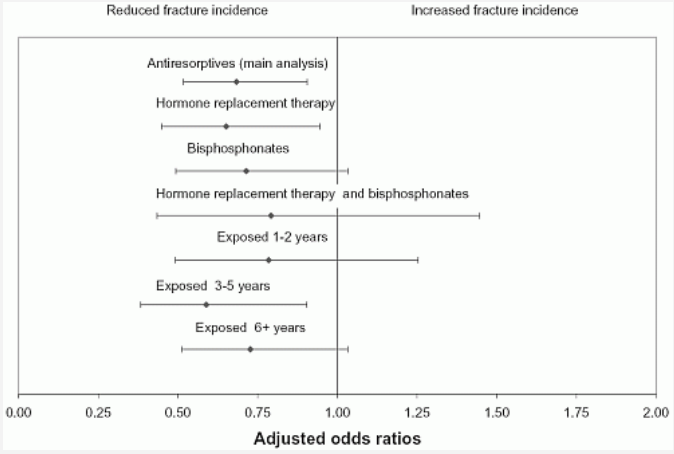

Fig. 10.2.158b Association between antiresorptive use and low trauma nonvertebral fracture analyzed according to type and duration. Reproduced from Osteoporos Int 2009;20:283-90 with permission from Springer.

10.2.159 Effectiveness of bisphosphonate therapy in a community setting
Feldstein AC, Weycker D, Nichols GA, Oster G, Rosales G, Boardman DL, Perrin N
Bone 2009;44:153-9

This retrospective cohort study compared time to clinical fracture in at-risk community women who initiated a bisphosphonate to those who did not. The study was conducted in an HMO in Oregon and Washington. 1829 subjectes were matched to 3658 controls. The treated group had more women with T-scores of ≤–2.5 (67.3% vs. 54.7%) and a lower mean weight (146.6 lb vs. 151.8 lb). Only about 45% of treated patients had a bisphosphonate medication possession ratio (MPR) of ≥0.80. During follow-up, 198 (10.8%) of patients in the treated group had incident fractures vs. 179 (9.8%) of patients in the comparison group. After adjustments, patients in the treated group were 0.91 (95% CI 0.74-1.13) as likely to have an incident fracture as the comparison patients (p=0.388). The treatment effect remained nonsignificant after accounting for MPR.

10.2.160 Outcomes after switching from one bisphosphonate to another in 146 patients at a single university hospital
Ideguchi H, Ohno S, Takase K, Ueda A, Ishigatsubo Y
Osteoporos Int 2008;19:1777-83

Among the 497 patients who discontinued bisphosphonate, 146 were switched to a second bisphosphonate. The cumulative probabilities of persistence after 3 years were 45% with the first bisphosphonate and 65% with the second (P=0.017). Age ≥65 years, switching bisphosphonates because of AEs, and male gender were associated (P<0.05) with low persistence of treatment with the second bisphosphonate. Discontinuation of the first drug because of AEs was associated with an increased rate of discontinuation of the second drug because of AEs (HR, 4.2; 95% CI 2.1-8.4).

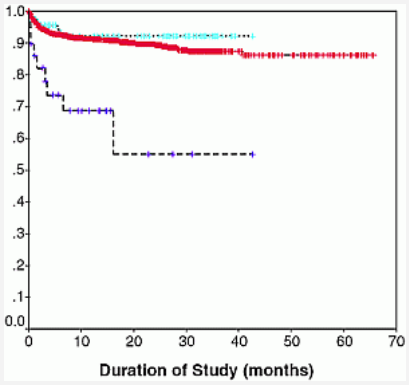

Fig. 10.2.160 Discontinuation of bisphosphonate therapy because of adverse events (AEs). Continuation rates shown are those for the first bisphosphonate (solid line); for the second drug in patients who stopped their first drug because of AEs (dashed line); and for the second drug in patients who stopped their first drug for reasons other than AEs (dotted line). Reproduced from Osteoporos Int 2008;19:1777-83 with permission from Springer.

10.2.161 Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients
Walter C, Al-Nawas B, du Bois A, Buch L, Harter P, Grotz KA
Cancer 2009;[Epub ahead of print]

117 patients with breast cancer fulfilled the inclusion criteria, and data for 75 still living patients were included. Of these 75, 4 patients developed a BP-ONJ, resulting in a prevalence of 5.3%: 3 patients received zoledronate only; 1 patient had first pamidronate followed by zoledronate and ibandronate. A tooth extraction could be identified as an additional trigger factor for 2 patients. With a prevalence of 5.3%, BP-ONJ in breast cancer patients has become a relevant disease that should be discussed with patients for whom bisphosphonates have been recommended.

10.2.162 The antiresorptive effects of a single dose of zoledronate persist for two years: A randomized, placebo-controlled trial in osteopenic postmenopausal women
Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR
J Clin Endocrinol Metab 2009;94:538-44

50 postmenopausal women with osteopenia received 5 mg zoledronate. Compared with placebo, zoledronate decreased markers of bone turnover by at least 38% (range 38-45%) for the duration of the study (P<0.0001 for each marker). After 2 yr, BMD was higher in the zoledronate group than the placebo group by an average of 5.7% (95% CI = 4.0-7.4) at the lumbar spine, 3.9% (2.2-5.7) at the proximal femur, and 1.7% (0.8-2.5) at the total body (P<0.0001 for each skeletal site). Between-groups differences in markers of bone turnover and BMD were similar at 12 and 24 months. Mild secondary hyperparathyroidism was present throughout the study in the zoledronate group. The antiresorptive effects of a single 5 mg dose of zoledronate are sustained for at least 2 yr. The magnitudes of the effects on markers of bone turnover and bone mineral density are comparable at 12 and 24 months.

10.2.163 The effect of a single infusion of zoledronic acid on early implant migration in total hip arthroplasty: A randomized, double-blind, controlled trial
Friedl G, Radl R, Stihsen C, Rehak P, Aigner R, Windhager R
J Bone Joint Surg Am 2009;91:274-81

50 patients were consecutively enrolled to receive either zoledronic acid or saline solution after cementless total hip arthroplasty. Subsidence of the stem of up to a mean (and standard deviation) of -1.2±0.6 mm at two years within the control group, and the cups had a mean medialization of 0.6±1.0 mm and a mean cranialization of 0.6±0.8 mm (p<0.001). Treatment with zoledronic acid minimized the migration of the cups in both the transverse and the vertical direction (mean, 0.15±0.6 mm and 0.06±0.6 mm, respectively; p<0.05), while only a trend to decreased subsidence of the stem was detected. The Harris hip score rapidly increased over time in both treatment groups, although this increase was more pronounced in the zoledronate-treated group than in the control group (analysis of variance, p=0.008).

10.2.164 Inhibition of bone resorption and growth of breast cancer in the bone microenvironment
Buijs JT, Que I, Lowik CW, Papapoulos SE, van der Pluijm G
Bone 2009;44:380-6

OPG and zoledronic acid (ZOL) on progression of MDA-231-B/Luc+ breast cancer cells in the bone microenvironment inhibited the development of osteolytic lesions and preserved trabeculae and prevented bone destruction. No TRAcP-positive osteoclasts were observed in tibiae preparations of animals treated with Fc-OPG, TRAcP-positive osteoclasts were still present in the animals treated with ZOL. Intrabone tumor burden was reduced with ZOL and Fc-OPG. Although there appeared to be a trend for less overall total tumor burden upon treatment with both compounds, this was not significant. Collectively, antiresorptive agents with different mechanisms of action – ZOL and OPG – reduced cancer-induced osteolysis and intraosseous tumor burden but failed to restrain local tumor growth. However, interference with the bone microenvironmental growth support could still be of therapeutic relevance when given to patients early in the course of bone metastatic disease.

10.2.165 Effect of combined local treatment with zoledronic acid and basic fibroblast growth factor on implant fixation in ovariectomized rats

Gao Y, Luo E, Hu J, Xue J, Zhu S, Li J
Bone 2009;44:225-32

40 OVX rats underwent bilateral tibiae implantation using hydroxyapatite (HA)-coated titanium implant. Bone area and contact, determined by histomorphometric analysis, were 2.7-fold and 1.8-fold in the ZOL-treated implants, 1.9-fold and 1.8-fold in the bFGF-treated implants, 3.6-fold and 2.3-fold in the both-treated implants compared with controls ($p<0.01$). Such significant effects were further confirmed by microstructure parameters, the bone volume ratio and the percentage osteointegration were increased by ZOL (3.0-fold and 1.8-fold), bFGF (1.2-fold and 1.9-fold) and ZOL+bFGF (3.3-fold and 2.7-fold) ($p<0.001$). In addition, push-out test showed that the maximum force and the corresponding interfacial shear strength of the implants treated by ZOL, bFGF and ZOL+bFGF was 8.4-fold and 8.6-fold, 3.8-fold and 3.7-fold, 10.8-fold and 10.7-fold of the control levels, respectively ($p<0.05$). The combined treatment was better than either treatment alone for force, but was not different from ZOL alone for interfacial strength.

10.2.166 Zoledronate reverses mandibular bone loss in osteoprotegerin-deficient mice
Sheng ZF, Xu K, Ma YL, Liu JH, Dai RC, Zhang YH, Jiang YB, Liao EY
Osteoporos Int 2009;20:151-9

Twenty-eight 6-week-old female mice (C57BL/6J), including OPG-/- (n=21) and wildtype (WT) (n=7) mice, were assigned to four groups after 2 weeks of acclimatization to local vivarium conditions: wild mice with vehicle (WT group); OPG-/- mice with vehicle (OPG-/- group); and OPG-/- mice that were subcutaneously injected with either 50 or 150 μg/kg zoledronate (Zol-50 and Zol-150 groups, respectively). Serum bone specific alkaline phosphatase (B-ALP) and tartrate resistant acid phosphatase 5b (TRACP-5b) were decreased in WT mice as compared to the levels in the OPG-/- mice ($P<0.05$). Zoledronate decreased the high serum B-ALP activity observed in OPG-/- mice to the levels seen in WT mice, while serum TRACP-5b concentrations were decreased to levels even lower than those in WT mice. Mandibular bone loss was less affected by OPG gene deprivation than the proximal tibia was. Both zoledronate groups showed greater BMD, trabecular BV/TV, Tb.Th, Tb.N, and Conn.D and a decrease in Tb.Sp and SMI as compared to the findings in OPG-/- mice ($P<0.05$). However, higher apparent BMD and more compact plate-like trabeculae were observed in the mandible after treatment with zoledronate as compared to the findings in the proximal tibia. Zoledronate reverses bone loss in mice mandibles induced by OPG gene deficiency.

10.2.167 Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomized, blinded, phase 3 trial
Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, Hadji P, Hofbauer LC, Alvaro-Gracia JM, Wang H, Austin M, Wagman RB, Newmark R, Libanati C, San Martin J, Bone HG
J Bone Miner Res 2009;24:153-61

1189 postmenopausal women with a T-score≤−2.0 at the lumbar spine or total hip were randomized to subcutaneous denosumab (60 mg every 6 mo [Q6M]) plus oral placebo weekly (n=594) or oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M (n=595). At the total hip, denosumab significantly increased BMD compared with alendronate at month 12 (3.5% versus 2.6%; $p<0.0001$). Furthermore, greater increases in BMD were observed with denosumab at all sites (12-mo treatment difference: 0.6%, femoral neck; 1.0%, trochanter; 1.1%, lumbar spine; 0.6%, one-third radius; $p\leq0.0002$ all sites). Denosumab led to greater reduction of turnover markers compared with alendronate. Adverse events and laboratory values were similar for denosumab- and alendronate-treated subjects.

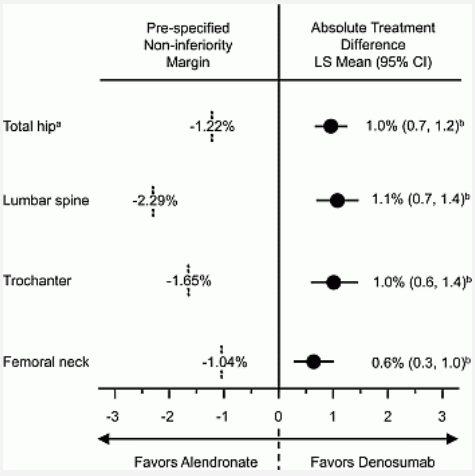

Fig. 10.2.167a Prespecified noninferiority margins for the total hip, femoral neck, trochanter, and lumbar spine are indicated on the left. The one-third radius was tested for superiority only; thus, a noninferiority margin was not prespecified for this skeletal site. The least squares mean (95% CI) treatment difference between the denosumab and alendronate groups are shown on the right; treatment differences were rounded to one decimal place; ([a]primary hypothesis; [b]significantly different from alendronate, p≤0.0001). Reproduced from J Bone Miner Res 2009;24:153-61 with permission of the American Society of Bone and Mineral Research.

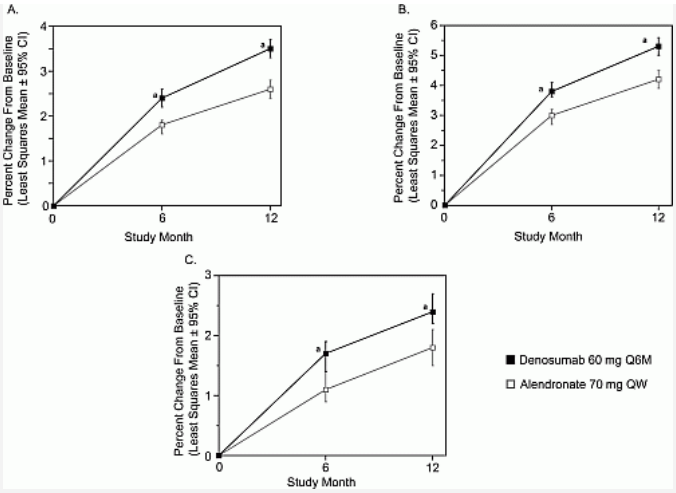

Fig. 10.2.167b Least squares mean (95% CI) percent change from baseline at months 6 and 12 in BMD at the (A) total hip, (B) lumbar spine, and (C) femoral neck in denosumab and alendronate groups (ᵃsignificantly different from alendronate, p≤0.0014). Reproduced from J Bone Miner Res 2009;24:153-61 with permission of the American Society of Bone and Mineral Research.

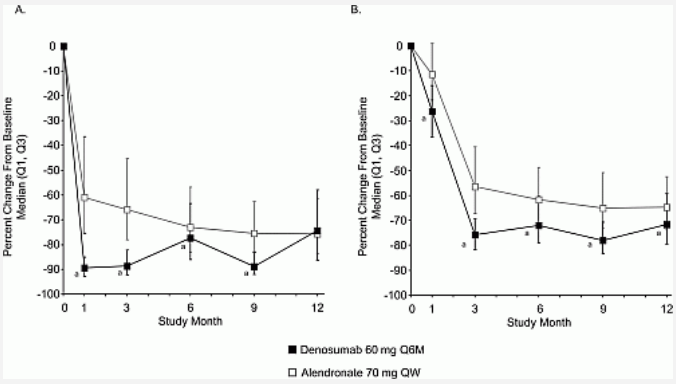

Fig. 10.2.167c Median (Q1, Q3) percent change from baseline in the bone turnover markers (A) sCTX1 and (B) P1NP through month 12 (ᵃsignificantly different from alendronate, p≤0.0001). Reproduced from J Bone Miner Res 2009;24:153-61 with permission of the American Society of Bone and Mineral Research.

10.2.168 Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis
Lewiecki EM, Keaveny TM, Kopperdahl DL, Genant HK, Engelke K, Fuerst T, Kivitz A, Davies RY, Fitzpatrick LA
J Clin Endocrinol Metab 2009;94:171-80

This randomized, double-blind, placebo-controlled study evaluated effects of once-monthly oral ibandronate in women aged 55-80 yr with BMD T-scores -2.0 or less to -5.0 or greater (n=93). 150 mg/month (n=47) or placebo (n=46) was administered for 12 months. Ibandronate increased integral total hip QCT BMD and DXA areal BMD more than placebo at 12 months (treatment differences: 2.2%, P=0.005; 2.0%, P=0.003). FEA-derived hip strength to density ratio and femoral, peripheral, and trabecular strength increased with ibandronate vs. placebo (treatment differences: 4.1%, P<0.001; 5.9%, P<0.001; 2.5%, P=0.011; 3.5%, P=0.003, respectively). Ibandronate improved vertebral, peripheral, and trabecular strength and anteroposterior bending stiffness vs. placebo [7.1% (P<0.001), 7.8% (P<0.001), 5.6% (P=0.023), and 6.3% (P<0.001), respectively]. HSA-estimated femoral narrow neck cross-sectional area and moment of inertia and outer diameter increased with ibandronate vs. placebo (respectively 3.6%, P=0.003; 4.0%, P=0.052; 2.2%, P=0.049. Once-monthly oral Ibandronate for 12 months improved hip and spine BMD measured by QCT and DXA and strength estimated by FEA of QCT scans.

10.2.169 Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss
McClung MR, Bolognese MA, Sedarati F, Recker RR, Miller PD
Bone 2009;44:418-22

This one-year, double-blind, placebo-controlled, randomized study enrolled ambulatory postmenopausal women aged 45-60 years with baseline lumbar spine (LS) BMD T-score<–1.0 and >–2.5 and baseline T-score>–2.5 at the total hip, trochanter, and femoral neck and no prior vertebral or low-trauma osteoporotic fractures at baseline. Subjects received 150 mg monthly oral ibandronate or placebo. 77 women received ibandronate and 83 received placebo. Subjects treated with ibandronate achieved larger increases in LS BMD after one year compared with subjects receiving placebo (3.7% vs. -0.4%). After 3 months, median serum C-terminal telopeptide of type I collagen levels were reduced by >55% in the ibandronate group and 4% in the placebo group. At one year, 88.2% of the participants treated with ibandronate achieved increases in LS BMD≥0% compared with 38.6% of subjects receiving placebo. Monthly ibandronate prevents bone loss in postmenopausal women with low bone mass.

10.2.170 Ibandronate dose response is associated with increases in bone mineral density and reductions in clinical fractures: Results of a meta-analysis
Sebba AI, Emkey RD, Kohles JD, Sambrook PN
Bone 2009;44:423-7

Individual patient data from the intent-to-treat population of the BONE, IV fracture prevention, MOBILE, and DIVA studies were included (n=8710 patients). The incidence of all clinical fractures was observed to decrease as lumbar spine BMD increased. A significant inverse linear relationship was observed between percent change in lumbar spine BMD and the rate of clinical

fractures (P=0.005). A nonsignificant curvilinear relationship was observed between percent change in total hip BMD and nonvertebral fracture rate. The authors infer increased ibandronate exposure is associated with increasing gains in the spine BMD and decreasing clinical fracture rates. A nonlinear relationship may exist between increases in the total hip BMD and nonvertebral fracture rate.

10.2.171 Ibandronate for the prevention of nonvertebral fractures: A pooled analysis of individual patient data
Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, Miller PD, Papapoulos S, Reginster JY, Sambrook PN, Silverman S, Siris E, Adachi JD
Osteoporos Int 2009;20:291-7

Eight randomized trials of ibandronate were reviewed for inclusion. Alternative definitions of high versus low doses based on annual cumulative exposure (ACE) were explored. A time-to-event analysis was conducted. Combining higher ACE doses of ≥10.8 mg (150 mg once monthly, 3 mg i.v. quarterly, and 2 mg i.v. every 2 months) versus ACE doses of 5.5 mg, from two trials, resulted in an HR 0.62 (95% CI 0.396-0.974, p=0.038). There was a dose-response trend with increasing ACE doses (7.2-12 mg) versus ACE of 5.5 mg.

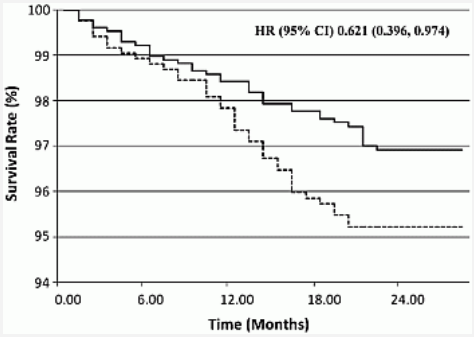

Fig. 10.2.171 Kaplan-Meier plot of time to nonvertebral fracture for higher versus lower ibandronate doses. Reproduced from Osteoporos Int 2009;20:291-7 with permission from Springer.

10.2.172 Intramuscular neridronate in postmenopausal women with low bone mineral density
Adami S, Gatti D, Bertoldo F, Sartori L, Di Munno O, Filipponi P, Marcocci C, Frediani B, Palummeri E, Fiore CE, Costi D, Rossini M
Calcif Tissue Int 2008;83:301-7

Neridronate, a nitrogen-containing bisphosphonate given intramuscularly, was tested in 188 postmenopausal osteoporotic women randomized to 25 mg every 2 weeks, 12.5 or 25 mg every 4 weeks, or placebo. The patients were treated for 12 months with 2-year post-treatment follow-up. After 12-months, all doses increased BMD. A dose-response relationship was observed for the BMD changes at the hip. Bone alkaline phosphatase decreased by 40-55%. Serum type I collagen C-telopeptide decreased by 58-79%, with a dose-response relationship (P<0.05). Two years after discontinuation, BMD declined by 1-2% in each group, with values still higher than baseline. Bone turnover markers increased, and on the second year of follow-up the values were higher than pretreatment baseline.

10.2.173 Bisphosphonate therapy ameliorates hearing loss in mice lacking osteoprotegerin
Kanzaki S, Takada Y, Ogawa K, Matsuo K
J Bone Miner Res 2009;24:43-9

Auditory ossicles are resorbed by osteoclasts in Opg(-/-) mice, which lack osteoprotegerin (OPG). Opg(-/-) mice exhibit progressive hearing loss and are a model for juvenile Paget's disease. Control Opg(-/-) mice exhibited thinning of all three ossicles and tibia. Risedronate inhibited bone loss in auditory ossicles as well as in long bones of Opg(-/-) mice. Bony fusion of the junction between the stapes and the otic capsule was reduced after treatment. Moreover, auditory brain stem response measurement showed that hearing in Opg(-/-) mice was improved by risedronate.

10.2.174 Comparison of effects of the bisphosphonate alendronate versus the RANKL inhibitor denosumab on murine fracture healing
Gerstenfeld LC, Sacks DJ, Pelis M, Mason ZD, Graves DT, Barrero M, Ominsky MS, Kostenuik PJ, Morgan EF, Einhorn TA
J Bone Miner Res 2009;24:196-208

The role of osteoclast-mediated resorption during fracture healing was assessed. The impact of two osteoclast inhibitors with different mechanisms of action, alendronate (ALN) and denosumab (DMAB), were examined during fracture healing. Male human RANKL knock-in mice that express a chimeric (human/murine) form of RANKL received unilateral transverse femur fractures. Mice were treated biweekly with ALN 0.1 mg/kg, DMAB 10 mg/kg, or PBS (control) 0.1 ml until death at 21 and 42 days after fracture. Serum TRACP 5b showed almost a complete elimination of TRACP 5b levels with DMAB but only 25% in the ALN-treated mice. Mechanical testing showed that fractured femurs from both ALN and DMAB groups had increased mechanical properties at day 42. μCT showed that callus tissues from DMAB-treated mice had greater percent bone volume and BMD than ALN-treated tissues at 21 and 42 days, whereas ALN-treated bones only had greater percent bone volume and BMC than control at 42 days. The 21- and 42-day ALN and DMAB groups had greater unresorbed cartilage or mineralized cartilage matrix compared with the controls, whereas unresorbed cartilage could still be seen in the DMAB groups at 42 days after fracture. Although ALN and DMAB delayed the removal of cartilage and the remodeling of the fracture callus, this did not diminish the mechanical integrity. In contrast, strength and stiffness were enhanced in these treatment groups compared with control bones.

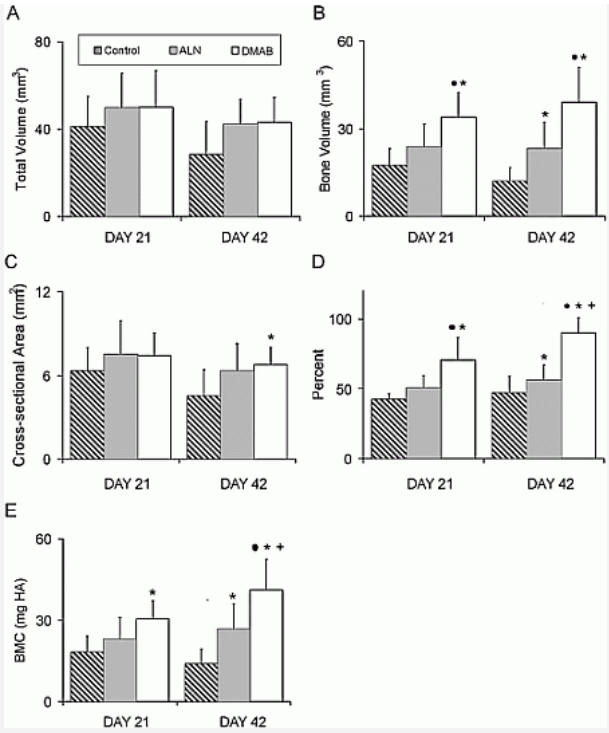

Fig. 10.2.174a Graphical analysis of μCT measurements of fracture calluses. (A) Total bone volume (TV). (B) Total bone volume (BV). (C) Mean cross-sectional area (CsAr). (D) Percent bone volume (BV/TV). (E) BMC based on calibration to a standard quantity of hydroxyapatite. For all graphs, error bars are ±SD. Cross indicates significance relative to the same treatment group at day 21. Dots indicate significance between ALN and DMAB treatment groups at the same time point. Asterisks indicate significance compared with the control at the same time point. Crosses indicate significance between time points for an individual experimental group. Significance is at p<0.05. Reproduced from J Bone Miner Res 2009;24:196-208 with permission of the American Society of Bone and Mineral Research.

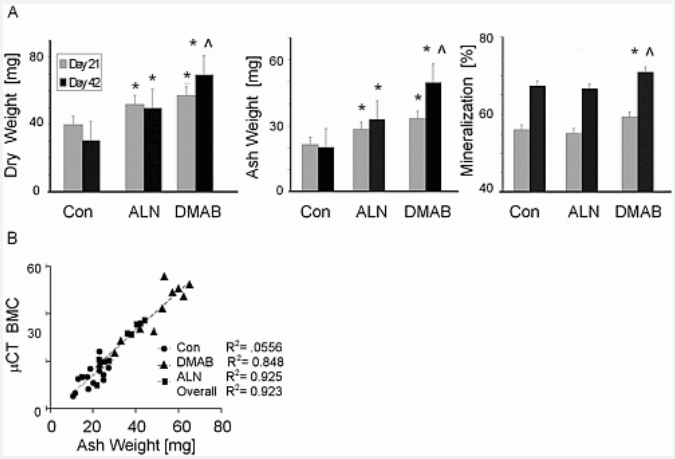

*Fig. 10.2.174b Results from ash analysis of fractured femurs after 21 and 42 days of treatment. (A) Ash analysis: left, dry weight; middle, ash weight; right, tissue mineralization as the ratio of ash weight to dry weight. *p<0.05 vs. control. ^p<0.05 vs. ALN. (B) Correlations between results from ash and μCT analyses in day 42 femurs. Femur ash weight was strongly correlated to callus vBMC as measured by μCT, both within and across all groups (r^2=0.556). Reproduced from J Bone Miner Res 2009;24:196-208 with permission of the American Society of Bone and Mineral Research.*

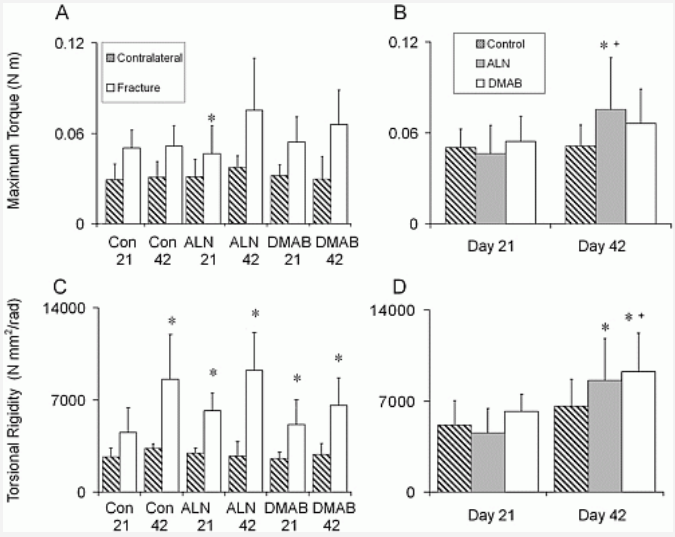

Fig. 10.2.174c Graphical analysis of torsion test results. One set of comparisons measure the differences between the contralateral bones and fractured bones (A and C), thereby providing a direct comparison of the regain of biomechanical competence to its unfractured state. The second set of measurements is the comparisons between the different drug groups and control across the two times within the fractured bones (B and D). This provides a direct comparison of the varying efficiencies of the two treatments vs. the control on the mechanical properties within the fractured bones themselves. The measure of the overall mechanical strength of the healing bones is presented in A and B. (A) Comparison of torque to failure between fractured bones and intact contralateral bones. (B) Comparison of fractured bones at between times and between experimental groups. Crosses indicate significance relative to the same treatment group at day 21. Asterisks indicate significance relative to the control at the same time point. (C) Comparison of torsional rigidity between fractured bones and intact contralateral bones. (D) Comparison of torsional rigidity between times and between experimental groups. Crosses indicate significance relative to the same treatment group at day 21. Asterisks indicate significance relative to the control at the same time point. For all graphs, error bars are ±SD. All p<0.5. Reproduced from J Bone Miner Res 2009;24:196-208 with permission of the American Society of Bone and Mineral Research.

10.2.175 Combination treatment with a selective androgen receptor modulator (SARM) and a bisphosphonate has additive effects in osteopenic female rats

Vajda EG, Hogue A, Griffiths KN, Chang WY, Burnett K, Chen Y, Marschke K, Mais DE, Pedram B, Shen Y, van Oeveren A, Zhi L, LÃ³pez FJ, Meglasson MD

J Bone Miner Res 2009;24:231-40

Combined selective androgen receptor modulator (SARM), LGD-3303, and a bisphosphonate was assessed in orchidectomized male rats orally administered LGD-3303 for 14 days. LGD-3303 increased the levator ani muscle weight above eugonadal levels but had greatly reduced activity on the prostate, never increasing the ventral prostate weight to >50% of eugonadal levels even at high doses. Ovariectomized female rats were treated with LGD-3303, alendronate, or both. LGD-3303 increased muscle weight in females rats. In addition, LGD-3303 increased BMD and BMC at both cortical and cancellous bone sites. At cortical sites, the effects were caused in part by anabolic activity on the periosteal surface. At every measured site, combination treatment was as effective as either single agent and in some cases showed added benefit. LGD. Combination therapy with LGD-3303 and alendronate had additive effects.

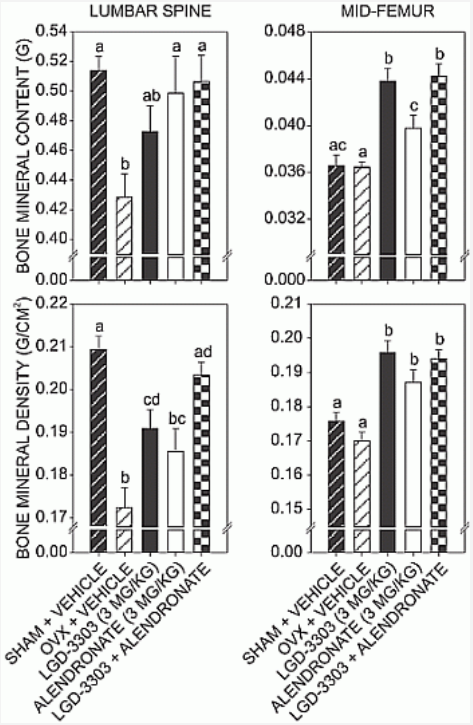

Fig. 10.2.175a LGD-3303 increases lumbar spine and femoral BMD and BMC in OVX female rats. At the lumbar spine, alendronate has similar effects but alendronate is less effective at increasing lumbar BMC at the midfemur. Combination treatment with LGD-3303 and alendronate enhances the activity at the lumbar spine. Combination treatment does not enhance or inhibit the LGD-3303 effect at the midfemoral diaphyis. Bars not sharing a common letter (abc) are significantly different (p<0.05). Mean±SE. Reproduced from J Bone Miner Res 2009;24:231-40 with permission of the American Society of Bone and Mineral Research.

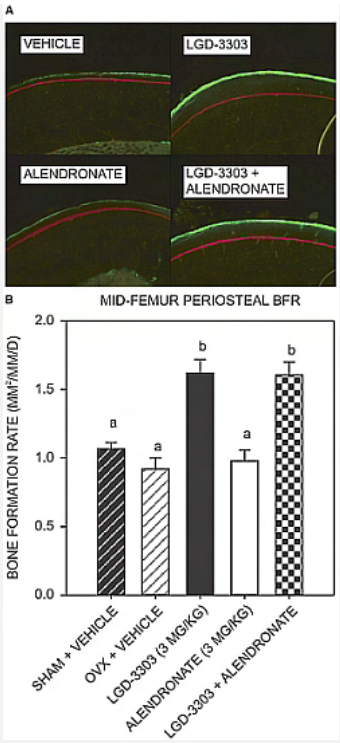

Fig. 10.2.175b (A) Photomicrograph of the periosteal surface of the midfemoral diaphysis viewed under epifluorescent light. OVX female rats were administered alizarin (red) at baseline and calcein (green) at the conclusion of the treatment period to label sites of new bone formation. (B) LGD-3303 increases periosteal bone formation at the midfemoral diaphysis in OVX female rats. Alendronate has no activity at this site. In combination, alendronate does not accentuate or diminish the effects of LGD-3303. Bars not sharing a common letter (abc) are significantly different (p<0.05). Mean±SE. Reproduced from J Bone Miner Res 2009;24:231-40 with permission of the American Society of Bone and Mineral Research.

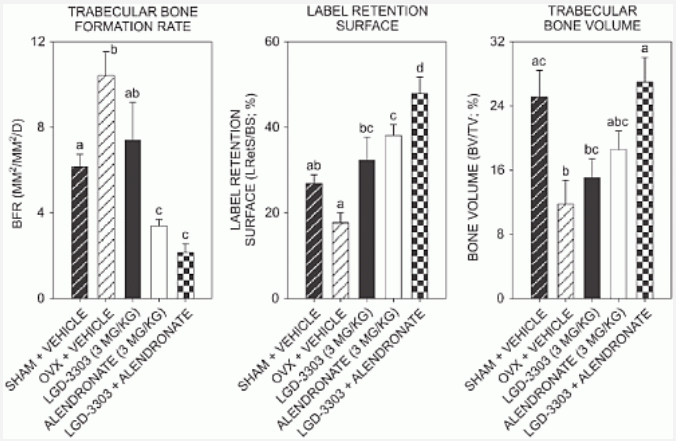

Fig. 10.2.175c Three-point bending test of the femur and compression test of the lumbar vertebral body. LGD-3303, alendronate, and the combination are all effective at increasing bone strength at both the midfemur and the lumbar spine in OVX female rats. Combination treatment was the most effective, with a significantly greater increase at the lumbar spine relative to alendronate treatment alone. Bars not sharing a common letter (abc) are significantly different (p<0.05). Mean±SE. Reproduced from J Bone Miner Res 2009;24:231-40 with permission of the American Society of Bone and Mineral Research.

10.2.176 Effect of raloxifene and low-dose percutaneous 17beta-estradiol on menopause symptoms and endometrium – A randomized controlled trial

Valiati B, Capp E, Edelweiss MI, de Freitas FM, Wender MC

Maturitas 2009;62:81-4

52 postmenopausal women with moderate to severe hot flushes were randomized to 60 mg raloxifene (RLX; n=20), 0.5 mg percutaneous 17β-estradiol plus 60 mg raloxifene (RLX+E(2); n=16) or placebo (PLC; n=16). Climacteric symptoms (Kupperman index) and vaginal bleeding were evaluated. At baseline, the mean Kupperman index was 23.7±1.8 in RLX group, 22.9±1.9 in RLX+E(2) group and 22.6±1.9 in the placebo group (NS). After 3 months, there was a significant reduction in Kupperman index mean values in both groups, but no statistical difference was observed between groups. However, RLX+E(2) and placebo were significantly superior to RLX in reducing hot flush severity (p<0.05). Endometrial thickness did not change in both groups. The association of percutaneous low-dose 17β-estradiol to raloxifene was not associated with proliferation of endometrium neither in hysteroscopies nor in endometrial biopsies at the third month of treatment. No vaginal bleeding was reported during the study.

10.2.177 Effects of raloxifene and hormone replacement therapy on forearm skin elasticity in postmenopausal women

Sumino H, Ichikawa S, Kasama S, Takahashi T, Kumakura H, Takayama Y, Kanda T, Murakami M, Kurabayashi M

Maturitas 2009;62:53-7

In a 12-month trial, 17 postmenopausal women (mean age, 66.4±7.8 years) received continuous raloxifene (60 mg/day), 19 women (56.2±6.4 years) received continuous 17β-estradiol using a patch (0.72 mg/2 days) plus cyclic medroxyprogesterone acetate (2.5 mg/day, for 12 days/month), and 11 women (58.1±7.3 years) did not receive therapy. Raloxifene and HRT increased

skin elasticity from 52.4±3.8% and 64.1±7.2% at baseline to 55.1±4.7% and 67.4±7.4% after 12 months, respectively (P<0.05, each), but the untreated subjects did not.

10.2.178 Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: Results from a 3-year, randomized, placebo- and active-controlled clinical trial
Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, Chines AA
J Bone Miner Res 2008;23:1923-34

In this 3-yr, randomized, double-blind, placebo- and active-controlled study, 6847 women in the intent-to-treat population with osteoporosis (55-85 yr of age) received bazedoxifene 20 or 40 mg/d, raloxifene 60 mg/d, or placebo. The incidence of new vertebral fractures was lower (p<0.05) with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) than placebo (4.1%); relative risk reductions of 42%, 37%, and 42%, respectively. The treatment effect was similar in subjects with or without prevalent vertebral fracture. Nonvertebral fractures were not reduced. In a posthoc analysis of women at higher fracture risk (femoral neck T-score≤–3.0 and/or ≥1 moderate or severe vertebral fracture or multiple mild vertebral fractures; n=1772), bazedoxifene 20 mg showed a 50% and 44% reduction in nonvertebral fracture risk relative to placebo (p=0.02) and raloxifene 60 mg (p=0.05), respectively. Bazedoxifene improved BMD and reduced bone marker levels. The incidence of vasodilatation, leg cramps, and venous thromboembolic events was higher with bazedoxifene and raloxifene than placebo.

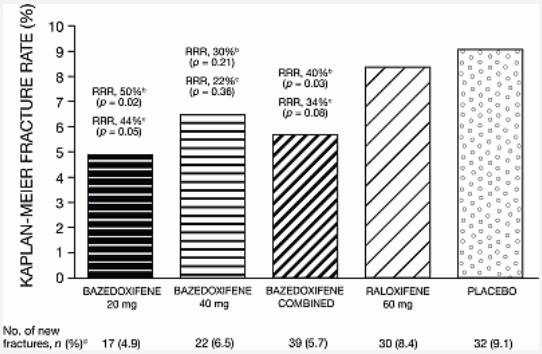

Fig. 10.2.178a Incidence of nonvertebral fractures in subjects at higher risk for fracture.[a] RRR, relative risk reduction. [a]Higher-risk subgroup (femoral neck T-score≤−3.0 and/or ≥1 moderate or severe vertebral fracture or multiple mild vertebral fractures); n=1772. [b]Relative to placebo. [c]Relative to raloxifene. [d]Major fracture sites, n (%): wrist [bazedoxifene 20 mg, 4 (0.8); bazedoxifene 40 mg, 5 (1.2); raloxifene 60 mg, 10 (2.2); placebo, 7 (1.6)]; hip [bazedoxifene 20 mg, 3 (0.7); bazedoxifene 40 mg, 2 (0.5); raloxifene 60 mg, 2 (0.4); placebo, 4 (0.9)]; humerus [bazedoxifene 20 mg, 5 (1.1); bazedoxifene 40 mg, 4 (0.9); raloxifene 60 mg, 7 (1.6); placebo, 3 (0.7)]; lower extremity, including femur, tibia/fibula, patella, ankle, tarsal/metatarsal [bazedoxifene 20 mg, 3 (0.7); bazedoxifene 40 mg, 7 (1.6); raloxifene 60 mg, 6 (1.3); placebo, 17 (3.8)]. Reproduced from J Bone Miner Res 2008;23:1923-34 with permission of the American Society of Bone and Mineral Research.

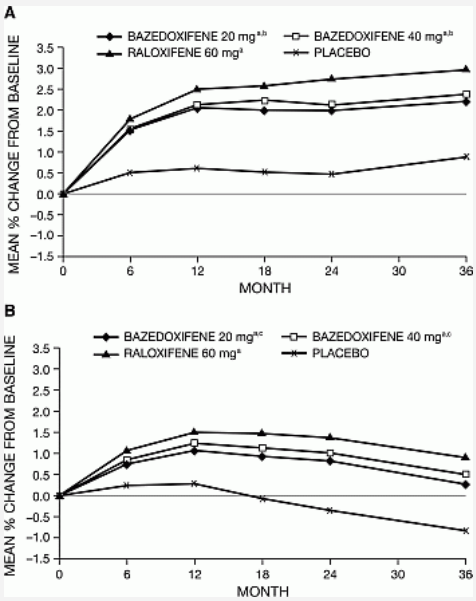

Fig. 10.2.178b (A) BMD response at the lumbar spine (L1-L4). The mean percent changes from baseline in lumbar spine BMD for the intent-to-treat population (no last observation carried forward) are presented. (B) BMD response at the total hip. The mean percent changes from baseline in total hip BMD for the intent-to-treat population (no last observation carried forward) are presented. BMD, bone mineral density. [a]p<0.001 vs. placebo at each time point. [b]p<0.05 vs. raloxifene at each time point. [c]p<0.01 vs. raloxifene at each time point. Reproduced from J Bone Miner Res 2008;23:1923-34 with permission of the American Society of Bone and Mineral Research.

10.2.179 Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL
Kostenuik PJ, Nguyen HQ, McCabe J, Warmington KS, Kurahara C, Sun N, Chen C, Li L, Cattley RC, Van G, Scully S, Elliott R, Grisanti M, Morony S, Tan HL, Asuncion F, Li X, Ominsky MS, Stolina M, Dwyer D, Dougall WC, Hawkins N, Boyle WJ, Simonet WS, Sulliva
J Bone Miner Res 2009;24:182-95

Recombinant human OPG-Fc reduced resorption and increased bone volume, density, and strength in rodents. To create mice that were responsive to denosumab, knock-in technology was used to replace exon 5 from murine RANKL with its human ortholog. The resulting “huRANKL” mice exclusively express chimeric (human/murine) RANKL that was measurable with a

human RANKL assay and that maintained bone resorption at slightly reduced levels versus wildtype controls. In young huRANKL mice, denosumab and OPG-Fc each reduced trabecular osteoclast surfaces by 95% and increased bone density and volume. In adult huRANKL mice, denosumab reduced bone resorption, increased cortical and cancellous bone mass, and improved trabecular microarchitecture. These huRANKL mice have potential utility for characterizing the activity of denosumab in a variety of murine bone disease models.

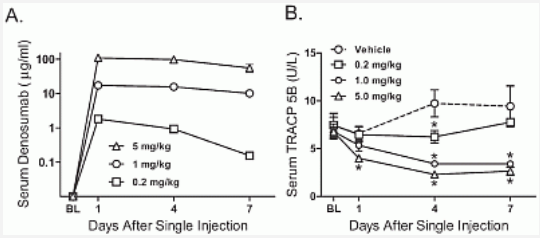

*Fig. 10.2.179a Pharmacokinetics and pharmacodynamics of denosumab in huRANKL mice. Female huRANKL mice (n=5-6/ group) were given single subcutaneous injections of vehicle (PBS) or denosumab at 0.2-5.0 mg/kg. Serum was obtained from blood drawn before treatment (baseline, BL) and on days 1, 4, and 7 after treatment. (A) Serum levels of denosumab were measured by an ELISA wherein serum samples were added to plates precoated with human RANKL, and denosumab was detected with a monoclonal anti-human IgG. (B) Bone resorption was assessed by measuring serum TRACP-5b. *Significantly different from Veh control, p<0.05 by ANOVA. Reproduced from J Bone Miner Res 2009;24:182-195 with permission of the American Society of Bone and Mineral Research.*

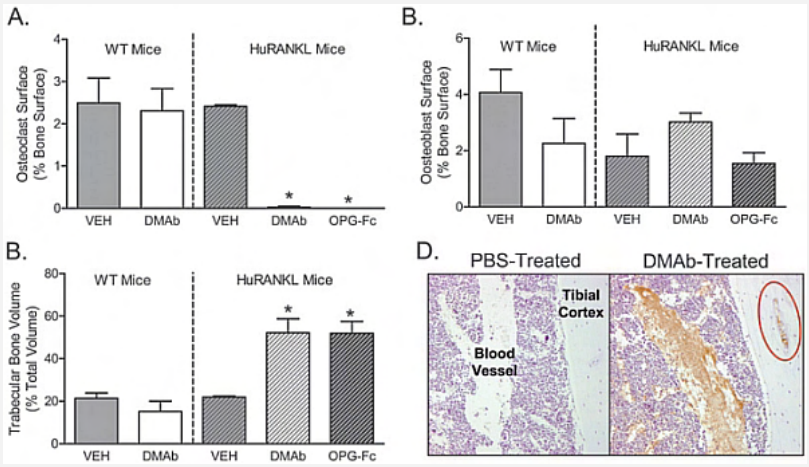

*Fig. 10.2.179b Effects of denosumab on bone histomorphometry in young (6-8 wk old) huRANKL mice. HuRANKL mice (n=3-4/ group) were treated with vehicle (PBS), denosumab, or human OPG-Fc (5 mg/kg, SC, twice per week) for 3 wk. WT littermate controls were treated with PBS or denosumab. Histomorphometry was performed on decalcified sections of the proximal tibial metaphysis. (A) Osteoclast surface (OcS/BS) was significantly lower in huRANKL mice treated with denosumab or OPG-Fc, whereas denosumab failed to reduce OcS/BS in WT controls. (B) Osteoblast surface (ObS/BS) was statistically similar in all groups. (C) Trabecular bone volume (BV/TV) was significantly greater in huRANKL mice treated with denosumab or OPG-Fc, whereas denosumab failed to increase BV/TV in WT controls. For A-C, *represents significant differences from huRANKL mice treated with PBS, p<0.05. (D) Immunohistochemical assessment of denosumab in the proximal tibia of a huRANKL mouse. Sections were incubated with rabbit anti-human IgG. (Left panel) Negligible specific staining was observed in bones from huRANKL mice treated with PBS. *Note for reference the large unstained blood vessel in the marrow of the diaphysis. (Right panel) In a denosumab-treated huRANKL mouse, strong staining was observed within a major blood vessel in the marrow diaphysis, and within a vessel penetrating the cortex (circle). Reproduced from J Bone Miner Res 2009;24:182-195 with permission of the American Society of Bone and Mineral Research.*

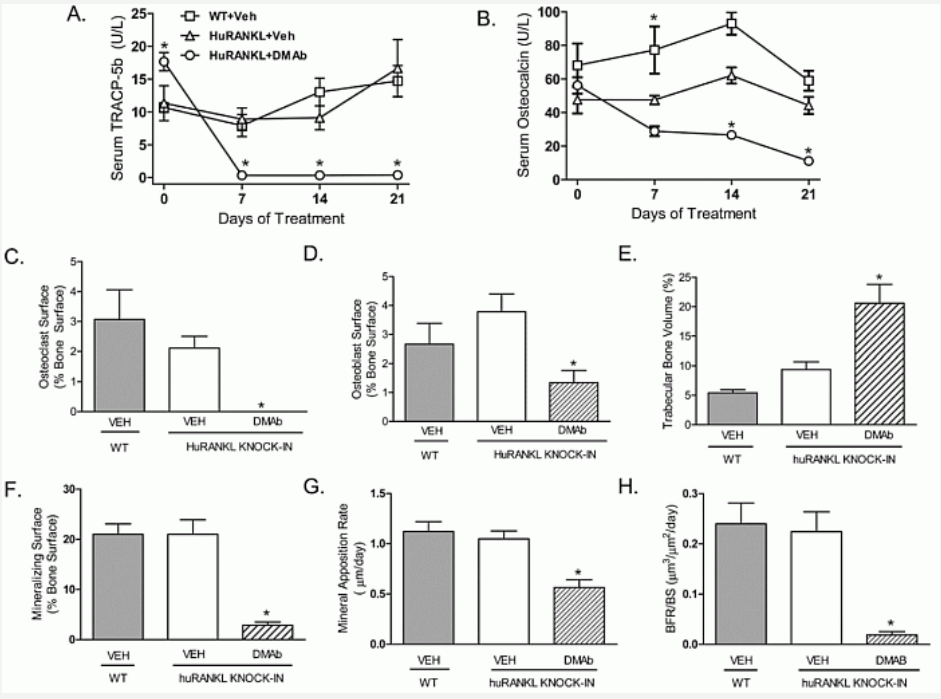

*Fig. 10.2.179c Effects of denosumab in adult (10 mo old) huRANKL mice (n=6/group). (A) Serum TRACP-5b was significantly reduced by denosumab at all time points during treatment. (B) Serum osteocalcin was significantly reduced by denosumab on days 14 and 21. (C-H) Histomorphometry of the proximal tibial metaphysis after 3 wk of treatment showed significant denosumab-related reductions in osteoclast surface, osteoblast surface, mineralizing surface, mineral apposition rate, and bone formation rate (BFR/BS) and significantly greater trabecular bone volume. *Significantly different from vehicle-treated huRANKL mice by ANOVA (p<0.05). Reproduced from J Bone Miner Res 2009;24:182-195 with permission of the American Society of Bone and Mineral Research.*

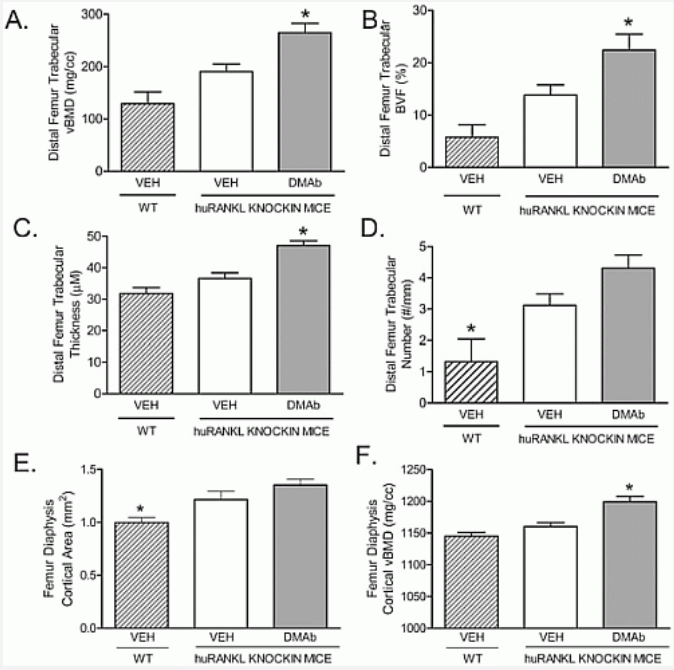

*Fig. 10.2.179d μCT assessment of femurs from adult (10 mo old) female huRANKL mice treated with denosumab (10 mg/kg) once per week for 3 wk (n=6/group). (A-D) Trabecular bone within the distal femoral metaphysis was analyzed by μCT to assess volumetric BMD (vBMD), trabecular bone volume fraction (BVF), trabecular thickness, and trabecular number. (E and F) Cortical bone in the femur diaphysis was analyzed by μCT to assess cortical area and vBMD. *Significantly different from vehicle-treated huRANKL mice by ANOVA (p<0.05). Reproduced from J Bone Miner Res 2009;24:182-195 with permission of the American Society of Bone and Mineral Research.*

10.2.180 The effects of strontium ranelate in Asian women with postmenopausal osteoporosis
Hwang JS, Chen JF, Yang TS, Wu DJ, Tsai KS, Ho C, Wu CH, Su SL, Wang CJ, Tu ST
Calcif Tissue Int 2008;83:308-14

In this 12-month multicenter, randomized, double-blind, placebo-controlled study, 125 women with osteoporosis were randomly given strontium ranelate 2 g daily or placebo. Subjects treated with strontium ranelate showed increases in BMD of 5.9% at the spine, 2.6% at the femoral neck, and 2.7% at the total hip, while the placebo group exhibited no change. Serum level of a formation marker (bone specific alkaline phosphatase) was also increased at 6 and 12 months.

10.2.181 The calcium-sensing receptor is involved in strontium ranelate-induced osteoclast apoptosis: New insights into the associated signaling pathways
Hurtel-Lemaire AS, Mentaverri R, Caudrillier A, Cournarie F, Wattel A, Kamel S, Terwilliger EF, Brown EM, Brazier M
J Biol Chem 2009;284:575-84

Using primary mature rabbit osteoclasts, strontium (Sr(o)(2+)) dose-dependently stimulates the apoptosis of mature osteoclasts mediated by the Ca(o)(2+)-sensing receptor, CaR, which in turn stimulates a phospholipase C-dependent signaling pathway and nuclear translocation of NF-κB. Sr(o)(2+)-induced osteoclast apoptosis was shown to depend on PKCβII activation and to be independent of inositol 1,4,5-trisphosphate action. Sr(o)(2+) and Ca(o)(2+) in combination were shown to exert a greater effect on mature osteoclast apoptosis than did either cation by itself. Altogether, our results show that Sr(o)(2+) acts through the CaR and induces osteoclast apoptosis through a signaling pathway similar to but different in certain respects from that of Ca(o)(2+). This difference in the respective signaling cascades enables Sr(o)(2+) to potentiate Ca(o)(2+)-induced osteoclast apoptosis and vice versa. In this manner, it is conceivable that Sr(o)(2+) and Ca(o)(2+) act together to inhibit bone resorption in strontium ranelate-treated patients.

10.2.182 Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans
Keaveny TM, Hoffmann PF, Singh M, Palermo L, Bilezikian JP, Greenspan SL, Black DM
J Bone Miner Res 2008;23:1974-82

The "PTH and Alendronate" or "PaTH" study compared the effects of PTH(1-84) and/or alendronate (ALN) in 238 postmenopausal, osteoporotic women. Finite element analysis on the QCT scans of 162 subjects. Patients were assigned to PTH, ALN, or their combination (CMB) in year 1 and were switched to either ALN or placebo (PLB) in year 2: PTH-PLB, PTH-ALN, CMB-ALN, and ALN-ALN (year 1–year 2). At year 1, the strength change from baseline was significant for PTH (mean, 2.08%) and ALN (3.60%), and at year 2, significant changes were seen for the PTH-ALN (7.74%), CMB-ALN (4.18%), and ALN-ALN (4.83%) not for PTH-PLB (1.17%). Strength increases were caused by changes in the trabecular density regardless of treatment group, but changes in cortical density and mass also played a role, the degree of which depended on treatment. For PTH at year 1 and for ALN-ALN at year 2, there were negative and positive strength effects, respectively, associated with a change in external geometry. The relation between change in femoral strength and change in aBMD was weak (r^2=0.14, pooled, year 2).

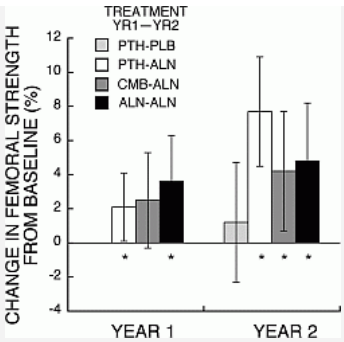

*Fig. 10.2.182 Average percent changes (mean±95% CIs) in FE-computed femoral strength at years 1 and 2 compared with baseline for the four treatment groups. For year 1, the two PTH groups are shown pooled (using a white fill) and combined have a smaller CI than the other treatment groups because of the larger sample size. *Change from baseline was significantly significant (p<0.05). Reproduced from J Bone Miner Res 2008;23:1974-82 with permission of the American Society of Bone and Mineral Research.*

10.2.183 Recombinant human parathyroid hormone (PTH 1-34) and low-intensity pulsed ultrasound have contrasting additive effects during fracture healing
Warden SJ, Komatsu DE, Rydberg J, Bond JL, Hassett SM
Bone 2009;44:485-94

Two interventions accelerate fracture healing are recombinant human parathyroid hormone [1-34] (PTH) and low-intensity pulsed ultrasound (LIPUS). Bilateral midshaft femur fractures were created in Sprague Dawley rats, and the animals treated 7 days/week with PTH (10 μg/kg) or a vehicle solution. Each animal also had one fracture treated for 20 min/day with active-LIPUS (spatial-averaged, temporal-averaged intensity [I(SATA)]=100 mW/cm^2) and the contralateral fracture treated with inactive-LIPUS (placebo). There were no interactions between PTH and LIPUS indicating that their effects were additive. These additive effects were contrasting with LIPUS primarily increasing total callus volume (TV) without influencing bone mineral content (BMC), and PTH having the opposite effect of increasing BMC without influencing TV. As a consequence of the effect of LIPUS on TV but not BMC, it decreased volumetric bone mineral density (vBMD) resulting in a less mature callus. The decreased maturity and persistence of cartilage at the fracture site when harvested offset any beneficial mechanical effects of the increased callus size with LIPUS. PTH on callus BMC but not TV resulted in increased callus vBMD and a more mature callus. This resulted in PTH increasing fracture site mechanical strength and stiffness. PTH may have utility in the treatment of acute bone fractures, whereas LIPUS at an I(SATA) of 100 mW/cm^2 does not appear to be indicated in the management of closed, diaphyseal fractures.

10.2.184 Cancellous and cortical bone architecture and turnover at the iliac crest of postmenopausal osteoporotic women treated with parathyroid hormone 1-84
Recker RR, Bare SP, Smith SY, Varela A, Miller MA, Morris SA, Fox J
Bone 2009;44:113-9

Iliac crest biopsies from postmenopausal osteoporotic women given placebo (n=8) or 100 μg PTH(1-84) for 18 (n=8) or 24 (n=7) months to assess cancellous and cortical bone formation and structure at 18 months revealed that cancellous bone volume (BV/TV) measured by microcomputed tomography and histomorphometry was 45-48% higher in subjects treated with PTH(1-84) versus placebo, a result of higher trabecular number (Tb.N) and thickness. The higher Tb.N appeared to result from intratrabecular tunnelling. Connectivity density was higher and structure model index was lower, indicating a better connected and more plate-like trabecular architecture. Cancellous bone formation rate (BFR) was 2-fold higher in PTH(1-84)-treated subjects, primarily because of greater mineralizing surface. Osteoblast and osteoid surfaces were a 58% and 35%, respectively, higher with PTH(1-84) treatment (NS). Osteoclast and eroded surface were unaffected by PTH(1-84). There were no effects of PTH(1-84) on cortical thickness, or endocortical or periosteal BFR, but cortical porosity tended to be higher. The bone produced had normal lamellar structure and mineralization.

10.2.185 Differential effects of intermittent PTH(1-34) and PTH(7-34) on bone microarchitecture and aortic calcification in experimental renal failure
Sebastian EM, Suva LJ, Friedman PA
Bone 2008;43:1022-30

PTH(1-84) and PTH(7-84) are elevated in chronic kidney disease. These peptides, as their shorter analogs PTH(1-34) and PTH(7-34) both promote PTH receptor (PTH1R) internalization but only PTH(1-34) and PTH(1-84) activate the receptor. Rats were treated with single daily doses of 40 μg/kg PTH(1-34), PTH(7-34), or vehicle. PTH(1-34) was more hypercalcemic than PTH(7-34) in parathyroidectomy (PTX) rats. Fractional bone volume in rats treated with PTH(1-34) increased in all groups. In addition, trabecular number, thickness and volumetric bone density increased in rats treated with PTH(1-34). In contrast, PTH(1-34) diminished vascular calcification. Bone and renal PTH1R mRNA expression was reduced as much or more in PTX/NPX (nephrectomy) rats as in NPX alone, whereas PTH(7-34) had no effect on PTH1R expression. Renal but not bone PTH1R mRNA increased in response to PTH(1-34). PTH(1-34) exerts greater hypercalcemic and anabolic effects in parathyroidectomized and/or nephrectomized rats than PTH(7-34). There was no evidence for bone or vascular actions of PTH(7-34).

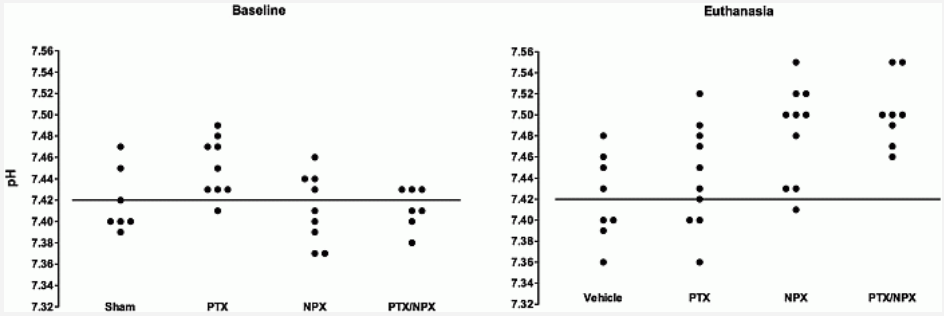

Fig. 10.2.185 Serum pH measurement. Serum pH was measured in the 4 experimental groups under baseline conditions (before surgery, day 3) and at euthanasia (day 52). Sham=Sham operation; PTX=parathyroidectomized; NPX=5/6 nephrectomized; PTX/NPX=parathyroidectomized+5/6 nephrectomized rats. Reproduced from Bone, 43:1022-30, Copyright (2008), with permission from Elsevier.

10.2.186 Lack of bone neoplasms and persistence of bone efficacy in cynomolgus macaques after long-term treatment with teriparatide [rhPTH(1-34)]
Vahle JL, Zuehlke U, Schmidt A, Westmore M, Chen P, Sato M
J Bone Miner Res 2008;23:2033-9

OVX mature cynomolgus monkeys (n=30 per group) were given teriparatide for 18 mo at either 0 or 5 µg/kg/d subcutaneously. After the 18-mo treatment period, vertebral BMD, BMC, and strength (ultimate load) increased by 29%, 36%, and 52%, respectively, compared with OVX controls. Proximal femur BMD, BMC, and strength were also increased by 15%, 28% and 33%, respectively. After 3 years without treatment, no differences in bone mass or strength at the vertebra were observed relative to OVX controls; however, the femoral neck showed persistence in stiffness (20%), BMC (14%), and trabecular BV/TV (53%). Teriparatide did not induce bone proliferative lesions over 4.5 years, including 18 mo of treatment and 3 years of follow-up. During the withdrawal, beneficial effects on the vertebra were lost; some effects on the proximal femur persisted for 3 years after cessation of treatment.

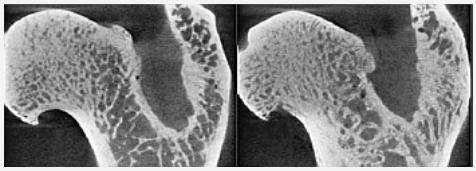

Fig. 10.2.186 µCT analysis of proximal femora after 18-mo treatment. (Left) OVX vehicle control. (Right) Teriparatide (5 µg/kg/d SC). Reproduced from J Bone Miner Res 2008;23:2033-9 with permission of the American Society of Bone and Mineral Research.

10.2.187 Parathyroid hormone (1-34) augments spinal fusion, fusion mass volume, and fusion mass quality in a rabbit spinal fusion model
O'Loughlin PF, Cunningham ME, Bukata SV, Tomin E, Poynton AR, Doty SB, Sama AA, Lane JM
Spine 2009;34:121-30

44 male New Zealand white rabbits underwent bilateral posterolateral spine fusion (L5-L6 level). 22 received daily injections of PTH (1-34) (10 µg/kg) and 22 received saline. Manual bending identified fusion in 30% (control) versus 81% (PTH) animals (P<0.001). µCT demonstrated a median mass of 3.5 cc (control) (range, 2.25-5.40 cc) versus 6.03 cc (PTH) (range, 4.34-10.58 cc) (P<0.001). Histology showed a median percentage bone area of14.3% (control) (n=12) versus 29.9% (PTH) (n=15) (P<0.001). The medianpercentage cartilage was 2.7% (control) (n=5) versus 26.6% (PTH) (n=5) (P<0.01). Osteoclast quantification revealed median values of 140.5 (control) (n=6) and 345.0 (PTH) (n=8) (P<0.001), respectively, and the percentage of osteoblasts revealed a median value of 31.4% (control) (n=6) versus 64.4% (PTH) (n=8) (P<0.001). PTH increased posterolateral fusion success.

10.2.188 Prolonged treatments with antiresorptive agents and PTH have different effects on bone strength and the degree of mineralization in old estrogen-deficient osteoporotic rats
Cheng Z, Yao W, Zimmermann EA, Busse C, Ritchie RO, Lane NE
J Bone Miner Res 2009;24:209-20

18-month-old female Fischer rats were ovariectomized (OVX) or sham-operated and left untreated for 60 days then treated with single doses of risedronate (500 µg/kg, i.v.), zoledronic acid (100 µg/kg, i.v.), raloxifene (2 mg/kg, PO, three times per week), hPTH (1-34) (25 µg/kg, SC, three times per week), or vehicle (NS; 1 ml/kg, three times per week). The trabecular bone volume, degree of bone mineralization, elastic modulus, and compressive bone strength were lower at day 60 post-OVX (pretreatment, day 0 study) than at baseline. After 60 days of all of treatments, bone mass and material measurements agent were restored. However, after 180 days, the OVX+PTH group further increased BV/TV (+30% from day 60, p<0.05 within group and between groups). In addition, after 180 days of treatment, there was more highly mineralized cortical and trabecular bone and increased cortical bone size and whole bone strength in OVX+PTH compared with other OVX+antiresorptives. PTH resulted in additional gains in bone quality and bone strength, suggesting that the maximal gains in bone strength in cortical and trabecular bone sites may require a longer treatment period with PTH.

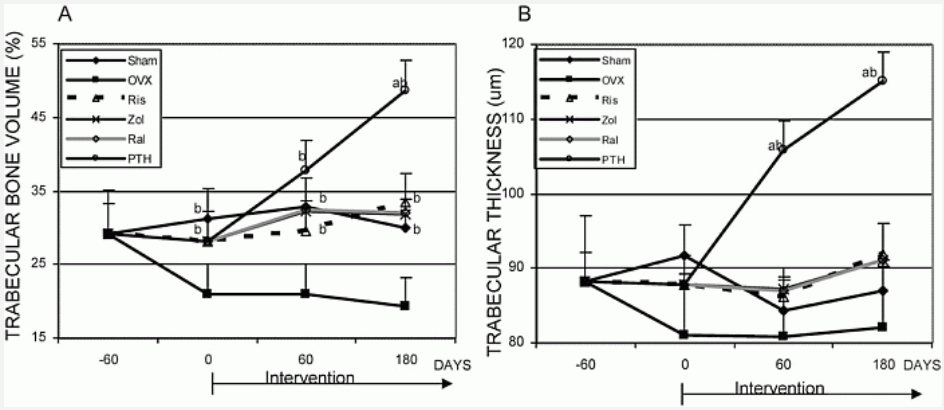

Fig. 10.2.188a Proximal tibial trabecular bone microarchitecture changes measured by µCT. Mean values and SD for (A) trabecular bone volume and (B) trabecular bone thickness from the right proximal tibial metaphyses obtained from groups of sham-operated (Sham) or OVX animals treated with vehicle (OVX), risedronate (Ris), zoledronic acid (Zol), raloxifene (Ral), and PTH(1-34) from days 0 to 180. [a]p<0.05 vs. sham-operated animals at the same time point; [b]p<0.05 vs. OVX + vehicle-treated animals at the same time point. Reproduced from J Bone Miner Res 2009;24:209-20 with permission of the American Society of Bone and Mineral Research.

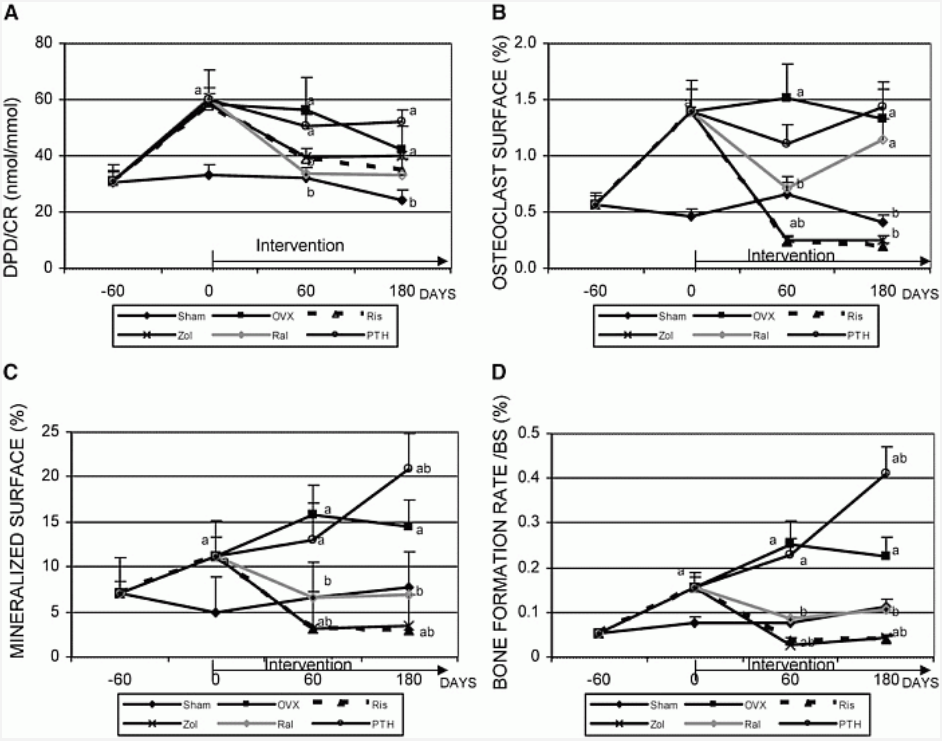

Fig. 10.2.188b Serum biochemical and surface based assessments of bone turnover. Mean values and SD for (A) urine DPD (nmol) cross-links and creatinine (Cr, mmol) measured by ELISA; (B) percent osteoclast surface (%); (C) percent mineralizing surface (%); and (D) percent surface-based bone formation rate (μm/d). (B-D) Measured from bone histomorphometry obtained from the proximal tibial metaphysis for groups of sham-operated (Sham) or OVX animals treated with vehicle (OVX), risedronate (Ris), zoledronic acid (Zol), raloxifene (Ral), and PTH(1-34) (PTH) from days 0 to 180. [a]p<0.05 vs. sham-operated animals at the same time point; [b]p<0.05 vs. OVX + vehicle-treated animals at the same time point. Reproduced from J Bone Miner Res 2009;24:209-20 with permission of the American Society of Bone and Mineral Research.

10.2.189 Intermittent PTH stimulates periosteal bone formation by actions on post-mitotic preosteoblasts
Jilka RL, O'Brien CA, Ali AA, Roberson PK, Weinstein RS, Manolagas SC
Bone 2009;44:275-86

Intermittent PTH increases cancellous osteoblast number partly by attenuating osteoblast apoptosis. Daily injections of 100 ng/g of PTH(1-34) to 4-6 month old mice increased the number of osteoblasts on the periosteum of lumbar vertebrae by 2- to 3-fold after two days. However, the prevalence of apoptotic periosteal osteoblasts was only 0.2% in vehicle treated animals, 20-fold lower than in cancellous osteoblasts. PTH did not have an effect on periosteal osteoblast apoptosis. BrdU failed to label periosteal osteoblasts. Cancellous osteoblasts were labelled under basal conditions, but PTH did not increase BrdU-positive cells. Thus, intermittent PTH does not increase cancellous or periosteal osteoblast number by stimulating the proliferation of progenitors. Consistent with high turnover of cancellous osteoblasts as compared to that of periosteal osteoblasts, ganciclovir-induced ablation of replicating osteoblast progenitors in mice expressing thymidine kinase under the control of the 3.6 kb rat Col1A1 promoter resulted in disappearance of osteoblasts from cancellous bone over a 7-14 day period, but periosteal osteoblasts were unaffected. 14 days of pretreatment with ganciclovir prevented PTH anabolism on periosteal bone. In cancellous bone, attenuation of osteoblast apoptosis by PTH increases osteoblast number because their rate of apoptosis is high. However, in periosteal bone where the rate of osteoblast apoptosis is low, PTH must exert pro-differentiating and/or pro-survival effects on postmitotic preosteoblasts.

10.2.190 Combined effects of recombinant human BMP-7 (rhBMP-7) and parathyroid hormone (1-34) in metaphyseal bone healing
Morgan EF, Mason ZD, Bishop G, Davis AD, Wigner NA, Gerstenfeld LC, Einhorn TA
Bone 2008;43:1031-8

The goal of this study was to determine the combined effects of rhBMP-7 and PTH(1-34) on metaphyseal bone healing. Combined rhBMP-7 and PTH resulted in increased callus total volume (TV), mineralized volume (BV), average cross-sectional area, and bone mineral content (BMC). BV and BMC were also higher in the combined group as compared to the BMP-7 group ($p<0.02$); however, tissue mineral density was highest in the BMP-7 group ($p=0.002$). New bone formation in the BMP-7 group was largely restricted to the defect site, while PTH promoted bone formation throughout the defect and surrounding regions. Combined treatment led to greater woven trabecular bone, increased trabecular thickness, decreased trabecular separation ($p<0.04$), and a trend towards increased numbers of osteoclasts ($p=0.09$). Combined treatment also increased torsional rigidity and compressive strength as compared to the control and BMP-7 groups ($p<0.001$). These results suggest that the improvements in mechanical function obtained with the combined treatment resulted from differing biological activities of rhBMP-7 and PTH. While the activities of rhBMP-7 appeared to be strictly anabolic, those of PTH appeared to work in the context of coupled remodelling.

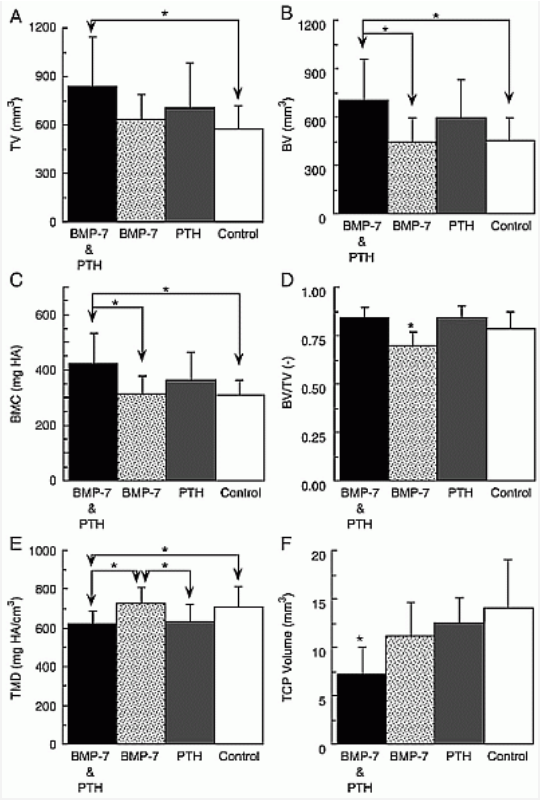

Fig. 10.2.190 Quantitative microcomputed tomography results: (A) total volume (TV), (B) mineralized volume (BV), (C) bone mineral content (BMC), (D) mineralized volume fraction, (E) tissue mineral density (TMD), and (F) TCP volume for each of the four groups at 4 weeks post-surgery. Column heights represent the group mean, and error bars indicate 1 standard deviation. Asterisks indicate significant differences ($p<0.05$). Reproduced from Bone, 43:1031-8, Copyright (2008), with permission from Elsevier.

10.2.191 Bone parameters are improved with intermittent dosing of vitamin D3 and calcitonin
Andresen CJ, Moalli M, Turner CH, Berryman E, Pero R, Bagi CM
Calcif Tissue Int 2008;83:393-403

Rats had Ovx at 8 weeks old and 4 weeks later were assigned to experimental groups: (1) sham vehicle, (2) Ovx vehicle, (3) Ovx + parathyroid hormone (PTH, 40 µg/kg), and (4) Ovx + calcitriol (2 µg/kg) + CT (2 µg/kg). Group 3 received PTH every week throughout the study, and group 4 received calcitriol at weeks 1, 3, 5, and 7 and CT at weeks 2, 4, 6, and 8. PTH improved bone mass and structure of cancellous bone at metaphyses of tibias and femurs as well as strength. Intermittent calcitriol and CT was less potent in correcting loss of cancellous bone relative to treatment with PTH and had no effect on cortical bone parameters. However, intermittent dosing with calcitriol and CT was robust enough to improve cancellous bone mass and structure through bone formation.

10.2.192 Vitamin D status and response to treatment in post-menopausal osteoporosis
Adami S, Giannini S, Bianchi G, Sinigaglia L, Di Munno O, Fiore CE, Minisola S, Rossini M
Osteoporos Int 2009;20:239-44

1515 women with postmenopausal osteoporosis treated with alendronate, risedronate, raloxifene for 13.1 months with an adherence >75%. The patients were classified as vitamin D deficient (N=514) or vitamin D repleted (N=1001) according to risk factors (N=1062) or the level of 25(OH) vitamin D above or below 50 nmol/l (N=453). Vitamin D deficient and vitamin D repleted subjects differed for annualized spine and hip BMD changes adjusted for all available confounding factors. 151 patients suffered from a new incident clinical fracture. The adjusted odds ratio for incident fractures in vitamin D deficient as compared to vitamin D repleted women was 1.77 (95% CI 1.20-2.59; p=0.004). Optimal vitamin D repletion seems to be necessary to maximize the response to antiresorbers in terms of both BMD changes and antifracture efficacy.

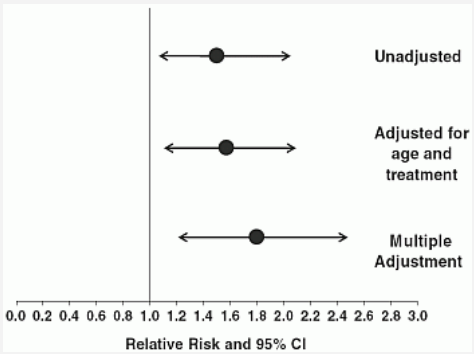

Fig. 10.2.192 Relative risk with 95% CI of annualized fracture incidence in vitamin D deficient relative to vitamin D repleted women, unadjusted and adjusted for age and treatment or for all potential confounders (type of treatment, age, previous clinical fractures, duration of follow-up, calcium intake, weight). Reproduced from Osteoporos Int 2009;20:239-44 with permission from Springer.

10.2.193 Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals
Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H
Osteoporos Int 2009;20:315-22

In 242 individuals (mean [±SD] age, 77±4 years). All serum 25-hydroxyvitamin D levels were below 78 nmol/l. Individuals received in a double blinded fashion either 1000 mg of calcium or 1000 mg of calcium plus 800 IU of vitamin D per day over 12 months, which was followed by a treatment-free but still blinded observation period of 8 months. Compared to calcium calcium plus vitamin D decreased in the number of subjects with first falls of 27% at month 12 (RR=0.73; CI=0.54-0.96) and 39% at month 20 (RR=0.61; CI=0.34-0.76) and improved quadriceps strength of 8%, a decrease in body sway of 28%, and a decrease in time needed to perform the TUG test of 11%.

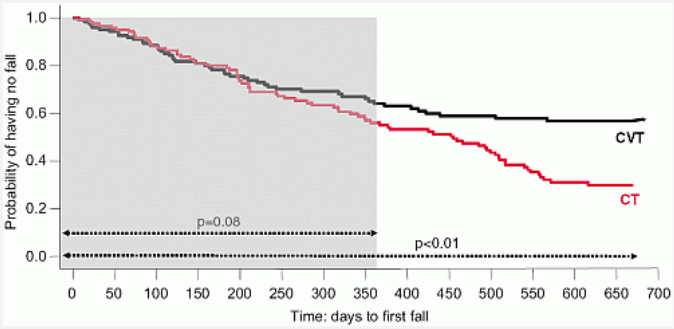

Fig. 10.2.193 Kaplan-Meier analysis demonstrating subjects with no falls. CVT Calcium plus vitamin D treatment, CT calcium mono treatment. Reproduced from Osteoporos Int 2009;20:315-22 with permission from Springer.

10.2.194 Hormone therapy improves femur geometry among ethnically diverse postmenopausal participants in the Women's Health Initiative hormone intervention trials
Chen Z, Beck TJ, Cauley JA, Lewis CE, Lacroix A, Bassford T, Wu G, Sherrill D, Going S
J Bone Miner Res 2008;23:1935-45

The authors hypothesized that hormone therapy improves the structural geometry of proximal femur cross-sections. In participants from Women's Health Initiative conjugated equine estrogen (CEE) only (N(placebo)=447, N(CEE)=422) trial or the estrogen (E) plus progestin (P) (N(placebo)=441, N(E+P)=503) trial were followed to 6 years. Femur geometry was derived from hip DXA scans using the hip structural analysis method. Treatment benefits (p<0.05) on femur geometry were observed at 1 year. From baseline to year 6, section modulus was preserved, and buckling ratio was decreased (p<0.05); the differences in the percent changes from baseline to year 6 between women on hormone intervention versus women on placebo were 2.3-3.6% for section modulus and -5.3% to -4.3% for buckling ratio.

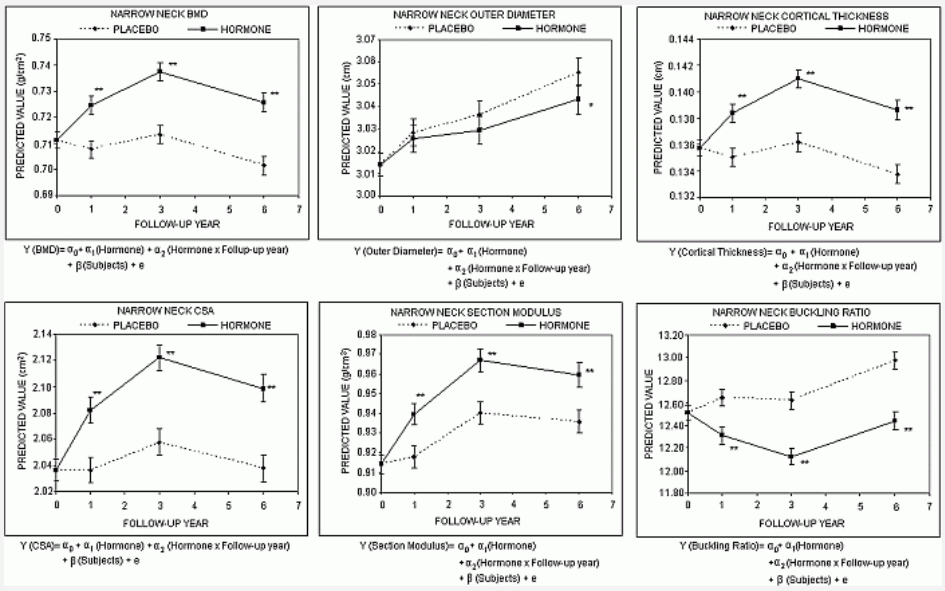

*Fig. 10.2.194 Predicted proximal femur geometry by intervention based on the random effects model (mean and SE). "Predicted value" is the predicted mean of HSA measurement based on the random effects model. α, fixed effects parameters; β, random effects parameters; e, residual error. *p<0.05, **p<0.01. Reproduced from J Bone Miner Res 2008;23:1935-45 with permission of the American Society of Bone and Mineral Research.*

10.2.195 Differential regulation of dehydroepiandrosterone and estrogen on bone and uterus in ovariectomized mice
Wang L, Wang YD, Wang WJ, Li DJ
Osteoporos Int 2009;20:79-92

Ovariectomized and sham BALB/c mice were given daily DHEA or E2 for three months. DHEA and E2 improved BMD and OB ultrastructure; E2 but not DHEA has increased uterus wet weight, endometrium epithelial and gland thickness. Dehydroepiandrosterone increased serum, femoral DHEA, DHEAS and E2 concentration uterine DHEA and DHEAS other than E2 concentration in site, while E2 only increased serum, uterine and femoral E2, but failed to alter the concentrations of DHEA and DHEAS. DHEA increased tibia P450arom enzyme activity, while E2 increased uterine and tibia aromatase activity. DHEA increased uterine ERβ and ERα, and ERβ transcription in the tibia, while E2 increased ERα transcription in the uterus and tibia. Dehydroepiandrosterone increased aromatase, ERα, ERβ and AR expression in OBs, and increased, but

E2 decreased the ratio of ERβ/ERα.

10.2.196 Fluoride effects on bone formation and mineralization are influenced by genetics
Mousny M, Omelon S, Wise L, Everett ET, Dumitriu M, Holmyard DP, Banse X, Devogelaer JP, Grynpas MD
Bone 2008;43:1067-74

This study assessed the effect of fluoride on bone formation, microarchitecture, mineralization and microhardness of the A/J, SWR/J and 129P3/J mouse strains. Fluoride had no effect on bone microarchitecture for any of the strains. All three strains demonstrated a significant increase in osteoid formation at the largest fluoride dose. Vertebral body trabecular bone BSE imaging revealed decreased mineralization heterogeneity in the SWR/J strain at 50 ppm and 100 ppm F(-). The trabecular and cortical bone mineralization profiles showed a nonsignificant shift towards higher mineralization with increasing F(-) dose in the three strains. Powder X-ray diffraction showed smaller crystals for the 129P3/J strain, and increased crystal width with increasing F(-) dose for all strains. There was no effect of F(-) on trabecular and cortical bone microhardness. The increased osteoid formation and decreased mineralization heterogeneity support the theory that F(-) delays mineralization of new bone. The increasing crystal width with increasing F(-) dose confirms earlier results and correlates with most of the decreased mechanical properties. An increase in bone F(-) may affect the mineral-organic interfacial bonding and/or bone matrix proteins, interfering with bone crystal growth inhibition on the crystallite faces as well as bonding between the mineral and organic interface.

10.2.197 Recollapse of previous vertebral compression fracture after percutaneous vertebroplasty
Heo DH, Chin DK, Yoon YS, Kuh SU
Osteoporos Int 2009;20:473-80

11 patients (7 females and 4 males; mean age, 69.91±5.49 years), out of a total of 343 patients, developed recollapse of the same vertebra after PVP. The 11 patients who developed recollapse comprised the "recollapse group", while the remaining 332 patients comprised the "well-maintained group". Pre-operative MRI revealed that the incidence of osteonecrosis was higher in the recollapse group than the well-maintained group ($p<0.05$). The degree of re-expansion of the compressed vertebral body after PVP was significantly higher in the recollapse group than in the well-maintained group ($p<0.05$). The most important predisposing factor for recollapse was pre-operative osteonecrosis. Recollapse was not related to trauma. Osteoporotic vertebral compression fracture with osteonecrosis or pseudoarthrosis has been regarded as a relative indication for PVP; however, the findings of this study suggest that this disease category may be a relative contraindication for PVP.

10.2.198 Suitability of a calcium phosphate cement in osteoporotic vertebral body fracture augmentation: A controlled, randomized, clinical trial of balloon kyphoplasty comparing calcium phosphate versus polymethylmethacrylate
Blattert TR, Jestaedt L, Weckbach A
Spine 2009;34:108-14

A prospective randomized controlled clinical study assessing calcium phosphate cement (CaP) in balloon kyphoplasty compared to polymethylmethacrylate (PMMA). 60 osteoporotic vertebral body fractures in 56 patients in 30 vertebrae each with 2-fracture-patients receiving only 1 type of cement for both vertebrae. All 60 fractures were classified compression fractures (type A). Of these, 27 were classified burst fractures (type A3). 52/56 patients experienced pain relief (7.9±1.9 to 1.8±2.1 on a Visual Analog Scale from 0 "best" to 10 "worst"). Bisegmental endplate angles were restored by 6.2 degrees ±5.9 degrees on average. Complications that turned out to be cement-specific were: vascular embolism (n=2) for PMMA; subtotal cement washout (n=1); and radiographic loss of correction (n=9) due to cement failure in burst fractures for CaP. There was no case of cement failure, when PMMA had been used. The routine use of the CaP tested is not recommended. Because of its low resistance against flexural, tractive, and shear forces compared to PMMA, in certain constellations (burst fractures), there is a higher risk of cement failure and subsequent loss of correction.

10.2.199 Incorporating adherence into health economic modelling of osteoporosis
Strom O, Borgstrom F, Kanis JA, Jonsson B
Osteoporos Int 2009;20:23-34

The objectives of this study were to develop a model that could address adherence and identify the important drivers of cost-effectiveness. An individual state transition model was constructed to compare medication with optimal adherence and was 50% more costly. Adherence was divided into persistence and compliance. Partial compliance was assumed to be associated with a 20% loss of antifracture effect. Nonpersistent patients had an offset time as long as their time on medication, to a maximum of 5 years. The potentially important drivers of cost-effectiveness include reduced drug effectiveness due to poor compliance, offset time, fracture risk, anti-fracture drug effect, and drug price. Optimal adherence was associated with fewer osteoporotic fractures, and the impact was more evident among those with prior fractures. However, the health benefits of adherence were often partially offset by increased intervention costs associated with the improved drug-taking behaviour. Adherence is likely to be associated with added value for healthcare systems, but should be used with care as a central health economic argument.

10.2.200 Initiation of anti-osteoporotic therapy in patients with recent fractures: A nationwide analysis of prescription rates and persistence
Roerholt C, Eiken P, Abrahamsen B
Osteoporos Int 2009;20:299-307

In 152,777 subjects treatment initiation within one year was highest after spine fracture: 39.6% of women began therapy in 2004 compared with 19.5% in 1997. In men, 16.5% began therapy in 2004 vs. 8.0% in 1997. Following hip fracture, 9.2% of women and 4.1% of men began therapy in 2004 vs. 3.4% and 0.7% in 1997, respectively. Median persistence (years) was 2.8 for daily alendronate, 3.8 for weekly alendronate, 2.5 for etidronate and 4.7 for raloxifene. The risk of discontinuing or changing therapy increased with age.

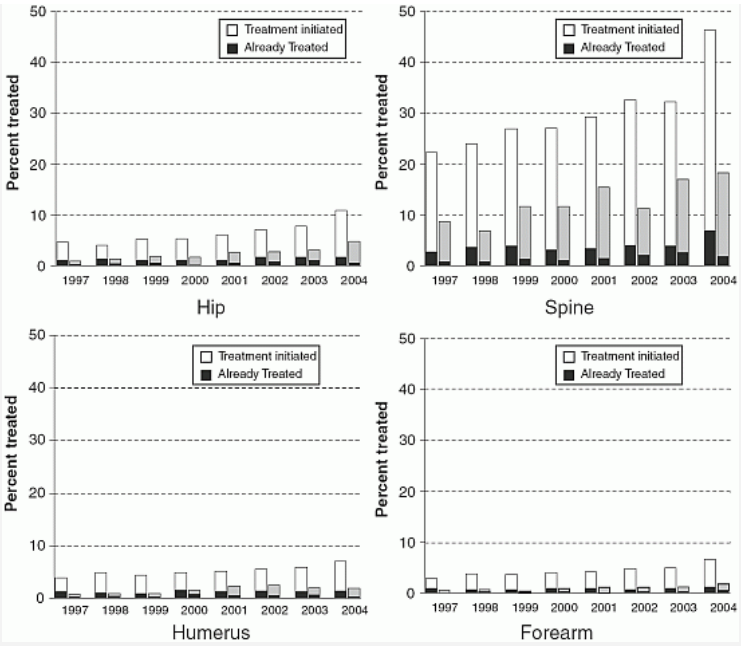

Fig. 10.2.200a Use of anti-osteoporotic treatment by fracture patients as a function of calendar year, sex and fracture location. Light bars indicate women and grey bars, men. Lower portion of stacked bars (black) indicates use of anti-osteoporotic medicine before the index fracture and upper portion indicates patients in whom therapy was begun in the first year following the index fracture. Reproduced from Osteoporos Int 2009;20:299-307 with permission from Springer.

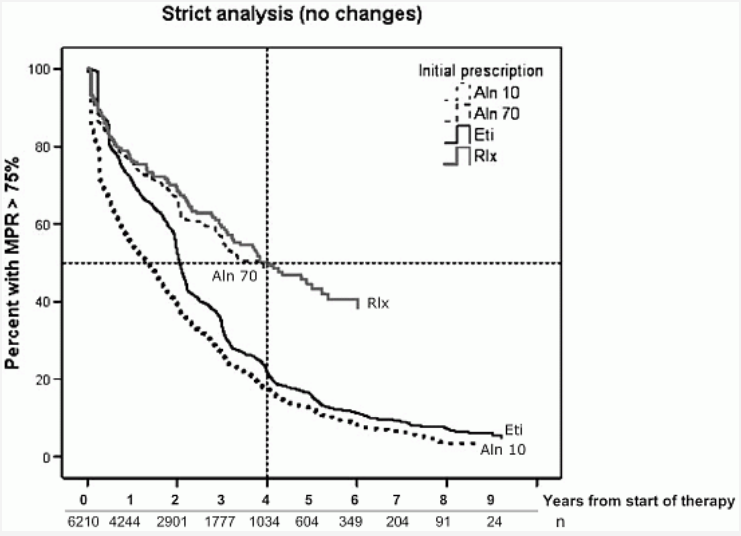

Fig. 10.2.200b Strict survival analysis for persistence – defined as maintenance of medication possession ratio (MPR) >75% over a 12-month period for the initially prescribed anti-osteoporotic drug, as a function of drug type and regime. Median duration of persistence was 1.3 years for alendronate 10 mg daily (Aln10), 3.7 years for alendronate 70 mg weekly (Aln70), 2.2 years for etidronate(Eti) and 4.0 years for raloxifene(Rlx). Reproduced from Osteoporos Int 2009;20:299-307 with permission from Springer.

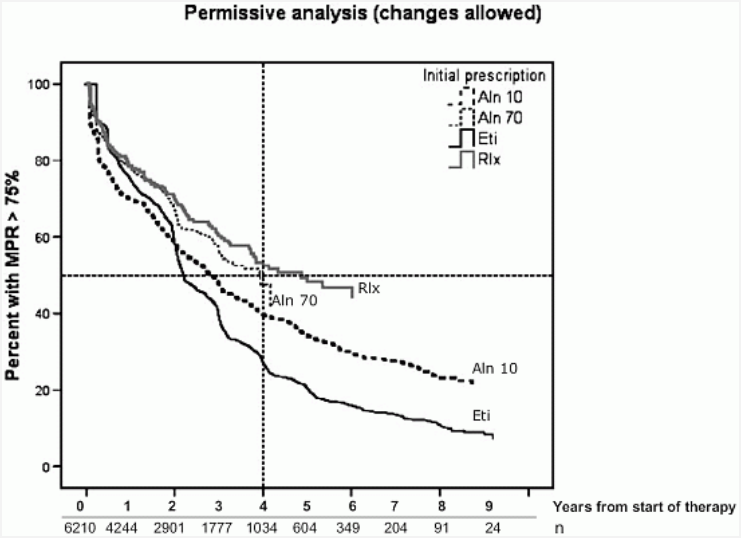

Fig. 10.2.200c Pragmatic survival analysis for persistence – defined as maintenance of medication possession ratio (MPR) >75% over a 12-month period allowing an unlimited number of changes between drugs – as a function of initial drug type and regime. Median duration of persistence was 2.8 years for alendronate 10 mg daily (Aln10), 3.8 years for alendronate 70 mg daily (Aln70), 2.5 years for etidronate (Eti), 4.7 years for raloxifene (Rlx). Reproduced from Osteoporos Int 2009;20:299-307 with permission from Springer.

Fig. 10.2.200d Strict survival analysis for persistence – defined as maintenance of medication possession ratio (MPR) >75% over a 12-month period for the initially prescribed anti-osteoporotic drug – as a function of year of treatment start. Median duration of persistence was 2.1 years before 2003 and 2.9 years for treatments initiated after 1/1/2003 (p<0.001). Raloxifene became available in Denmark in 1997 and once-weekly alendronate in 2000. Reproduced from Osteoporos Int 2009;20:299-307 with permission from Springer.

10.2.201 Management of osteoporosis in primary care in Australia
Chen JS, Hogan C, Lyubomirsky G, Sambrook PN
Osteoporos Int 2009;20:491-6

This study reviewed factors influencing the management of individuals at risk for osteoporosis in primary care settings in Australia and examined risk profiles of patients for osteoporosis. Patients (n=37,957, mean age 71) were recruited over a 12-month period and interviewed. 12.6% of patients reported a history of prior minimal trauma fracture, 7.5% reported a family history of osteoporosis, 7.4% reported they were current smokers, 11.4% reported low dietary calcium intake, 31.8% reported no regular weekly physical exercise and 10.3% reported current use of glucocorticoids. Of those with a prior fracture, only 29.7% were currently on specific medication for osteoporosis. Radiography (n=17,754) demonstrated a prior vertebral fracture in 30.1%, but only 3.8% of the 17,754 patients reported current use of specific osteoporosis medication.

10.2.202 A multifaceted intervention to improve treatment of osteoporosis in postmenopausal women with wrist fractures: A cluster randomized trial
Cranney A, Lam M, Ruhland L, Brison R, Godwin M, Harrison MM, Harrison MB, Anastassiades T, Grimshaw JM, Graham ID
Osteoporos Int 2008;19:1733-40

10.2.203 Prediction of changes in bone mineral density in postmenopausal women treated with once-weekly bisphosphonates
Burnett-Bowie SA, Saag K, Sebba A, de Papp AE, Chen E, Rosenberg E, Greenspan SL
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.2.204 Atorvastatin may have no effect on acute phase reaction in children after intravenous bisphosphonate infusion
Srivastava T, Haney CJ, Alon US
J Bone Miner Res 2009;24:334-7

10.2.205 Randomized, active-controlled study of once-weekly alendronate 280 mg high dose oral buffered solution for treatment of Paget's disease
Hooper M, Faustino A, Reid IR, Hosking D, Gilchrist NL, Selby P, Wu M, Salzmann G, West J, Leung A
Osteoporos Int 2009;20:141-50

10.2.206 Potential use of an estrogen-glucocorticoid receptor chimera as a drug screen for tissue selective estrogenic activity
Maru BS, Tobias JH, Rivers C, Caunt CJ, Norman MR, McArdle CA
Bone 2009;44:102-12

10.2.207 Estrogen and testosterone attenuate extracellular matrix loss in collagen-induced arthritis in rats
Ganesan K, Tiwari M, Balachandran C, Manohar BM, Puvanakrishnan R
Calcif Tissue Int 2008;83:354-64

10.2.208 In vitro and in vivo evidence for stimulation of bone resorption by an EP4 receptor agonist and basic fibroblast growth factor: Implications for their efficacy as bone anabolic agents
Downey ME, Holliday LS, Aguirre JI, Wronski TJ
Bone 2009;44:266-74

10.2.209 Beneficial effects of tocotrienol and tocopherol on bone histomorphometric parameters in Sprague Dawley male rats after nicotine cessation
Hermizi H, Faizah O, Ima-Nirwana S, Ahmad Nazrun S, Norazlina M
Calcif Tissue Int 2009;84:65-74

10.2.210 Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma
Brunello A, Saia G, Bedogni A, Scaglione D, Basso U
Bone 2009;44:173-5

10.2.211 Spinal extension exercises prevent natural progression of kyphosis
Ball JM, Cagle P, Johnson BE, Lucasey C, Lukert BP
Osteoporos Int 2009;20:481-9

10.2.212 Design of the POSSIBLE UStrade mark Study: Postmenopausal women's compliance and persistence with osteoporosis medications
Barrett-Connor E, Ensrud K, Tosteson AN, Varon SF, Anthony M, Daizadeh N, Wade S
Osteoporos Int 2009;20:463-72

10.2.213 Improving detection and treatment of osteoporosis: Redesigning care using the electronic medical record and shared medical appointments
Ayoub WT, Newman ED, Blosky MA, Stewart WF, Wood GC
Osteoporos Int 2009;20:37-42

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Exercise

10.2.214 A longitudinal study of the relationship of physical activity to bone mineral accrual from adolescence to young adulthood
Baxter-Jones AD, Kontulainen SA, Faulkner RA, Bailey DA
Bone 2008;43:1101-7

Data were from 154 subjects (82 females and 72 males) who participated in the University of Saskatchewan's Pediatric Bone Mineral Accrual Study (1991-1997), entry age 8-15 years. Participants returned for follow-up as young adults (2002-2006), follow-up age 23-30 years. Subjects were ranked into three adolescent activity groups: active, average and inactive (top, middle two, and bottom quartiles, respectively). When compared to the inactive group, active males had 8% greater adjusted BMC at the TB, 13% at the LS and 11% at the TH ($p<0.05$) in adolescence. Active females also had 8% and 15% more adjusted BMC ($p<0.05$) at the TB and LS, respectively, during adolescence. In young adulthood the male and female adolescent active groups were still more active than their peers ($p>0.05$). It was found that active adolescent males had 8-10% more adjusted BMC at the TB, TH and FN ($p<0.05$) in young adulthood and that active adolescent females had 9% and 10% more adjusted BMC at the TH and FN.

10.2.215 The effects of frequency-dependent dynamic muscle stimulation on inhibition of trabecular bone loss in a disuse model
Lam H, Qin YX
Bone 2008;43:1093-100

56 skeletally mature Sprague Dawley rats were divided into seven groups for the 4-week experiment: hindlimb suspended (HLS), and HLS with muscle stimulation at 1 Hz, 20 Hz, 50 Hz, and 100 Hz. HLS alone for 4 weeks resulted in an amount of trabecular bone loss and structural deterioration. Muscle contraction at 1 Hz was not sufficient to inhibit trabecular bone loss and resulted in a similar amount of loss to that of HLS alone. Bone quantity and structure were improved by applying muscle stimulation at midfrequency (20 Hz and 50 Hz). Dynamic stimulation at 50 Hz demonstrated the greatest preventive effect on the skeleton against functional disused alone animals (up to +147% in bone volume fraction, +38% in trabecular number and -36% in trabecular separation). Histomorphometric analysis showed that the stimulation, regardless of its frequency, did not have an effect on the bone formation indices.

10.2.216 Physical activity and bone turnover markers: A cross-sectional and a longitudinal study
Adami S, Gatti D, Viapiana O, Fiore CE, Nuti R, Luisetto G, Ponte M, Rossini M
Calcif Tissue Int 2008;83:388-92

10.2.217 The effect of exercise and estrogen on osteoprotegerin in premenopausal women
West SL, Scheid JL, De Souza MJ
Bone 2009;44:137-44

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Men

10.2.218 Genetic variation in sex hormone genes influences heel ultrasound parameters in middle-aged and elderly men: Results from the European Male Aging Study (EMAS)
Limer KL, Pye SR, Thomson W, Boonen S, Borghs H, Vanderschueren D, Huhtaniemi IT, Adams JE, Ward KA, Platt H, Payne D, John SL, Bartfai G, Casanueva F, Finn JD, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Silman AJ, Wu FC, O'Neill
J Bone Miner Res 2009;24:314-23

In 2693 men, associations were observed between multiple SNPs in a linkage disequilibrium block within CYP19A1, peaking at the TCT indel with the deletion allele associating with reduced ultrasound BMD in heterozygotes (β=–0.016, p=–0.005) and homozygotes (β=–0.029, p=0.001). Significant associations with QUS parameters were also observed for the CAG repeat in AR and SNPs in CYP17A1, LHCGR, and ESR1.

10.2.219 Vertebral fractures are associated with increased cortical porosity in iliac crest bone biopsy of men with idiopathic osteoporosis
Ostertag A, Cohen-Solal M, Audran M, Legrand E, Marty C, Chappard D, de Vernejoul MC
Bone 2009;44:413-7

93 bone biopsies from men with idiopathic osteoporosis (40 and 70 yrs of age) were studied. Patients were divided into two groups on the basis of the presence (n=46) or absence (n=47) of prevalent vertebral fracture (VFX). Patients with VFX had lower trabecular bone volume (BV/TV: 12.4±3.8 vs. 14.7±3.1% (m±SD), p<0.01), higher trabecular separation (Tb.Sp: 871±279 vs. 719 ±151 µm, p<0.01), and higher marrow star volume (V(m.space): 1.617±1.257 vs. 0.945±0.466 mm^3, p<0.01). Cortical thickness (Ct.Th) was the same in patients with or without VFX, cortical porosity (Ct.Po) was higher in patients with VFX (6.5±2.6 vs. 5.0 ±2.0%, p<0.01), because their Haversian canals had higher mean areas (8291±4135 vs. 5438±2809 $µm^2$, p<0.001). There was no correlation between any trabecular and cortical microarchitectural parameters. Using a logistic regression model, we evaluated the VFX as a function of the V(m.space) and Ct.Po, adjusted for age. The odds-ratio of having a VFX was 3.89 (95% CI 1.19-12.7, p=0.02) for the third tertile of V(m.space) (adjusted on age and Ct.Po), and 4.07 (95% CI 1.25-13.3, p=0.02) for the third tertile of Ct.Po (adjusted on age and V(m.space)).

10.2.220 Sex steroids and bone turnover markers in men with symptomatic vertebral fractures
Tuck SP, Scane AC, Fraser WD, Diver MJ, Eastell R, Francis RM
Bone 2008;43:999-1005

In 57 men with vertebral fractures and 57 age-matched male control subjects, men with vertebral fractures had lower weight and BMD. Serum total testosterone and estradiol did not differ between the two groups, but calculated free androgen and free oestradiol indices were lower in the fracture group than the controls due to higher SHBG (46.6 vs. 36.1 nmol/L; p=0.005). The men with vertebral fractures had higher mean bone ALP (15.8 vs. 11.8 µg/L; p=0.002) and fDPD/Cr (5.5 vs. 4.0 nmol/mmol; p=0.03). Body weight was the best predictor of BMD. In the fracture group, weight predicted between 19.7% and 30.7% of the variance in BMD, and in control subjects this was between 12.3% and 13.2%. SHBG contributed to the model for hip BMD in the fracture group alone, so that weight and SHBG together accounted for 32-42.9% of the variance.

10.2.221 Vitamin D deficiency in older men
Orwoll E, Nielson CM, Marshall LM, Lambert L, Holton KF, Hoffman AR, Barrett-Connor E, Shikany JM, Dam T, Cauley JA
J Clin Endocrinol Metab 2009;[Epub ahead of print]

1606 older men enrolled in the Osteoporotic Fractures in Men Study Setting. Deficiency (25(OH)D <20 ng/mL) was present in 26% and insufficiency (<30 ng/mL) in 72%. Deficiency was particularly common among men during the winter and spring (especially in the Northern communities), and in the oldest and more obese men. For instance, in Caucasian men in winter or spring who were >80 years, did not engage in lawn/garden work, and had a BMI >25 and vitamin D intake <400 IU/day, the prevalence of vitamin D deficiency was 86%. 25(OH)D2 levels were present in a small fraction of men, and accounted for a low proportion of total 25(OH) D levels. The use of vitamin D supplements was reported by 58% of men, but supplement use had a small effect on total 25(OH) D levels and despite supplement use low levels remained frequent. Vitamin D deficiency is common in older men, and is especially prevalent in obese, sedentary men living at higher latitudes. Use of vitamin D supplements at levels reported here did not result in adequate vitamin D nutrition.

10.2.222 Wintertime vitamin D supplementation inhibits seasonal variation of calcitropic hormones and maintains bone turnover in healthy men
Viljakainen HT, Väisänen M, Kemi V, Rikkonen T, Kröger H, Laitinen EKA, Rita H, Lamberg-Allardt C
J Bone Miner Res 2009;24:346-52

Subjects (N=48) were healthy white men 21-49 years of age from the Helsinki area with a mean habitual dietary intake of vitamin D of 6.6±5.1 (SD) µg/d. This was a 6-month double-blinded vitamin D intervention study, in which subjects were allocated to three groups of 20 µg (800 IU), 10 µg (400 IU), or placebo. Supplementation inhibited the winter elevation of PTH (p=0.035), decreased the S-BALP concentration (p<0.05), but benefited cortical BMD (p=0.09) only slightly. A daily intake of vitamin D in the range of 17.5-20 µg (700-800 IU) seems to be required to prevent winter seasonal increases in PTH and maintain stable bone turnover in young, healthy white men.

10.2.223 Serum 25-hydroxyvitamin D and bone mineral density among Hispanic men
Araujo AB, Travison TG, Esche GR, Holick MF, Chen TC, McKinlay JB
Osteoporos Int 2009;20:245-55

358 Hispanic males 30-79 years of age were studied. Logistic regression models assessed variation in odds of vitamin D deficiency (<20 ng/mL) and low BMD (T-score<–1) by ethnicity, with and without adjustment for risk factors (age, smoking, occupation, physical activity, body mass index, and sunlight exposure). Vitamin D deficiency was most common among Puerto Rican (26%), compared with Dominican (21%), Central American (11%), and South American (9%) men. Percentages with low BMD were: South American (44%), Puerto Rican (34%), Dominican (29%), and Central American (23%). Adjustment for age and risk factors failed to account for Hispanic subgroup differences in vitamin D deficiency and low BMD.

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Calcif Tissue Int 2008;83:365-7

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Rosen CJ
J Bone Miner Res 2008;23:1881-3

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Melton LJ, 3rd, Marquez MA
Osteoporos Int 2008;19:1679-81

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J Bone Miner Res 2009;24:3-7

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Bone 2009;44:11-6

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Little DG
J Bone Miner Res 2009;24:179-81

10.2.230 Osteal macrophages: A new twist on coupling during bone dynamics
Pettit AR, Chang MK, Hume DA, Raggatt LJ
Bone 2008;43:976-82

10.2.231 Regulation of osteoarthritis development by Wnt-beta-catenin signaling through the endochondral ossification process
Kawaguchi H
J Bone Miner Res 2009;24:8-11

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Williams BO, Insogna KL
J Bone Miner Res 2009;24:171-8

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Briggs AM, Straker LM, Wark JD
Osteoporos Int 2009;20:209-19

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10.2.234 Infantile malignant, autosomal recessive osteopetrosis: The rich and the poor
Villa A, Guerrini MM, Cassani B, Pangrazio A, Sobacchi C
Calcif Tissue Int 2009;84:1-12

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10.2.235 International society for clinical densitometry 2007 adult and pediatric official positions
Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, Kalkwarf HJ, Langman CB, Plotkin H, Rauch F, Zemel BS, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Silverman S
Bone 2008;43:1115-21

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10.2.236 Clinical review 1: Bisphosphonate use in childhood osteoporosis
Bachrach LK, Ward LM
J Clin Endocrinol Metab 2009;94:400-9

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10.2.237 Biochemical markers of bone turnover: Potential use in the investigation and management of postmenopausal osteoporosis
Szulc P, Delmas PD
Osteoporos Int 2008;19:1683-704

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10.2.238 Risk factors for low bone mass in healthy 40-60 year old women: A systematic review of the literature
Waugh EJ, Lam MA, Hawker GA, McGowan J, Papaioannou A, Cheung AM, Hodsman AB, Leslie WD, Siminoski K, Jamal SA
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Anagnostis P, Karagiannis A, Kakafika AI, Tziomalos K, Athyros VG, Mikhailidis DP
Osteoporos Int 2009;20:197-207

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Bianchi ML, Bardella MT
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Seeman E
Osteoporos Int 2009;20:187-95

10.2.242 Osteonecrosis of the jaw – Who gets it, and why?
Reid IR
Bone 2009;44:4-10

10.2.243 Osteonecrosis of the jaw
Reid IR, Cundy T
Skeletal Radiol 2009;38:5-9

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Campaign Description

Campaign Vision

The IOF Invest in Your Bones campaign vision is of a world without osteoporotic fractures through increasing awareness and understanding of osteoporosis. The emphasis is also on improving quality of life and on the healthcare budget. In addition, the Invest in Your Bones campaign aims to sensitise health professionals, including general practitioners, radiologists and orthopaedic surgeons.

About the Campaign

In 2002, IOF inaugurated the first phase of the Invest in Your Bones Campaign. The campaign, now in its fourth phase (beginning in 2008), supports projects aimed at improving access to, and reimbursement of, diagnosis and proven therapies in individuals at high risk of fragility fracture. It has a geographic focus on France, Germany, Italy, Spain and the UK.

The campaign also helps the IOF to support the 'Call for Action' at the EU, through various policy and lobbying activities, including support to the European Parliament Osteoporosis Interest Group and EU Osteoporosis Consultation Panel.

Other key ongoing projects supported by the campaign include the Osteoporosis Education Program to Improve the Recognition and Reporting of Vertebral Fractures by Radiologists; an initiative involving orthopaedic surgeons aimed at optimizing the care of fragility fracture patients; the development of health economics studies in osteoporosis; and support to the development of new guidelines for assessing fracture risk in individuals.

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Michelangelo (1475-1564): Last Judgement - detail (Saint Bartholomew) [before restoration], Vatican, Sistine Chapel ©1990. Photo Scala, Florence

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International Osteoporosis Foundation

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IOF News

IOF WCO–ECCEO10
May 5 - 8, 2010
Florence, Italy
More information

FRAX® – WHO Fracture Risk Assessment Tool
Helping health professionals worldwide to improve identification of patients at high risk of fracture for treatment . More information

2010 IOF-Servier Young Investigator Research Grant

Applications are now being accepted. This grant supports young scientists who are carrying out outstanding original research of international relevance in the field of osteoporosis. More information

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Life is short, the art long, opportunity fleeting,
experiment treacherous, judgement difficult.

Hippocrates

Overview

Treating everyone

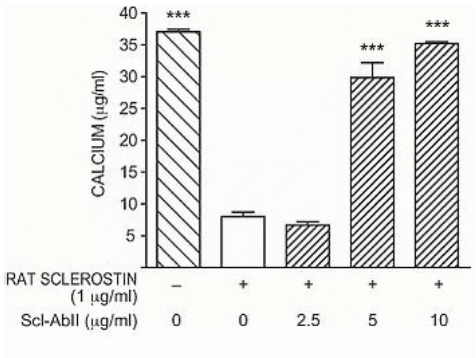
While the aim of treatment is to eliminate fractures as a public health problem, this goal is a formidable challenge as treatment must be safe and cost effective. Densitometry is not sensitive or specific. The BMD measurement identifies only half of all the persons who come to fracture and many people with osteoporosis do not fracture; there are many reasons for this. So there is an option – treat everyone from an early age. This would be feasible, like vaccination against small pox, provided the treatment was safe, effective, inexpensive, and easily administered. Well, treatments have not been shown to be effective in all persons. Indeed, there are many problems. Most drugs reduce vertebral fractures by only 50%; of the few drugs shown to reduce nonvertebral and hip fractures, the antifracture efficacy is about 20% for the former and 50% for the latter. Compliance is a problem and these drugs are not free from side effects or free in terms of cost. So, there are cogent arguments for not treating whole populations.

Donaldson et al estimated the proportion of older white women who would be recommended for pharmacologic treatment by the new U.S. National Osteoporosis Foundation Guidelines. The new Guidelines include recommending pharmacologic treatment based on history of hip or vertebral fracture, femoral neck (FN), or spine BMD T-scores ≤–2.5 and presence of low bone mass at the FN or spine plus a 10-yr risk of hip fracture ≥3% or of major osteoporotic fracture ≥20%. Application of NOF guidelines to SOF

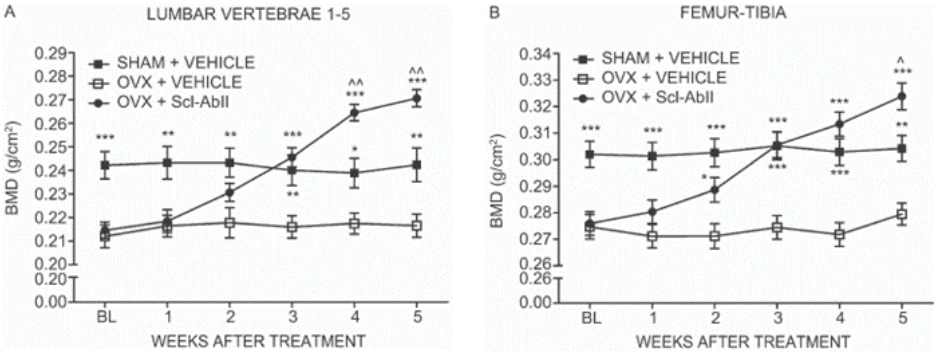
data estimated that at least 72% of U.S. white women ≥65 yr of age and 93% of those ≥75 yr of age would be recommended for drug treatment. **J Bone Miner Res 2009;24:675-80**

Advances in treatment

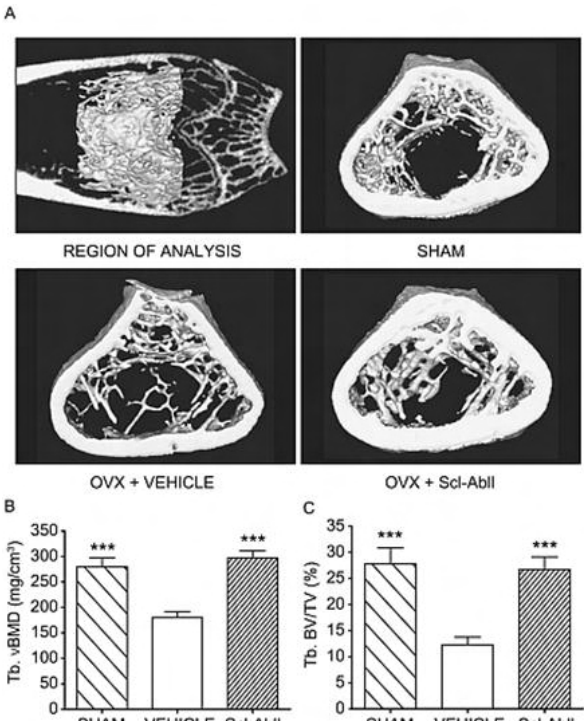
The search for an anabolic agent continues. While parathyroid hormone appears to confer some structural benefits, newer approaches are needed for a range of reasons. **Li et al** present the first clinical data supporting a role for sclerostin antibody as a new kid on the anabolic block. Scl-AbII was administered for 5 wk and increased bone formation on trabecular, periosteal, endocortical and intracortical surfaces. This not only resulted in complete reversal, at several skeletal sites, but also further increased bone mass and strength to levels greater than those found in nonovariectomized control rats. **J Bone Miner Res 2009;24:578-88**

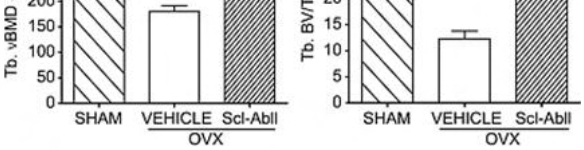


Neutralization of recombinant rat sclerostin by Scl-AbII in a 12-day osteoblast-lineage cell differentiation and mineralization assay using mouse MC3T3-E1 cells. Mineralization (crystalline calcium phosphate formation) represents an in vitro model of bone formation. The extent of mineralization was quantified by solubilizing crystalline calcium phosphate and measuring total calcium. Scl-AbII is a hybridoma-derived mouse IgG1 mAb. Data represent mean±SE; n=3 per group. ***p<0.001 vs. cell cultures treated with rat sclerostin and no Scl-AbII. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.



Scl-AbII treatment increases areal BMD at lumbar vertebrae and femur-tibia. Six-month-old female rats underwent OVX or sham surgery and were aged 13 mo to allow for estrogen deficiency–induced bone loss. By the end of the aging period, baseline (BL) BMD in OVX rats was significantly lower than in sham-operated animals. A group of OVX rats (19 mo old) was treated for 5 wk with Scl-AbII. Sham-operated and OVX rats treated with vehicle were the control groups. BMD was measured in vivo by DXA at BL just before treatment and weekly thereafter at lumbar vertebrae (A) and femur-tibia (B). y-axes were truncated for clarity. Data represent mean±SE for 11-12 rats/group. *p<0.05, **p<0.01, and ***p<0.001 vs. OVX+vehicle. ^p<0.05 and ^^p<0.01 vs. Sham+vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.

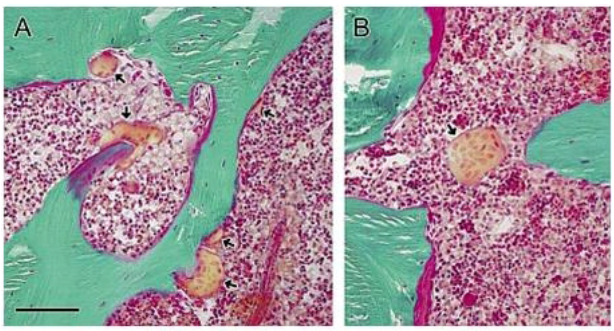




Scl-AbII treatment in osteopenic rats restores trabecular BMD and bone volume back to sham levels at distal femur. (A) The distal femur region of analysis (top left panel) and representative 3D µCT images of a 1-mm central section (with attached cortices) from each of the three groups. Representative 3D images were selected based on the median trabecular bone volume (Tb. BV/TV) of each group. (B) Values for trabecular volumetric BMD (Tb.vBMD). (C) Values for Tb.BV/TV. Data represent mean±SE for 11-12 rats/group. ***p<0.001 vs. OVX+vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.

Giant osteoclasts and bisphosphonate therapy

Cheung et al report that pamidronate therapy increased osteoclast diameter and the mean number of nuclei per osteoclast, but no structural abnormalities accompanied these changes in morphology. Indeed, a higher cancellous bone volume per tissue volume was observed in this study of children with osteogenesis imperfecta. The mechanisms responsible for the large osteoclasts and the insights this observation may provide regarding bisphosphonate action remain elusive. **J Bone Miner Res 2009;24:669-74**



Iliac bone specimen from a 17-yr-old adolescent with OI type IV after 2.9 yr of pamidronate treatment. Osteoclasts are marked by arrows. The magnification bar corresponds to 100 µm. (A) Both osteoclasts with bloated appearance and osteoclasts with normal size are visible. (B) Large osteoclast, which appears to be detached from the bone surface. Reproduced from J Bone Miner Res 2009;24:669-74 with permission of the American Society of Bone and Mineral Research.

Bisphosphonates cause fractures

Odvina et al report 13 patients who sustained atraumatic midshaft fractures, 10 were on alendronate and 3 were on risedronate therapy and other therapy as well. This is likely due to prolonged suppression of bone turnover, which could lead to accumulation of microdamage and development of hypermineralized bone. At present, the scope of this complication in the larger context of patients receiving bisphosphonate therapy is not known but appears to be small. **Clin Endocrinol (Oxf) 2009; [Epub ahead of print]**

Does life imitate art?

Eswaran et al report that T10 vertebral bodies from skeletally mature female beagle dogs where treated with risedronate for one year. Stiffness of the whole vertebra and the trabecular compartment increased while the computed stiffness of the cortical shell was unaltered. Despite higher cortical thickness, maximum load taken by the shell was lower and changes in the compressive stiffness was attributable to the changes in the trabecular compartment than in the cortical shell. The authors held tissue material density constant in this calculation even though bisphosphonates increase tissue mineral density. **J Biomech 2009;42:517-23**

Is osteonecrosis mucosal in origin?

Scheper et al suggest that osteonecrosis of the jaw originates as damage to soft tissues of the oral mucosa. The authors report that human gingival fibroblast and keratinocyte cell lines exposed to zoledronic acid produced apoptosis and cell proliferation reversed using siRNA against caspase 3 or 9. Zoledronic acid rapidly and directly affected the oral mucosal tissues though the induction of a gene-regulated apoptosis. **Br J Haematol 2009;144:667-76**

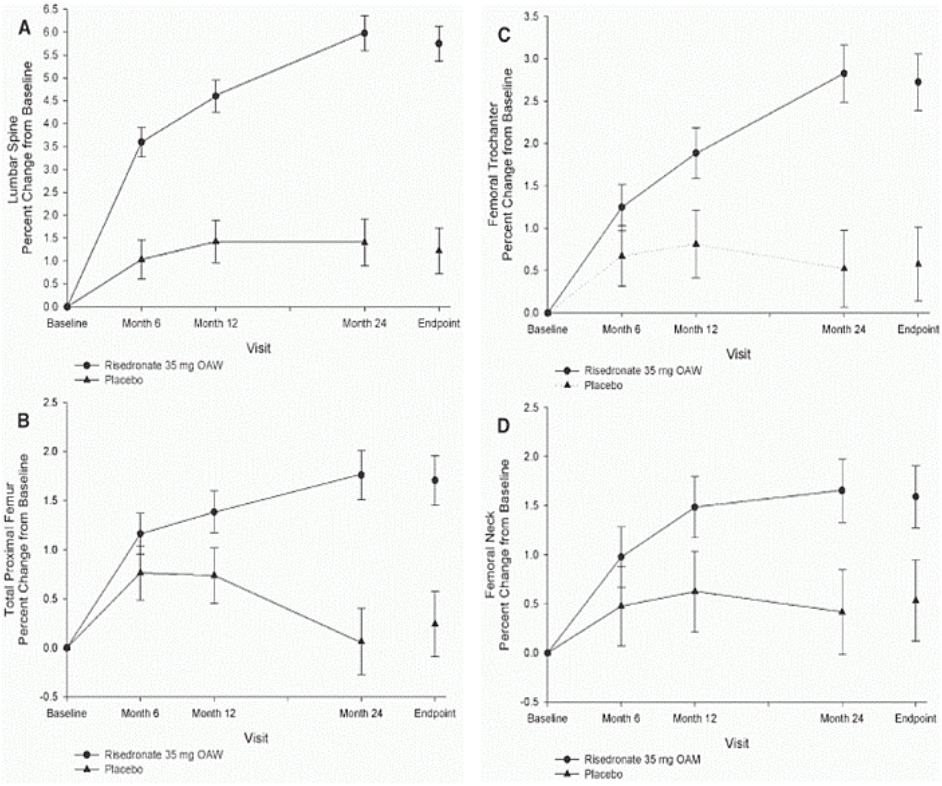
Study structure

Brennan et al illustrate the need to study the structural basis of bone strength when therapy is used. In this animal model, pamidronate (APD), raloxifene, PTH(1-34) or vehicle were given for 16 wk. PTH induced greater maximal load than APD or raloxifene, as well as greater absorbed energy, BMD, and increased bone turnover markers. PTH increased trabecular bone volume and connectivity higher than sham. Animals treated with APD had BV/TV values higher than OVX but lower than sham, whereas raloxifene had no effect. Tissue hardness was identical in PTH-treated and OVX untreated controls. APD reversed the decline in strength, reduced bone turnover, and increased hardness. Raloxifene increased cortical hardness and elastic modulus. These results show the different mechanisms by which these drugs reduce fracture risk. PTH influences microarchitecture, whereas bisphosphonates alter material level bone properties. Raloxifene improved the material stiffness. **J Bone Miner Res 2009;24:800-8**

Men

Boonen et al report one of the few trials of antiresorptives in men. This multinational, 2-yr, randomized, double-blind, placebo-controlled study was conducted to determine the efficacy and safety of 35 mg once-a-week risedronate in 284 men with osteoporosis. Treatment increased spine BMD compared with placebo (4.5%; 3.5-5.6%). There was a reduction from baseline

in BTMs and therapy was well tolerated and was rapidly effective as indicated by BTM decreases at month 3 and BMD increases at month 6. **J Bone Miner Res 2009;24:719-25**



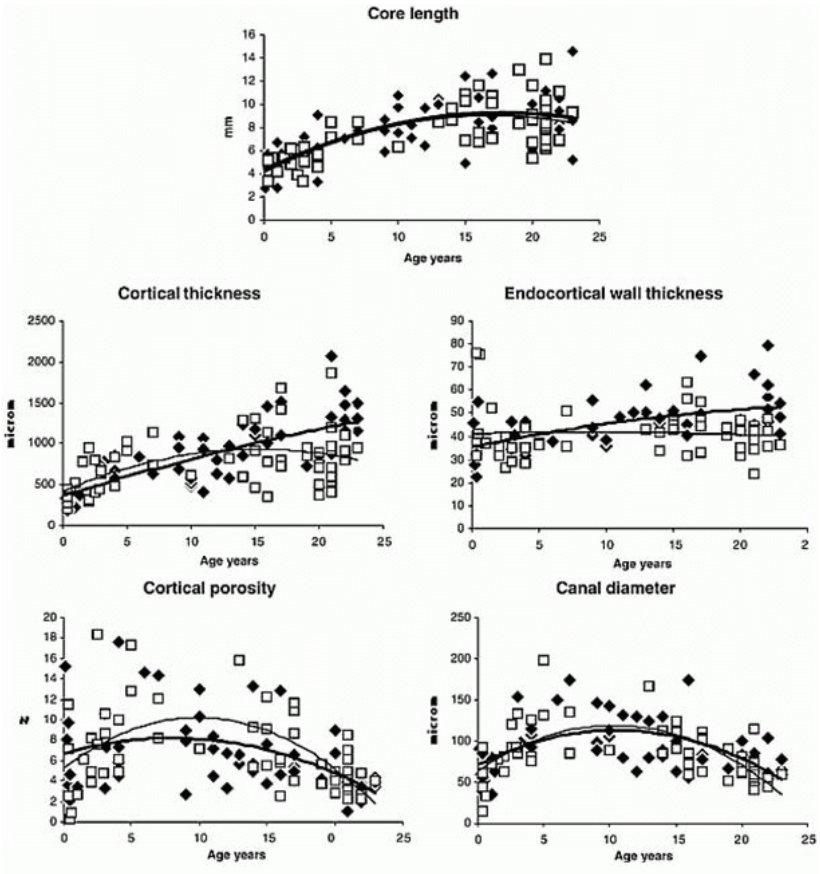
Least squares mean percent change from baseline (±SE) in BMD (intent-to-treat population): (A) lumbar spine BMD, (B) total proximal femur BMD, (C) femoral trochanter BMD, and (D) femoral neck BMD. Reproduced from J Bone Miner Res 2009;24:719-25 with permission of the American Society of Bone and Mineral Research.

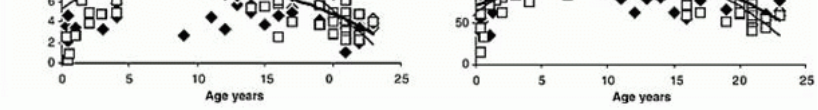
Roles of cortical and trabecular bone in whole bone strength

Holzer et al present interesting data suggesting that trabecular bone plays a minor role in proximal femur strength in vitro. In this study, the authors removed trabecular bone from the femoral neck and report that differences between forces needed to fracture excavated and intact femurs was 7.0%, so the contribution of trabecular in respect to bone strength in the femoral neck seems to be marginal. **J Bone Miner Res 2009;24:468-74**

Youth is wasted on the Old

Schnitzler et al report that the structural basis of racial differences in bone fragility in adulthood originates during growth. In one of the few histomorphometric studies in children, the authors report similar increases with age in cortical thickness by race until age 15 where after it continued to increase in Blacks. Canal number was lower in Blacks. **Bone 2009;44:603-11**

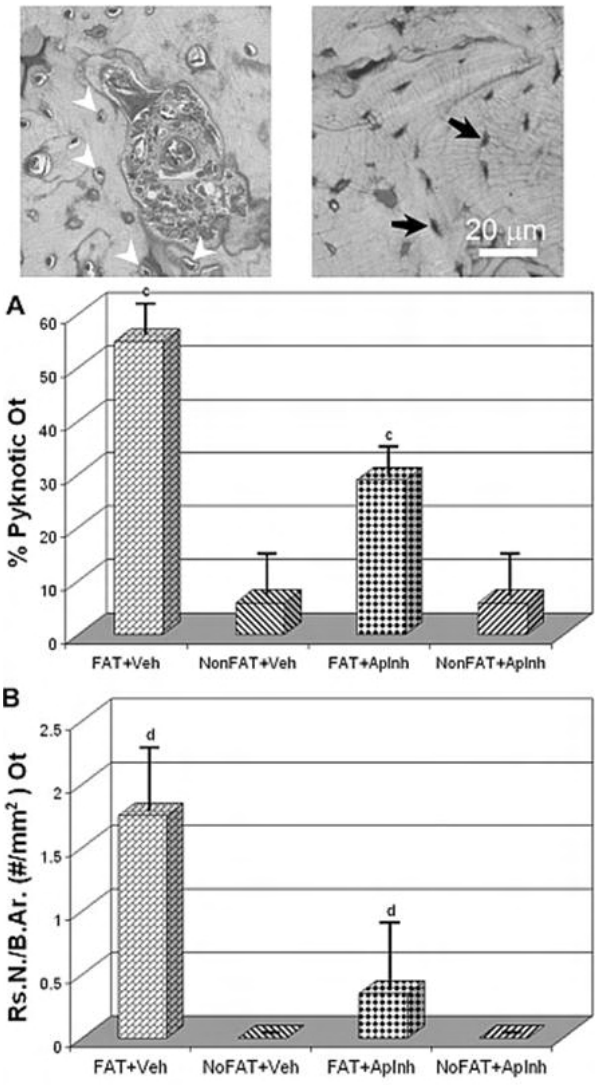




Scatterplots and polynomial regression lines on age for core length, cortical thickness, endocortical wall thickness, cortical porosity and canal diameter of transiliac bone samples from black and white children. Blacks: black diamonds and bold regression lines. Whites: empty squares and thin regression lines. Reproduced from Bone, 44:603-11, Copyright (2009), with permission from Elsevier.

Initiation of remodelling

The initial steps in initiation of bone remodelling remain uncertain. However, the role of osteocyte apoptotic death seems to be a potential candidate. In a very elegant study by **Cardoso et al**, in vivo fatigue loading of ulna in Sprague Dawley rats induced microdamage and apoptotic osteocytes colocalized with resorption in the region. Prevention of apoptotic death blocked activation of osteoclastic resorption, whereas short-term caspase inhibition was during only the first two days after fatigue. Osteocyte apoptosis is necessary to initiate intracortical remodelling in response to fatigue microdamage; a dose-response relationship exists between the two processes, and early apoptotic events after fatigue-induced microdamage may play a substantial role in determining tissue remodelling. **J Bone Miner Res 2009;24:597-605**



Effects of short-duration apoptosis inhibition on osteocyte apoptosis and intracortical resorption at 14 days after loading. Treatment with Q-VD-OPh for 2 days immediately after fatigue loading resulted in a nearly 50% reduction of osteocyte apoptosis compared with vehicle treated animals. Data are shown for pyknotic osteocytes (A; $^{c}p<0.01$); the accompanying photomicrographs show pyknotic, retracted osteocytes (left photo, white arrows) and normal osteocytes in control bone (right photo, black arrows). Acute treatment with apoptosis inhibitor suppressed the fatigue-induced activation of intracortical resorption by; 75% relative to vehicle-treated animals (B, $^{d}p<0.025$). Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.

Bone loss by intracortical remodelling

Rittweger et al give new insights into immobilization-induced bone loss based on observations in 10 healthy male volunteers in whom relative losses were larger from cortical than from trabecular compartments and cortical thinning occurred from within, by trabecularization of the subendocortical layer of cortex. **Bone 2009;44:612-8**

Treatment and FRAX®

Kanis et al report drug efficacy in relation to fracture risk derived from FRAX® algorithms. The relationship between pre hoc 10-year fracture probabilities and efficacy of bazedoxifene was found with a 39% decrease in incident morphometric vertebral fractures and a nonsignificant 16% decrease in all clinical fractures. Hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability. In patients with 10-year fracture probabilities at or above 16%,

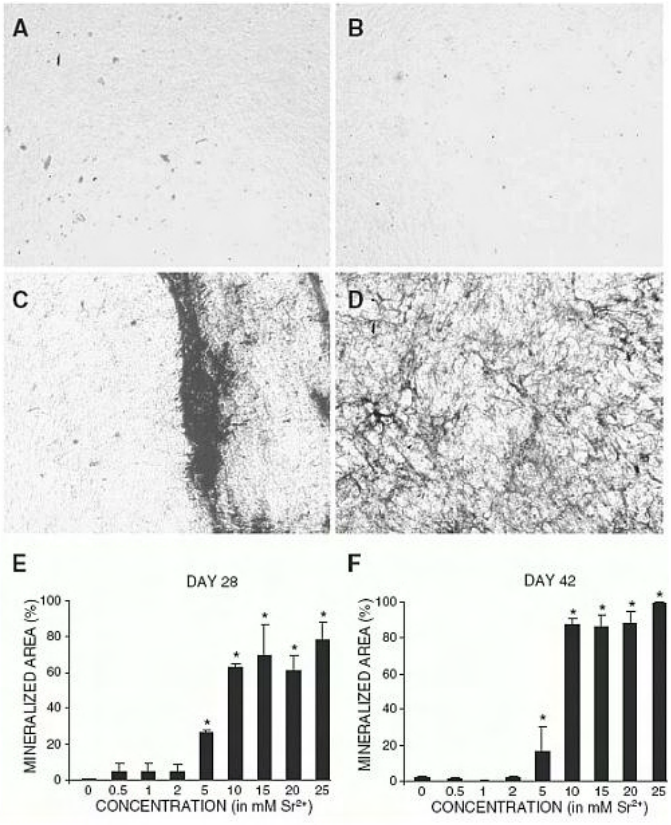
bazedoxifene decreased the risk of all clinical fractures. In patients with 10-year fracture probabilities above 6.9%, bazedoxifene decreased the risk of morphometric vertebral fractures. Bazedoxifene (20 and 40 mg doses combined) decreased the risk of all clinical fractures and morphometric vertebral fractures in women at or above a FRAX® based fracture probability threshold. **Bone 2009;44:1049-54**

PTH and CatK

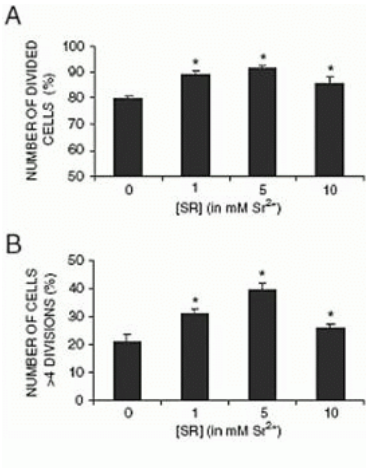
Yamane et al report that mice treated with cathepsin K inhibitor, alendronate with or without PTH (1-34) have differing responses. CatK inhibitor and alendronate increased the BMD and the bone volume. CatK inhibitor augmented PTH while alendronate had the same effect on the BMD and bone volume only at the primary spongiosa. CatK inhibitor did not decrease serum osteocalcin while alendronate did. CatK inhibitor did not decrease osteoclast number or bone formation rate with or without PTH, while alendronate decreased those values and increased osteoclast apoptosis. PTH and CatK inhibitor together increased alkaline phosphatase-positive CFU-F formation and c-fos, osterix, and osteocalcin mRNA expressions of bone marrow cells as well as PTH alone, while PTH and alendronate decreased those values. Alendronate enhances the anabolic action of PTH at the primary spongiosa, but blunts it in the remodelling trabecular bone, while CatK inhibitor enhances the action at both sites. **Bone 2009;44:1055-62**

Strontium and bone formation

Atkins et al report that adult human primary osteoblasts exposed to strontium ranelate (SR) increased osteoblast replication, induced an osteocyte-like phenotype, and increased in vitro mineralization. mRNA levels of dentin matrix protein (DMP)-1 and sclerostin suggest the presence of osteocytes. SR also increased the OPG/RANKL ratio throughout the culture period. This study suggests that SR can promote osteoblast maturation and an osteocyte-like phenotype. **Osteoporos Int 2009;20:653-64**



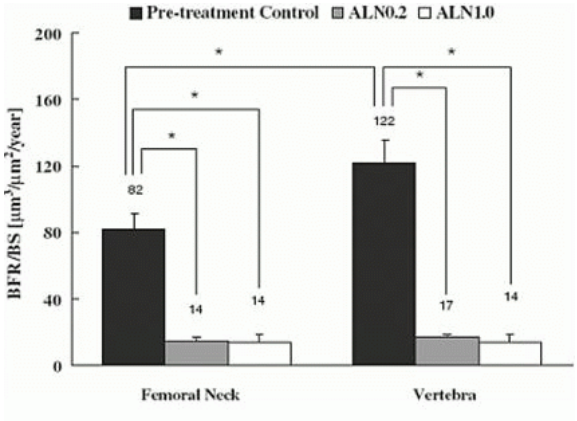
Effect of SR on in vitro mineralization. NHBC were cultured for up to 6 weeks under either control mineralizing conditions or in the presence of SR, at concentrations between 0 and 25 mM. Cultures were then fixed and processed for von Kossa staining. Typical staining patterns at 5 weeks are shown for: (a) control, or SR at (b) 1 mM, (c) 5 mM, and (d) 10 mM. Quantification of von Kossa staining observed over entire dose range (e) at 28 days and (f) 42 days, showing the percentage of the culture well surface area that was mineralized. Data shown are means of quadruplicate readings±SD. Similar results were obtained for cells from four other donors. Statistical difference to no SR control is indicated by *p<0.05. Reproduced from Osteoporos Int 2009;20:653-64 with permission from Springer.



Effect of SR on cell proliferation. NHBC were labeled with CFSE, cultured for 12 days and analyzed by flow cytometry. The fluorescence intensity of nondivided cells was determined from CFSE-labeled, colchicine-treated cells. Listmode data were then analyzed using ModFit software to allocate cells according to number of cell divisions. (a) The percentages of cells that divided during the culture period under the different treatments. (b) The percentages of cells that underwent four or more cell divisions during the culture period. Data shown are means±SD of quadruplicate stains of cells from a representative donor. Similar results were obtained for cells from two other donors. Asterisks indicate statistical difference to the no SR control ($p<0.001$). Reproduced from Osteoporos Int 2009;20:653-64 with permission from Springer.

Remodelling and drug therapy

Diab et al report histomorphometric results in trabecular bone of the femoral neck and lumbar vertebrae from mature beagles treated with alendronate, which resulted in similar absolute levels of bone turnover, although the femoral neck had 33% lower pretreatment remodelling rate. The high and low dose suppressed turnover to similar absolute levels suggesting that sites of low pretreatment remodelling rate are not more susceptible to oversuppression. **Osteoporos Int 2009;20:647-52**



Trabecular bone formation rate (BFR/BS) at the femoral neck and vertebra following 3 years of alendronate treatment. Three years of alendronate treatment resulted in similar bone formation rates between the femoral neck and vertebra. Numbers above bars represent the actual BFR/BS in each group. *$p<0.05$. Data are presented as +SE mean. Reproduced from Osteoporos Int 2009;20:647-52 with permission from Springer.

Nonenzymatic glycation with risedronate or alendronate

Tang et al report alendronate or risedronate for 1-yr accumulated AGEs at high doses but not at doses equivalent to those used for the treatment of postmenopausal osteoporosis. Postyield work-to-fracture of the tissue was reduced at these high doses. AGE accumulation inversely correlated with postyield work-to-fracture ($r^2=0.45$; $p<0.001$). **Osteoporos Int 2009;20:887-94**

Meta-analysis and fracture risk reduction with vitamin D

Bischoff-Ferrari et al report a meta-analysis of 12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures (n=42,279) and 8 RCTs for hip fractures (n=40,886). To incorporate adherence, the authors multiplied the dose by the percentage of adherence to estimate the mean received dose for each trial. The pooled relative risk (RR) was 0.86 (0.77-0.96) for nonvertebral fractures and 0.91 (0.78-1.05) for hip fractures. Including all trials, antifracture efficacy increased with a higher dose and higher achieved 25-D for both endpoints. Pooling trials with a higher dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (0.72-0.89; n=33,265 subjects, 9 trials) for nonvertebral fractures and 0.82 (0.69-0.97; n=31,872 subjects, 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (-29%) and institutionalized older individuals (-15%). **Arch Intern Med. 2009;169:551-61**

Rocco Well ... wise guy!?

McCloud I don't know.
Rocco You don't know! I thought you knew all the answers, that you were a wise guy from way back ...
McCloud He knows what he wants ... don't yah, Rocco?
Rocco Sure ... sure …
McCloud Tell 'em Rocco ...
Rocco Well ... I want ... er...
McCloud He wants more, don't you, Rocco?
Rocco Yeh, that's it, I want more, that's what I want ... more.

From the film *Key Largo*
starring Humphrey Bogart as 'Frank McCloud'
and Edward G. Robinson as 'Johnny Rocco'

Note from the Editor

The purpose of *Progress in Osteoporosis* is to provide the reader with a summary of the most important literature published in the preceding three to four months in the field of osteoporosis. Most reviews and original research are cited. In addition, summaries and figures are provided for readers who may not have easy access to all the specialist literature. The summaries are based on the contents of abstracts, which have been abbreviated to concisely convey the main theme. The contents of the abstracts and figures should be used only as a means of directing the reader to the original literature and should not be quoted verbatim or cited as a reference. The opinions expressed in the Overview are my own and do not necessarily reflect those of the International Osteoporosis Foundation.

Ego Seeman

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Epidemiology

10.3.1 Secular trends in hip fracture incidence and recurrence
Melton LJ, 3rd, Kearns AE, Atkinson EJ, Bolander ME, Achenbach SJ, Huddleston JM, Therneau TM, Leibson CL
Osteoporos Int 2009;20:687-94

All hip fracture events among Olmsted County, Minnesota residents in 1980-2006 were identified. 2752 hip fractures (median age, 83 years; 76% female) were observed, including 311 recurrences. Between 1980 and 2006, the incidence of a first-ever hip fracture declined by 1.37%/year for women (p<0.001) and 0.06%/year for men (p=0.917). Among 2434 residents with a first-ever hip fracture, the cumulative incidence of a second hip fracture after 10 years was 11% in women and 6% in men with death treated as a competing risk. Accounting for the reduction in first-ever hip fracture rates over time, hip fracture recurrence appeared to decline after 1997.

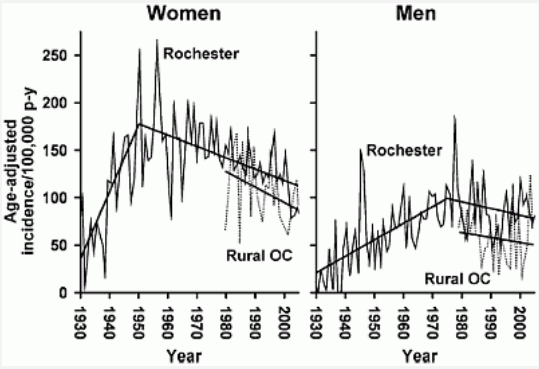


Fig. 10.3.1a Age-adjusted incidence (per 100,000 person-years) of first-ever hip fracture among women and men residing in Rochester (1928-2006) or rural Olmsted County (1980-2006), Minnesota, by calendar year. Reproduced from Osteoporos Int 2009;20:687-94 with permission from Springer.

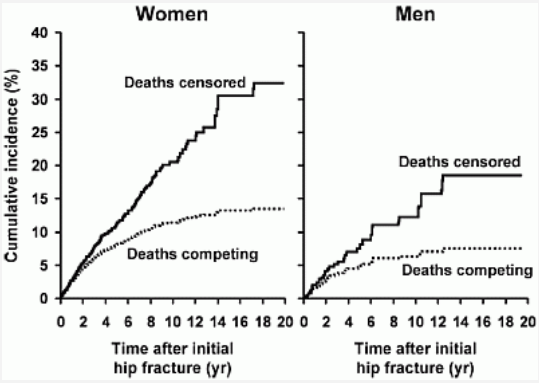


Fig. 10.3.1b Cumulative incidence of a recurrent hip fracture among 2434 Olmsted County, Minnesota women and men who had a first-ever hip fracture in 1980-2006 with follow-up censored at death or with deaths treated as a competing risk. Reproduced from Osteoporos Int 2009;20:687-94 with permission from Springer.

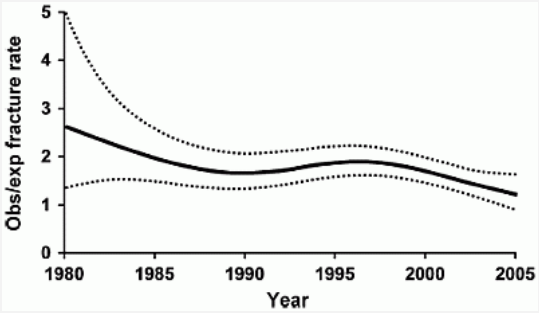


Fig. 10.3.1c Observed compared to expected recurrent hip fractures over time among 2434 Olmsted County, Minnesota residents with a firstever hip fracture in 1980-2006. Dotted lines indicate the 95% CI. Reproduced from Osteoporos Int 2009;20:687-94 with permission from Springer.

10.3.2 Recent trends in the incidence and lifetime risk of hip fracture in Tottori, Japan
Hagino H, Furukawa K, Fujiwara S, Okano T, Katagiri H, Yamamoto K, Teshima R
Osteoporos Int 2009;20:543-8

All hip fractures in patients aged 35 years and older occurring between 2004 and 2006 were surveyed in all of the hospitals from the Tottori prefecture. The survey identified 851, 906, and 1059 patients aged 35 years and older, in 2004, 2005, and 2006 respectively. The residual lifetime risk of hip fracture for individuals at 50 years of age was estimated to be 5.6% for men and 20.0% for women. The estimated number of patients from 1986 to 2006 showed a significant increase over time for both genders. The age- and gender-specific incidence of hip fracture in the Tottori prefecture, Japan has not plateaued for either gender.

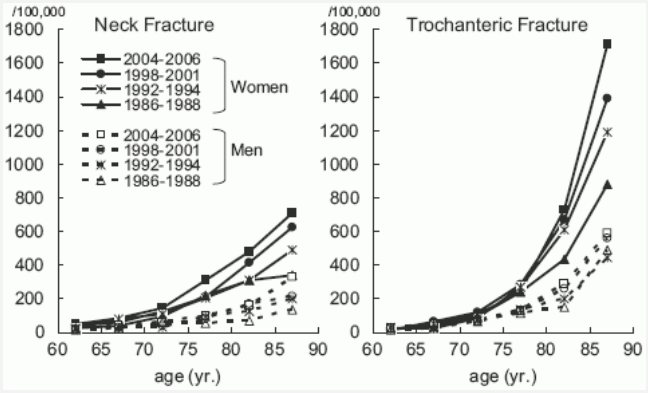


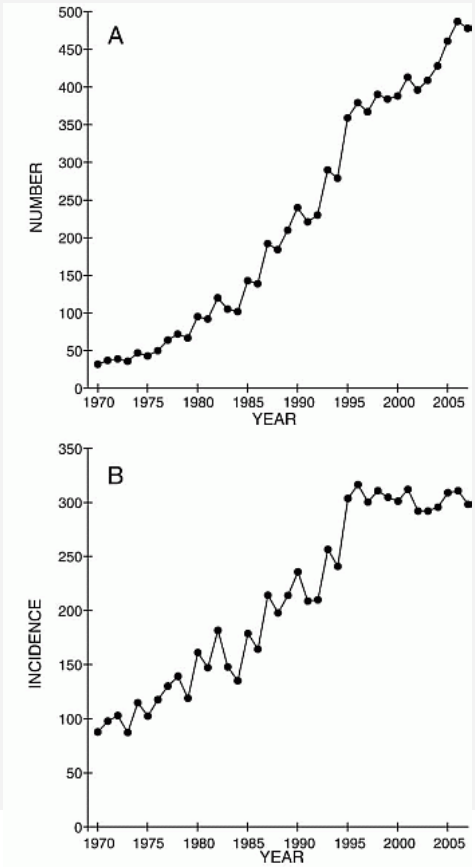
Fig. 10.3.2 Age- and gender-specific incidence of neck and trochanteric fractures between 1986 and 2006. Incidence data are per 100,000 person years. Incidence from the periods 1986-1988, 1992-1994, and 1998-2001, which we have previously reported were used for comparison. Reproduced from Osteoporos Int 2009;20:543-8 with permission from Springer.

10.3.3 Interstate variation in the burden of fragility fractures
King AB, Tosteson AN, Wong JB, Solomon DH, Burge RT, Dawson-Hughes B
J Bone Miner Res 2009;24:681-92

In 2000, mean hospital charges for incident fractures varied 1.7-fold across states. For hip fracture, mean charges ranged from $16,700 (MA) to $29,500 (CA), length of stay from 5.3 (AZ) to 8.9 days (NY), and discharge rate to long-term care from 43% (NY) to 71% (CA). In 2005, projected fracture incidence rates ranged from 199 (CA) to 266 (MA) per 10,000. Total cost ranged from $270 million (AZ) to $1,434 million (CA). Men accounted for 26-30% of costs. Across states, hip fractures constituted on average 77% of costs; "other" fractures (e.g., leg, arm), 10%; pelvic, 6%; vertebral, 5%; and wrist, 2%. By 2025, Hispanics are projected to represent 20% of fractures in AZ and CA and Asian/Other populations to represent 27% of fractures in NY.

10.3.4 Rate of proximal humeral fractures in older Finnish women between 1970 and 2007
Kannus P, Palvanen M, Niemi S, Sievanen H, Parkkari J
Bone 2009;44:656-9

The authors assessed the trend in the number and rate (per 100,000 persons) of low-trauma fractures of the proximal humerus among 80-year-old or older women in Finland, a European Union country with a well defined white population of 5.3 million, by taking into account all women who were admitted to our hospitals for primary treatment of such fracture in 1970-2007. The number of low-trauma fractures of the proximal humerus among 80-year-old or older Finnish women rose continuously between 1970 (32 fractures) and 2007 (478 fractures), but because of a simultaneous, sharper rise in population at risk, the age-adjusted fracture rate (showing a rise from 88 fractures per 100,000 persons in 1970 to 304 fractures in 1995) stabilized between 1995 and 2007 (298 fractures per 100,000 persons in 2007). In conclusion, the clear rise in the rate of low-trauma fractures of the proximal humerus in Finnish elderly women from early 1970s until mid 1990s has been followed by stabilized fracture rates.



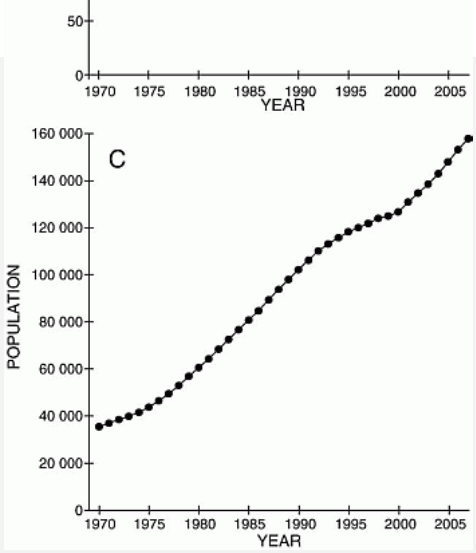


Fig. 10.3.4a The number (A) and age-adjusted incidence (per 100,000 individuals) (B) of proximal humeral fractures in women 80 years of age or older in Finland from 1970 to 2007. For comparison, the growth of this population is also demonstrated (C). Reproduced from Bone, 44:656-9, Copyright (2009), with permission from Elsevier.

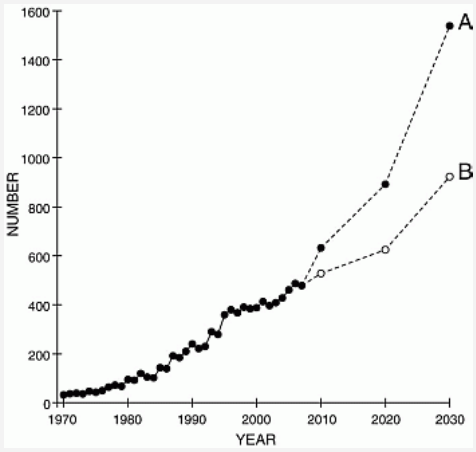


Fig. 10.3.4b Prediction of the number of proximal humeral fractures in women 80 years of age or older in Finland until the year 2030, as calculated using a regression model. The upper curve (A) denotes to a fracture development-model in which the age-adjusted incidence of fracture continues to rise at the average rate observed in 1970-2007, while the lower curve (B) to a model in which the incidence becomes stabilized to the 2007 level. The size of the 80-year-old or older female population is predicted to increase from 0.16 million in 2007 to 0.30 million in 2030. Reproduced from Bone, 44:656-9, Copyright (2009), with permission from Elsevier.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Morbidity/Mortality

10.3.5 Hip fracture in the elderly: Does counting time from fracture to surgery or from hospital admission to surgery matter when studying in-hospital mortality?
Vidal EI, Moreira-Filho DC, Coeli CM, Camargo KR, Jr., Fukushima FB, Blais R
Osteoporos Int 2009;20:723-9

The debate regarding the influence of time to surgery in hip fracture (HF) mortality is one of the most controversial issues in the HF medical literature. In 3754 hospital admissions of elderly patients due to HF the performance as predictors of in-hospital mortality of the delay from admission to surgery and the actual gap from fracture to surgery using univariate and multiple logistic regression analysis. The mean times from fracture to surgery and from admission to surgery were 1.84 and 1.02 days (P<0.001), respectively. On univariate logistic regression, both times were significant as mortality predictors, yielding similar odds ratios of 1.08 (P<0.001) for time from fracture to surgery and 1.11 (P<0.001) for time from admission to surgery. The gap from admission to surgery may be used as a surrogate of the actual delay from fracture to surgery when studying in-hospital HF mortality.

10.3.6 Sequential change in quality of life for patients with incident clinical fractures: A prospective study
Hagino H, Nakamura T, Fujiwara S, Oeki M, Okano T, Teshima R
Osteoporos Int 2009;20:695-702

10.3.7 The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study
Papaioannou A, Kennedy CC, Ioannidis G, Sawka A, Hopman WM, Pickard L, Brown JP, Josse RG, Kaiser S, Anastassiades T, Goltzman D, Papadimitropoulos M, Tenenhouse A, Prior JC, Olszynski WP, Adachi JD
Osteoporos Int 2009;20:703-14

10.3.8 Morphometric vertebral fractures of the lower thoracic and lumbar spine, physical function and quality of life in men
Pasco JA, Henry MJ, Korn S, Nicholson GC, Kotowicz MA
Osteoporos Int 2009;20:787-92

10.3.9 Association of reduction in bone mineral density with mortality in male hemodialysis patients
Kohno K, Inaba M, Okuno S, Maeno Y, Maekawa K, Yamakawa T, Ishimura E, Nishizawa Y
Calcif Tissue Int 2009;84:180-5

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Financial Cost

10.3.10 Utilization of inpatient care before and after hip fracture: A population-based study
Lonnroos E, Kautiainen H, Sund R, Karppi P, Hartikainen S, Kiviranta I, Sulkava R
Osteoporos Int 2009;20:879-86

The study covered hip fracture (HF) patients and the 70+ general population (26,000) living in Central Finland. In 2002-2003, 498 residents (mean age 82 SD 7, 74.9% women) of the study area sustained HF. Among them, the number of hospital days was 23, 107, and 52 per person-year in the prefracture, first and second postfracture year, respectively. In the 70+ general population, the number was constantly 11 per year. The age- and gender-adjusted rate ratio of hospital days between the two groups was 1.30 (95% CI 1.27-1.32), 6.91 (95% CI 6.85-7.00), and 3.61 (95% CI 3.55-3.67) for the prefracture, first and second postfracture year, respectively. Hospital days due to injuries were more prevalent in the HF group throughout the period. Moreover, excess of days was seen in six other diagnostic classes in the first and in four classes in the second postfracture year.

10.3.11 An updated systematic review of Health State Utility Values for osteoporosis related conditions
Peasgood T, Herrmann K, Kanis JA, Brazier JE
Osteoporos Int 2009;20:853-68

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

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Genetics

10.3.12 Bivariate genome-wide linkage analysis of femoral bone traits and leg lean mass: Framingham study
Karasik D, Zhou Y, Cupples LA, Hannan MT, Kiel DP, Demissie S
J Bone Miner Res 2009;24:710-8

A genome-wide scan (using 636 microsatellite markers) for linkage analyses was performed on 1346 adults from 327 extended families of the Framingham study. The results indicated substantial shared heritability for leg lean mass (LLM) (0.42 ±0.07) that was comparable to bone geometry traits. Phenotypic correlations between LLM and bone geometry phenotypes ranged from 0.033 with NSA (p>0.05) to 0.251 with S_Z (p<0.001); genetic correlations ranged from 0.087 (NSA, p>0.05) to 0.454 (S_Z, p<0.001). Univariate linkage analysis of covariate adjusted LLM identified no chromosomal regions with LOD scores ≥2.0; however, bivariate analysis identified two loci with LOD scores >3.0, shared by LLM with S_CSA on chromosome 12p12.3-12p13.2, and with NSA, on 14q21.3-22.1.

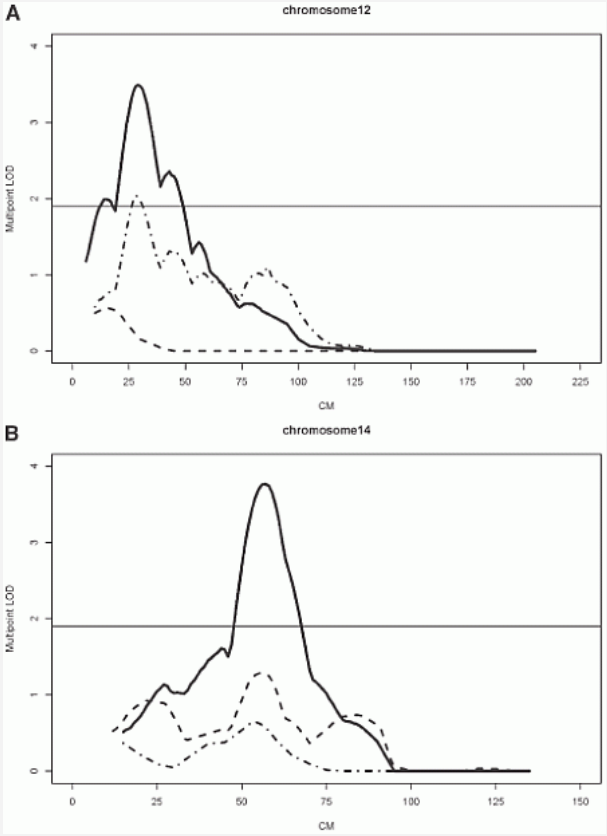

Fig. 10.3.12 Univariate and bivariate linkage results (multipoint LOD scores). Horizontal line, "suggestive" linkage threshold; solid line, bivariate linkage; dashed line, univariate, LLM; broken line, univariate, geometric trait. (A) S_CSA, LLM, and combination of LLM and S_CSA, chromosome 12. (B) NSA, LLM, and combination of LLM and NSA, chromosome 14. Reproduced from J Bone Miner Res 2009;24:710-8 with permission of the American Society of Bone and Mineral Research.

10.3.13 A rare haplotype in the upstream regulatory region of COL1A1 is associated with reduced bone quality and hip fracture
Jin H, Stewart TL, Hof RV, Reid DM, Aspden RM, Ralston S
J Bone Miner Res 2009;24:448-54

Genotypes and haplotypes of the COL1A1 gene were related to the biomechanical properties ex vivo in samples of femoral head of 98 consecutive patients undergoing surgery for low-trauma hip fractures. Genotype and haplotype frequencies in the hip fracture cases were compared with 3418 population-based controls. The association between -1663InsdelT and +1245G/T alleles, yield strength, and toughness remained significant after adjusting for material density of the core and other confounding factors. A haplotype comprising the unfavorable allele at all three polymorphic sites (-1997T/-1663delT/+1245T) was also associated with yield strength, modulus, and toughness after adjusting for confounding factors. This haplotype was carried by 19/94 (20.2%) patients with hip fracture compared with only 2/3399 (0.06%) female controls drawn from the general population (p<0.0001).

10.3.14 Associations of genetic lactase non-persistence and sex with bone loss in young adulthood
Laaksonen MM, Impivaara O, Sievanen H, Viikari JS, Lehtimaki TJ, Lamberg-Allardt CJ, Karkkainen MU, Valimaki M, Heikkinen J, Kroger LM, Kroger HP, Jurvelin JS, Kahonen MA, Raitakari OT
Bone 2009;44:1003-9

Genetic lactase nonpersistence (lactase C/C(-13910) genotype) is suggested to increase risk for inadequate calcium intake predisposing to poorer bone health. Subjects aged 20-29 participated in baseline BMD measurements (n=358), and in follow-

up measurements 12 years later (n=157). During the follow-up, bone loss at both bone sites was greater in males (LS BMD: -1.1%, FN BMD: -5.2%) than in females (LS BMD: +2.1%, FN BMD: -0.7%) (both sites p=0.001). Younger age predicted greater loss of FN BMC and BMD in females (p=0.013 and p=0.001, respectively). Increased calcium intake predicted FN BMD gain in both sexes (in females B=0.007 g/cm^2/mg, p=0.002; in males B=0.006, p=0.045), and increased physical activity LS BMD gain in females (B=0.091 g/cm^2/physical activity point, p=0.023). Peak bone mass did not differ between the lactase genotypes, but males with the CC(-13910) genotype seemed to be prone to greater bone loss during the follow-up (LS BMD: C/C vs. T/T p=0.081).

10.3.15 No association between hip geometry and four common polymorphisms associated with fracture: The Danish osteoporosis prevention study
Nissen N, Madsen JS, Bladbjerg EM, Beck Jensen JE, Jorgensen NR, Langdahl B, Abrahamsen B, Brixen K
Calcif Tissue Int 2009;84:276-85

10.3.16 Identification and association analysis of single nucleotide polymorphisms in the human noggin (NOG) gene and osteoporosis phenotypes
Moffett SP, Dillon KA, Yerges LM, Goodrich LJ, Nestlerode C, Bunker CH, Wheeler VW, Patrick AL, Zmuda JM
Bone 2009;44:999-1002

10.3.17 An in vivo genome wide gene expression study of circulating monocytes suggested GBP1, STAT1 and CXCL10 as novel risk genes for the differentiation of peak bone mass
Lei SF, Wu S, Li LM, Deng FY, Xiao SM, Jiang C, Chen Y, Jiang H, Yang F, Tan LJ, Sun X, Zhu XZ, Liu MY, Liu YZ, Chen XD, Deng HW
Bone 2009;44:1010-4

10.3.18 Joint loading-driven bone formation and signaling pathways predicted from genome-wide expression profiles
Zhang P, Turner CH, Yokota H
Bone 2009;44:989-98

10.3.19 Comparison of whole genome linkage scans in premenopausal and postmenopausal women: No bone-loss-specific QTLs were implicated
Yan H, Liu YJ, Zhou Q, Xiao P, Recker RR, Deng HW
Osteoporos Int 2009;20:771-7

10.3.20 LCT 13910 C/T polymorphism, serum calcium, and bone mineral density in postmenopausal women
Bacsi K, Kosa JP, Lazary A, Balla B, Horvath H, Kis A, Nagy Z, Takacs I, Lakatos P, Speer G
Osteoporos Int 2009;20:639-45

10.3.21 Association analysis of WNT10B with bone mass and structure among individuals of African ancestry
Zmuda JM, Yerges LM, Kammerer CM, Cauley JA, Wang X, Nestlerode CS, Wheeler VW, Patrick AL, Bunker CH, Moffett SP, Ferrell RE
J Bone Miner Res 2009;24:437-47

10.3.22 Multiple osteoporosis susceptibility genes on chromosome 1p36 in Chinese
Huang Q-Y, Li GHY, Kung AWC
Bone 2009;44:984-8

10.3.23 A recurrent mutation c.617G>A in the ACVR1 gene causes fibrodysplasia ossificans progressiva in two Chinese patients
Sun Y, Xia W, Jiang Y, Xing X, Li M, Wang O, Zhang H, Hu Y, Liu H, Meng X, Zhou X
Calcif Tissue Int 2009;84:361-5

10.3.24 Identification of novel mutations in WISP3 gene in two unrelated Chinese families with progressive pseudorheumatoid dysplasia
Yue H, Zhang ZL, He JW
Bone 2009;44:547-54

10.3.25 Refined genomic localization of the genetic lesion in the osteopetrosis (op) rat and exclusion of three positional and functional candidate genes, Clcn7, Atp6v0c, and Slc9a3r2
Perdu B, Odgren PR, Van Wesenbeeck L, Jennes K, Mackay CC, Van Hul W
Calcif Tissue Int 2009;84:355-60

10.3.26 Genome-wide analysis of genes related to kidney stone formation and elimination in the calcium oxalate nephrolithiasis model mouse: Detection of stone-preventive factors and involvement of macrophage activity
Okada A, Yasui T, Hamamoto S, Hirose M, Kubota Y, Itoh Y, Tozawa K, Hayashi Y, Kohri K
J Bone Miner Res 2009;24:908-24

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Measurement of Bone Mass

10.3.27 Assessment of trabecular bone structure of the calcaneus using multi-detector CT: Correlation with microCT and biomechanical testing
Diederichs G, Link TM, Kentenich M, Schwieger K, Huber MB, Burghardt AJ, Majumdar S, Rogalla P, Issever AS
Bone 2009;44:976-83

30 calcanei in 15 intact cadavers were scanned using three different protocols on a 64-slice MDCT scanner with an in-plane pixel size of 208 µm and 500 µm slice thickness. Bone cores were harvested from each specimen and µCT images with a voxel size of 16 µm were obtained. After image coregistration, trabecular bone structure and texture were evaluated in identical regions on the MDCT images. Significant correlations between MDCT- and µCT-derived measures of bone volume fraction (BV/TV), trabecular thickness (Tb.Th) and trabecular separation (Tb.Sp) were found (range, R^2=0.19-0.65, p<0.01 or 0.05). The MDCT-derived parameters of volumetric BMD, app. BV/TV, app. Tb.Th and app. Tb.Sp were capable of predicting 60%, 63%, 53% and 25% of the variation in bone strength (p<0.01). When combining those measures with one additional texture index (either GLCM, TOGLCM or MF.euler), prediction of mechanical competence was significantly improved to 86%, 85%, 71% and 63% (p<0.01).

10.3.28 Regional differences in hip bone mineral density levels in Norway: The NOREPOS study
Omsland TK, Gjesdal CG, Emaus N, Tell GS, Meyer HE
Osteoporos Int 2009;20:631-8

10.3.29 Local topological analysis of densitometer-generated scan images of the proximal femur for differentiation between patients with hip fracture and age-matched controls
Boehm HF, Lutz J, Horng A, Notohamiprodjo M, Panteleon A, Pfeifer KJ, Reiser M
Osteoporos Int 2009;20:617-24

10.3.30 Reanalysis precision of 3D quantitative computed tomography (QCT) of the spine
Engelke K, Mastmeyer A, Bousson V, Fuerst T, Laredo JD, Kalender WA
Bone 2009;44:566-72

10.3.31 muCT-based measurement of cortical bone graft-to-host union
Reynolds DG, Shaikh S, Papuga MO, Lerner AL, O'Keefe RJ, Schwarz EM, Awad HA
J Bone Miner Res 2009;24:899-907

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Bone Material

10.3.32 Spectroscopic markers of bone quality in alendronate-treated postmenopausal women
Boskey AL, Spevak L, Weinstein RS
Osteoporos Int 2009;20:793-800

Comparison of infrared spectroscopic images of sections from biopsies of placebo-treated postmenopausal women and women treated for 3 years with 10 mg/day alendronate demonstrated increases in cortical bone mineral content, no alterations in other spectroscopic markers of "bone quality," but a decrease in tissue heterogeneity. The mineral content (mineral/matrix ratio) in the cortical bone of the treated women's biopsies was higher than that in the untreated control women. Crystallinity, carbonate/protein, and collagen maturity indices were not significantly altered; however, the pixel distribution was significantly narrowed for all cortical and trabecular parameters with the exception of collagen maturity in the alendronate treatment group.

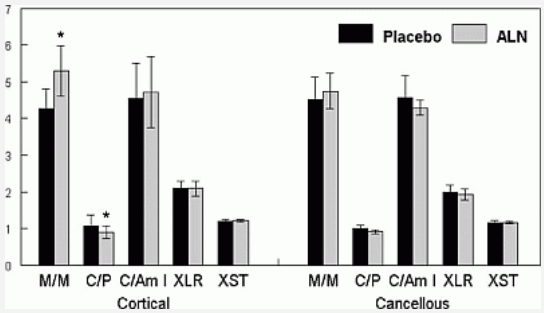

*Fig. 10.3.32a Mean±SD for each parameter measured from three to five FTIR images of cortical and cancellous bone per biopsy in patients treated with alendronate (ALN) or a placebo. Values shown are mineral/matrix ratio (M/M); carbonate/phosphate ratio (C/P), this value has been multiplied by 100 for ease of presentation; carbonate/amide I ratio (C/Am I) also multiplied by 100; crystallinity (XST); and collagen maturity ratio (XLR). For each parameter, *p<0.05 relative to placebo control. Reproduced from Osteoporos Int 2009;20:793-800 with permission from Springer.*

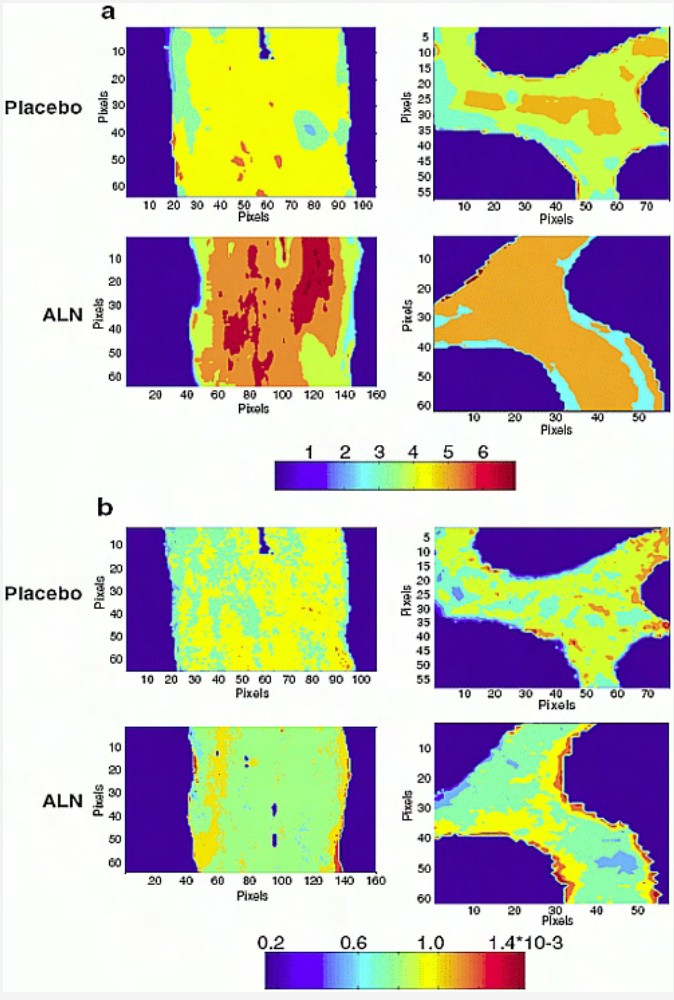

Fig. 10.3.32b Typical FTIRI images and pixel histograms for cortical (left) and cancellous (right) bone from one placebo and one ALN-treated case; (a) mineral/matrix, (b) carbonate/phosphate. Reproduced from Osteoporos Int 2009;20:793-800 with permission from Springer.

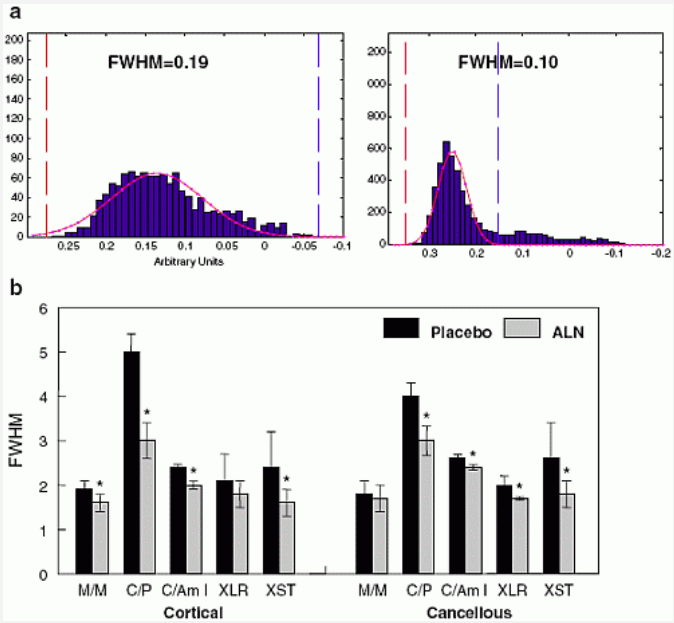

*Fig. 10.3.32c Heterogeneity was calculated from FWHM of pixel histograms as illustrated in a and b. The mean±SD for FWHM for each parameter in the cortical and cancellous bones of the ALN and placebo groups are shown. Values shown for carbonate/phosphate ratio (C/P) and carbonate/amide I ratio have been multiplied by 100 for ease of presentation, crystallinity (XST), and collagen maturity ratio (XLR) values multiplied by 10. *p<0.05 relative to placebo control. Reproduced from Osteoporos Int 2009;20:793-800 with permission from Springer.*

10.3.33 Normative data on mineralization density distribution in iliac bone biopsies of children, adolescents and young adults
Fratzl-Zelman N, Roschger P, Misof BM, Pfeffer S, Glorieux FH, Klaushofer K, Rauch F
Bone 2009;44:1043-8

qBEI analyses were performed on bone samples from 54 individuals between 1.5 and 23 years without metabolic bone diseases, which were previously used as study population to establish normative histomorphometric standards. In the trabecular compartment, none of the BMDD parameters showed a significant correlation with age. The BMDD was shifted towards lower mineralization density (CaMean -5.6%, p<0.0001; CaPeak -5.6%, p<0.0001; CaLow +39.0% p<0.001; CaHigh -80.7%, p<0.001) and the inter-individual variation was higher compared to the adult population. The cortices appeared to be markedly less mineralized (CaMean -3.1%, p<0.0001) than cancellous bone due to higher amounts of low mineralized secondary bone. However, the cortical BMDD parameters showed a strong correlation (r=0.38 to 0.85, with p<0.001 to<0.0001) with cancellous BMDD parameters. In conclusion, BMDD parameters in growing healthy subjects are relatively constant and that these data can be used as normative references in pediatrics osteology.

10.3.34 Deformation of mineral crystals in cortical bone depending on structural anisotropy
Giri B, Tadano S, Fujisaki K, Sasaki N
Bone 2009;44:1111-20

Using X-ray diffraction, the authors quantified the mineral strains, degree of orientation of the crystallites and their evolution under different applied step-loads in bovine femoral cortical specimens having different alignment with the femoral axis direction. The mineral strains in the compliant specimens, i.e., 0 and 30° oriented specimens were observed to differ with the stiffer specimens, i.e., 75 and 90° oriented specimens, whereas the 45° oriented specimen show almost equal strains at different loads. These were explained by the degree of orientation with reference to the loading direction and the preferential orientation direction of the specimens. On the basis of observed parameters, deformation of mineral particles occur in different stages, which consist of redistribution stage, elastic strain stage and inelastic strain stage. These phenomena are expected to occur at different scales and rates depending on the orientation and distribution of crystals.

10.3.35 Inhomogeneous fibril stretching in antler starts after macroscopic yielding: Indication for a nanoscale toughening mechanism
Krauss S, Fratzl P, Seto J, Currey JD, Estevez JA, Funari SS, Gupta HS
Bone 2009;44:1105-10

Antler bone has high fracture resistance. The authors used time-resolved synchrotron small angle X-ray diffraction with tensile testing of antler cortical tissue and measured the deformation at the nanoscale from changes in the meridional diffraction pattern during macroscopic stretch-to-failure tests. Fibrils are strained only half as much as the whole tissue and the fibril strain increases linearly with tissue strain, both during elastic and inelastic deformation. Most remarkably, following macroscopic yielding we observe a straining of some fibrils equal to the macroscopic tissue strain while others are hardly stretched at all, indicating an inhomogeneous fibrillar strain pattern at the nanoscale. This behavior is unlike what occurs in plexiform bovine bone and may explain the extreme toughness of antler compared to normal bone.

10.3.36 A new tool to assess the mechanical properties of bone due to collagen degradation
Wynnyckyj C, Omelon S, Savage K, Damani M, Chachra D, Grynpas MD
Bone 2009;44:840-8

10.3.37 Confocal laser Raman microspectroscopy of biomineralization foci in UMR 106 osteoblastic cultures reveals temporally synchronized protein changes preceding and accompanying mineral crystal deposition
Wang C, Wang Y, Huffman NT, Cui C, Yao X, Midura S, Midura RJ, Gorski JP

J Biol Chem 2009;284:7100-13

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Bone Structure

10.3.38 Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women
Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD
J Bone Miner Res 2009;24:737-43

Bone architecture and volumetric density (vBMD) were assessed at the distal radius and tibia with HR-pQCT in 100 women with VFx (age, 74±9 yr) of different S (GI, n=23; GII, n=35; GIII, n=42) and in 362 women (age, 69±7 yr) without peripheral or VFx (G0) from the OFELY study. Among all women, at the radius and after adjustment for age and aBMD, there were trends in lower vBMD, cortical thickness (Cort.Th), trabecular number (Tb.N) and thickness (Tb.Th), higher trabecular separation (Tb.Sp), and distribution of separation (Tb.Sp.SD) with greater VFx S and N. Among women with VFx, lower Cort.Th and cortical vBMD (D.Cort) were associated with severe (GIII) and multiple (n>2) VFx (p<0.05). The age-adjusted OR for each SD decrease of Cort. Th was 2.04 (95% CI, 1.02-4.00) after adjustment for aBMD. At the tibia, there were trends for lower vBMD, Tb.N, Tb.Th, and higher Tb.Sp and Tb.Sp.SD with greater VFx S and N (p<0.001). Among women with VFx, lower Cort.Th and D.Cort were associated with severe and multiple (n>3) VFx (p<0.01).

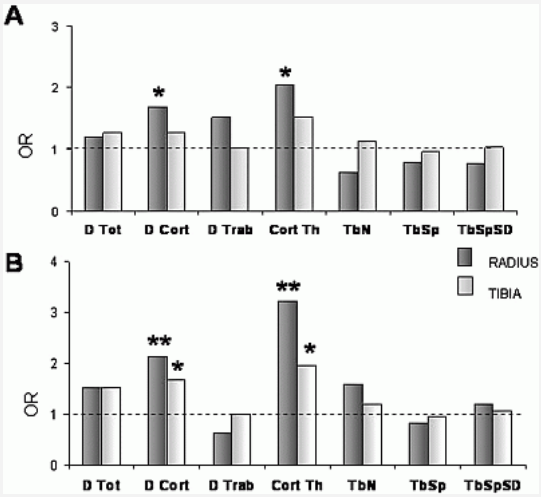

*Fig. 10.3.38 Association of microarchitecture alterations at the radius and tibia with severe and multiple VFx, expressed in ORs. *p<0.05 and **p<0.01, adjusted for age and spine aBMD vs. reference group. (A) GIII and N>2, Ref. group=(GI or GII) and (N1 or N2), n=30. (B) GIII and N>3, Ref group=(GI or GII) and (N1 or N2 or N3), n=21. Reproduced from J Bone Miner Res 2009;24:737-43 with permission of the American Society of Bone and Mineral Research.*

10.3.39 Phenotypic integration among trabecular and cortical bone traits establishes mechanical functionality of inbred mouse vertebrae
Tommasini SM, Hu B, Nadeau JH, Jepsen KJ
J Bone Miner Res 2009;24:606-20

It is not known whether trait covariation is important for mechanical function in corticocancellous structures. Covariation among trabecular, cortical, and compositional bone traits was examined in the context of mechanical functionality for L4 vertebral bodies across a panel of 16-wk-old female AXB/BXA recombinant inbred (RI) mouse strains. The unique pattern of randomization of the A/J and C57BL/6J (B6) genome among the RI panel provides a tool to measure trait covariation and to study the biology of complex traits. The authors tested the hypothesis that genetic variants affecting vertebral size and mass are buffered by changes in the relative amounts of cortical and trabecular bone and overall mineralization. Despite inheriting random sets of A/J and B6 genomes, the RI strains inherited nonrandom sets of cortical and trabecular bone traits. Path analysis, which is a multivariate analysis that shows how multiple traits covary simultaneously when confounding variables like body size are taken into consideration, showed that RI strains that tended to have smaller vertebrae relative to body size achieved mechanical functionality by increasing mineralization and the relative amounts of cortical and trabecular bone. The interdependence among corticocancellous traits in the vertebral body indicated that variation in trabecular bone traits among inbred mouse strains, which is often thought to arise from genetic factors, is also determined in part by the adaptive response to variation in traits describing the cortical shell. The covariation among corticocancellous traits has important implications for genetic analyses and for interpreting the response of bone to genetic and environmental perturbations.

10.3.40 Tibial geometry in individuals with neurofibromatosis type 1 without anterolateral bowing of the lower leg using peripheral quantitative computed tomography
Stevenson DA, Viskochil DH, Carey JC, Slater H, Murray M, Sheng X, D'Astous J, Hanson H, Schorry E, Moyer-Mileur LJ
Bone 2009;44:585-9

10.3.41 A comparison of cortical and trabecular bone from C57 Black 6 mice using Raman spectroscopy
Goodyear SR, Gibson IR, Skakle JM, Wells RP, Aspden RM
Bone 2009;44:899-907

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Biomechanics

10.3.42 Predictive value of femoral head heterogeneity for fracture risk
Tanck E, Bakker AD, Kregting S, Cornelissen B, Klein-Nulend J, Van Rietbergen B
Bone 2009;44:590-5

The authors hypothesized that osteoporotic femoral heads have 1) an increased anisotropy; 2) a more heterogenic distribution of bone volume fraction (BV/TV) throughout the femoral head; and, 3) a more heterogenic distribution of the trabecular thickness (Tb. Th.) throughout the femoral head. To test these hypotheses, we used 7 osteoporotic femoral heads from patients who fractured their femoral neck and 7 nonfractured femoral heads from patients with osteoarthrosis (OA). Bone structural parameters from the entire trabecular region were analyzed using µCT. The degree of anisotropy was higher in the fractured femoral heads, i.e., 1.72, compared to 1.61 in the nonfractured femoral heads. The BV/TV and Tb.Th. and their variations throughout the femoral head, however, were all lower in the fractured group. Hence, the first hypothesis was confirmed, whereas the other two were rejected. The variation of Tb.Th. throughout the femoral head provided a 100% discrimination between the OP and OA groups, i.e. for the same BV/TV, all fractured cases had a less heterogenic distribution. In conclusion, bone loss in OP takes place uniformly throughout the femoral head, leading to an overall decrease in bone mass and trabecular thickness.

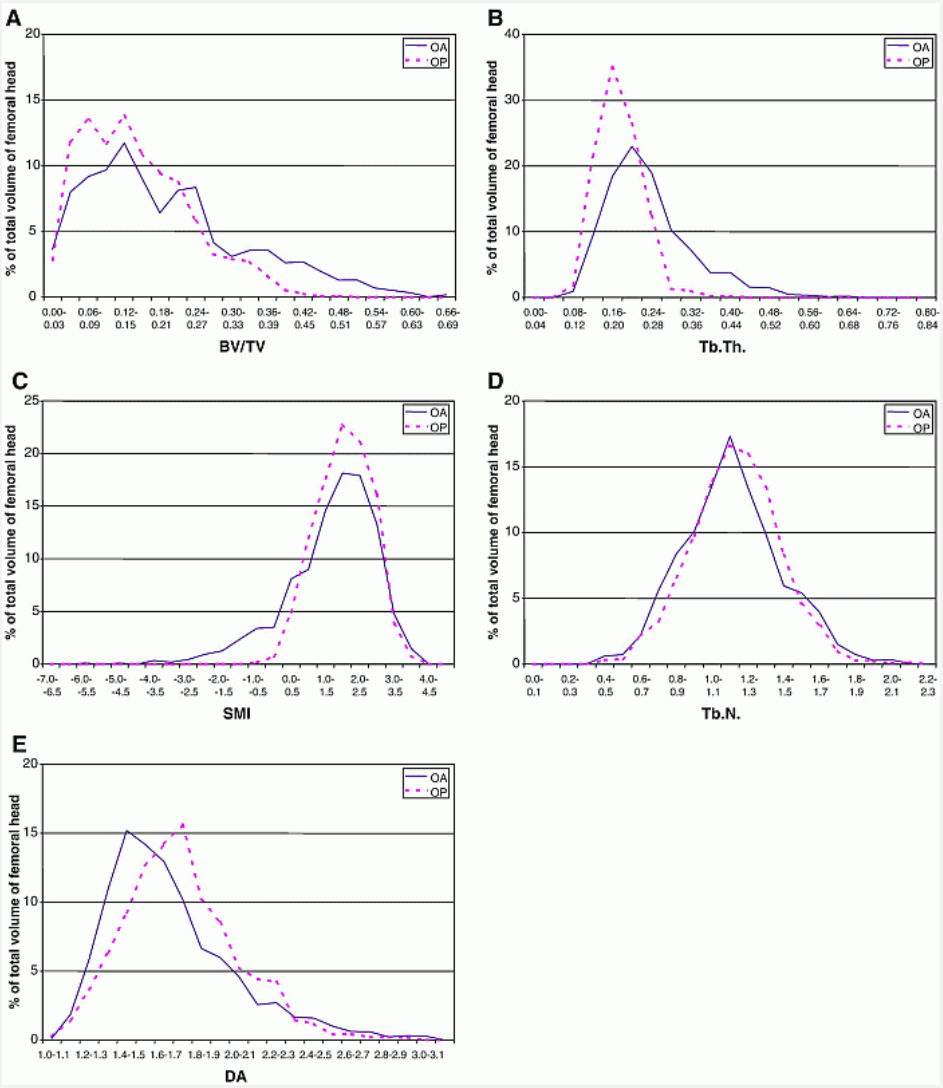

Fig. 10.3.42 Frequency plots of the bone parameters in the femoral heads of patients with OA and OP; bone volume fraction (A), trabecular thickness (B), structure model index (C), trabecular number (D), and degree of anisotropy (E). Per interval the average of 7 femoral heads was taken. Reproduced from Bone, 44:590-5, Copyright (2009), with permission from Elsevier.

10.3.43 Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength
Holzer G, von Skrbensky G, Holzer LA, Pichl W
J Bone Miner Res 2009;24:468-74

In one femur from each pair of 18 human cadaver femurs (5 female; 4 male), trabecular bone was removed from the femoral neck. Differences between forces needed to fracture excavated and intact femurs (DeltaF/F mean) was 7.0% (4.6-17.3%). CSA of removed spongiosa did not correlate with difference of fracture load (DeltaF/F mean), nor did BMD. The relative contribution of trabecular versus cortical bone in respect to bone strength in the femoral neck seems to be marginal and seems to explain the subordinate role of trabecular bone.

10.3.44 Identify fracture-critical regions inside the proximal femur using statistical parametric mapping
Li W, Kornak J, Harris T, Keyak J, Li C, Lu Y, Cheng X, Lang T
Bone 2009;44:596-602

The authors hypothesized that BMD measured in subvolumes discriminate hip fracture risk better than BMD in standard regions. They transformed hip QCT images of 37 patients with hip fractures and 38 age-matched controls into a voxel-based statistical atlas. By evaluating fracture discrimination power based on ROC analysis, the fracture-driven ROI had an AUC (area under curve) of 0.92, while anatomic ROIs (including the entire proximal femur, the femoral neck, trochanter and their cortical and trabecular compartments) had AUC values between 0.78 and 0.87. Fracture patients had lower BMD (p=0.014) in a small region near the femoral neck and the femoral head, and patients with trochanteric fractures had lower BMD in trochanteric regions such as in the internal calcar septum (p=0.006). The power to predict fracture can be improved, by focusing on BMD measurements in the fracture-critical regions, rather than in standard ROIs.

10.3.45 Density and architecture have greater effects on the toughness of trabecular bone than damage
Garrison JG, Slaboch CL, Niebur GL
Bone 2009;44:924-9

The effects of damage on the toughness of 35 bovine trabecular specimens were studied. Damage was induced by compressing to 1.5% or 2.5% strain, then to 7.5% strain. The overloads decreased modulus and elastic toughness, with greater decreases for the high-damage than the low-damage group. Elastic toughness of the high-damage group was lower than the undamaged elastic toughness of the control. In contrast, there was no effect of damage level on toughness measured to 7.5% strain. Toughness increased linearly with BMD (R^2=0.50) and by a power law relationship with volume fraction (BV/TV) (R^2=0.65). Microarchitecture predicted toughness. Toughness decreased with increasing slenderness (Tb.Sp/Tb.Th) and structure model index (SMI) (R^2=0.68, multiple regression), independent of damage level, suggesting that failure is influenced by trabecular buckling. Variations in toughness due to density and architecture dominate the changes due to damage at the levels induced in this study. Toughness is sensitive to the final strain, as differences found in the elastic and initial plastic regions were undetectable at higher strains. The self-limiting nature of microcracks in trabecular bone, or the trabecular architecture itself, may inhibit microcracks from propagating to macroscopic trabecular fractures, thereby limiting the effect of damage on toughness and making it difficult to detect in comparison to normal population variability.

10.3.46 Trabecular bone strength predictions using finite element analysis of micro-scale images at limited spatial resolution
Bevill G, Keaveny TM
Bone 2009;44:579-84

Linear and nonlinear FE analyses were conducted in 46 trabecular cores using element sizes ranging from 20 to 120 μm to obtain apparent yield stress and elastic modulus, and these measures were correlated with predicted yield stress from the 20 μm models (the gold standard strength). When considering all samples and any resolution, yield stress and elastic modulus were both predictors of strength (R^2>0.99). When only low-density samples (BV/TV<0.15) were considered, yield stress was better correlated with 20 μm-strength than was elastic modulus (R^2 increased from 0.93 to 0.99 at 40 μm and from 0.90 to 0.95 at 80 μm). However, at a voxel size of 120 μm, the predictive ability of yield stress was slightly less than that of stiffness due to errors with larger element sizes. A limit was observed in the ability of elastic modulus to predict strength – the predictive ability of elastic modulus measured at 20 μm was comparable to that of yield strength at 80 μm. Strength predictions from FE models at clinical-type resolutions had nearly the same power to detect bone quality effects via variations in strength-density relationships as did high-resolution models. Nonlinear FE models account for additional variations in strength relative to linear models when using images at resolutions of approximately 80 μm and less, and such models offer a promising method for examining microarchitecture-related bone quality effects associated with aging, disease, and treatment.

10.3.47 The influence of boundary conditions and loading mode on high-resolution finite element-computed trabecular tissue properties
Bevill G, Eswaran SK, Farahmand F, Keaveny TM
Bone 2009;44:573-8

25 cores of human vertebral trabecular bone under two different boundary conditions (endcap and PMMA embedding) and loading modes (compression and torsion). High-resolution (20 μm) finite element models were constructed and sensitivity studies were performed to quantify errors arising from uncertainties between model and experiment. Mean (±SD) effective tissue modulus for the four groups ranged from 9.6±1.9 to 11.5±3.5 GPa, and the overall mean was 10.3±2.4 GPa. For the endcap tests, mean values were the same regardless of loading mode, suggesting that the effective tissue modulus is representative of true material behavior. However, on a specimen-specific basis, the various repeated measures of effective tissue modulus were only moderately correlated with each other (R^2=27% to 81%), indicating that the individual measures can be subject to random errors. The sensitivity studies on the endcap tests indicated that models using lower resolution (40 μm element size) and roller-type platens boundary conditions overestimated effective tissue modulus by 42% on average, although preliminary tests with higher-density femoral neck bone indicated less sensitivity to modeling issues.

10.3.48 The mouse fibula as a suitable bone for the study of functional adaptation to mechanical loading
Moustafa A, Sugiyama T, Saxon LK, Zaman G, Sunters A, Armstrong VJ, Javaheri B, Lanyon LE, Price JS
Bone 2009;44:930-5

The right tibiae/fibulae in C57BL/6 mice were subjected to a single period of axial loading (40 cycles at 10 Hz with 10-second intervals between each cycle; approximately 7 min/day, 3 alternate days/week, 2 weeks). The left tibiae/fibulae were used as nonloaded, internal controls. Both left and right fibulae and tibiae were analyzed by microcomputed tomography at the levels of the midshaft of the fibula and 25% from its proximal and distal ends. The effects of intermittent parathyroid hormone (iPTH) on the (re)modelling response to 2 weeks of loading and the effect of 2 consecutive days of loading on osteocytes' sclerostin expression. These in vivo experiments confirmed that the fibula showed similar loading-related (re)modelling responses to those previously documented in the tibia and similar synergistic increases in osteogenesis between loading and iPTH. The numbers of sclerostin-positive osteocytes at the proximal and middle fibulae were markedly decreased by loading.

10.3.49 Focal adhesion kinase is important for fluid shear stress-induced mechanotransduction in osteoblasts
Young SR, Gerard-O'Riley R, Kim JB, Pavalko FM
J Bone Miner Res 2009;24:411-24

When bone is loaded, movement of fluid within the spaces generates fluid shear stress (FSS) that stimulates osteoblasts. Focal adhesions are prime candidates for transducing external stimuli. Focal adhesion kinase (FAK), a nonreceptor tyrosine kinase found in focal adhesions, may play a role in mechanotransduction. The role of FAK in osteoblast mechanotransduction was examined using short interfering RNA (siRNA), overexpression of a dominant negative FAK, and FAK(-/-) osteoblasts. Osteoblasts were subjected to oscillatory fluid flow (OFF) from 5 min to 4 h, and several readouts of mechanotransduction were analyzed including: extracellular signal-related kinase 1/2 phosphorylation, upregulation of c-fos, cyclooxygenase-2, and osteopontin, and release of prostaglandin E(2). Osteoblasts with disrupted FAK signaling exhibited severely impaired mechanical responses. These data indicate the importance of FAK for both short and long periods of FSS-induced mechanotransduction in osteoblasts.

10.3.50 Medial-to-lateral ratio of tibiofemoral subchondral bone area is adapted to alignment and mechanical load
Eckstein F, Hudelmaier M, Cahue S, Marshall M, Sharma L
Calcif Tissue Int 2009;84:186-94

Volume 10, Issue 3, 2009

Growth

10.3.51 Ethnic differences in bone geometry and strength are apparent in childhood
Wetzsteon RJ, Hughes JM, Kaufman BC, Vazquez G, Stoffregen TA, Stovitz SD, Petit MA
Bone 2009;44:970-5

pQCT was used to assess bone parameters at the radius and tibia in Caucasian (CA, n=21), African American (AA, n=23), and Hispanic (HI, n=29) children (10.9±0.1 yrs). At the distal site (8%), compressive bone strength (BSI), trabecular and total bone density, and total bone area were assessed. Polar strength-strain index, total and cortical bone area, and cortical density were assessed at the midshaft (50%). Muscle cross-sectional area (CSA) and fat CSA were measured at the tibia (66%) and the radius (50%). AA children were taller and had longer bones. At all sites, AA and HI children had higher bone strength (SSIp and BSI + 10-37%) than CA children due mainly to greater bone tissue density (2-18%>CA) at the distal sites of the radius and tibia. The greater bone strength at the midshaft was due to both a higher bone density (2-5%) and greater bone area than CA (7-18%). AA and HI children have higher bone strength than CA children, due to greater bone volumetric density and greater cortical area. AA and HI children also have higher bone strength relative to load.

10.3.52 Cortical bone development in black and white South African children: Iliac crest histomorphometry
Schnitzler CM, Mesquita JM, Pettifor JM
Bone 2009;44:603-11

Fragility fracture rates are lower in blacks (B) than in whites (W). In adults this difference may in part be explained by histomorphometric findings in iliac crest cortical bone of B of thicker, less porous cortices, greater endocortical (Ec) wall thickness, fewer canals and greater osteoid thickness accompanied by greater mineral apposition rate and bone formation rate compared to W. In 57 B and 56 W aged 0-23 yrs the effects of growth as expressed in differences between external and internal cortex were similar in B and W children. Cortical thickness increased with age similarly in B and W until about age 15 whereafter it continued to increase only in B. Ec wall thickness rose with age in B but did not change in W. After age 11 canal number was lower in B. Cortical porosity was highest between ages 6 and 15 with a tendency to lower values in the external cortex in B. Bone turnover as reflected in osteoid surface and eroded surface declined with age similarly in B and W but osteoid thickness did not change with age. Greater osteoid thickness in B children could reflect greater vigor of osteoblasts and greater osteoblast team performance as it did in B adults and may have contributed to the structural advantage in B children. B children showed greater values for osteoid thickness, endocortical wall thickness and cortical thickness, and a tendency to lower porosity compared to W children.

10.3.53 Bone mineral accrual across growth in a mixed-ethnic group of children: Are Asian children disadvantaged from an early age?
Burrows M, Baxter-Jones A, Mirwald R, Macdonald H, McKay H
Calcif Tissue Int 2009;84:366-78

In 80 Caucasian and 74 Asian boys and 81 Caucasian and 64 Asian girls at baseline and 155 children across all 7 years aligned on peak height velocity height and lean mass accounted for 51.8% and 44.1% of BMC accrual in children. There was a difference in physical activity, calcium intake, and lean mass between Asians and Caucasian boys and girls at baseline and conclusion ($p<0.05$). In boys, physical activity and ethnicity predicted BMC accrual at the FN. In girls, Asians had lower total proximal femur and FN BMC. Calcium was a predictor of whole body BMC accrual in boys and girls. Physical activity, dietary calcium, and lean mass positively influence bone accrual and are lower in Asian compared to Caucasian children.

10.3.54 How does body fat influence bone mass in childhood? A Mendelian randomization approach
Timpson NJ, Sayers A, Davey-Smith G, Tobias JH
J Bone Miner Res 2009;24:522-33

Genotyping was retrieved for variants of two loci associated with adiposity (the fat mass and obesity-related gene FTO and that upstream of the MC4R locus) within 7470 children with total body DXA scans done at a mean of 9.9 yr. Total fat mass was related to total body, spinal, and upper and lower limb BMC (ratio of geometric means [RGM]: 1.118 [95% CI: 1.112, 1.123], 1.110 [95% CI: 1.102, 1.119], 1.101 [95% CI: 1.093, 1.108], 1.146 [95% CI: 1.143, 1.155]; $p<10(-10)$ [adjusted for sex, height, and sitting height]). Equivalent or larger effects were obtained from instrumental variable (IV) regression including the same covariates (1.139 [95% CI: 1.064, 1.220], 1.090 [95% CI: 1.010, 1.177], 1.142 [95% CI: 1.049, 1.243], 1.176 [95% CI: 1.099, 1.257]; p=0.0002, 0.03, 0.002, and 2.3(-6) respectively). Similar results were obtained after adjusting for puberty, when truncal fat mass was used in place of total fat, and when bone area was used instead of bone mass. In analyses where total body BMC adjusted for bone area was the outcome (reflecting volumetric BMD), linear regression with fat mass showed evidence for association (1.004 [95% CI: 1.002, 1.007], p=0.0001). IV regression also showed a positive effect (1.031 [95% CI: 1.000, 1.062], p=0.05).

10.3.55 Tracking of bone mass from childhood to adolescence and factors that predict deviation from tracking
Foley S, Quinn S, Jones G
Bone 2009;44:752-7

DXA measures from age 8-16 years was used in 116 males and 67 females. All DXA measures tracked after adjustment for change in height and change in weight (males: R^2 BMC 24-62%; aBMD 41-48%; BMAD 30-37%, females: R^2 BMC 45-72%; aBMD 36-56%; BMAD 30-48%). Factors that predicted subjects would deviate positively or remain in the highest tertile of spine and hip aBMD included having been breastfed, increase in bone free lean mass (LM), fitness at age 8 and sport participation in males. LM at age 8 was beneficial in males while in females; fat mass (FM) at age 8 predicted subjects would deviate positively. Boys who gained absolute and percent FM and girls who gained percent FM, were more likely to deviate negatively or remain in the lowest tertile of spine and hip aBMD. ICS use at age 8 also predicted subjects, particularly males would not improve in bone mass relative to their peers. DXA measures track from childhood to adolescence.

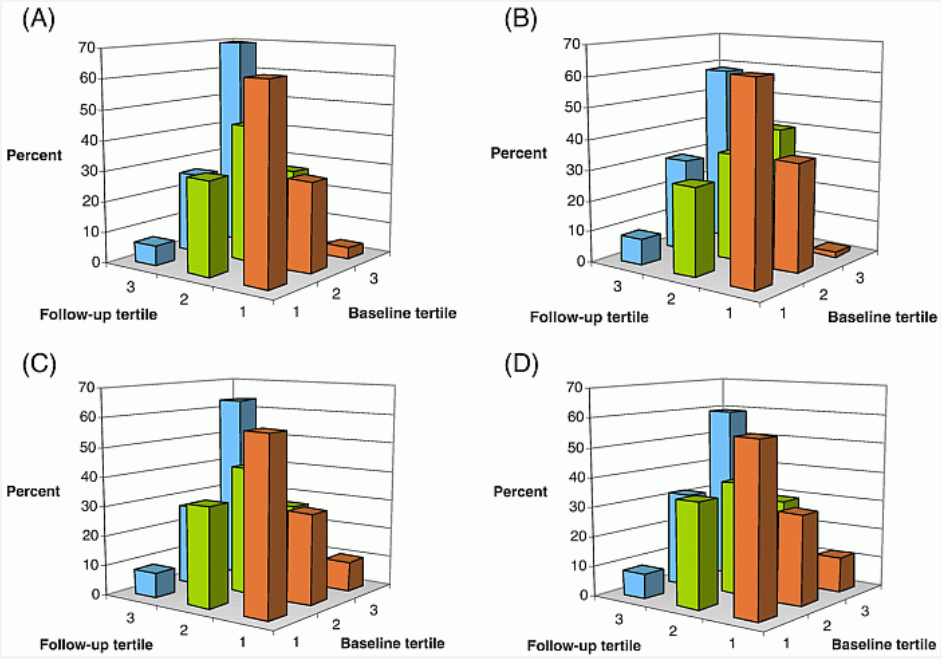

Fig. 10.3.55 The proportion of subjects that were in the first (lowest), second and third (highest) tertile of DXA measurements for (A) spine aBMD, (B) hip aBMD, (C) spine BMAD and (D) hip BMAD as 8-yr olds that were in the first (lowest), second and third (highest) tertile of DXA measurements as adolescents. The majority of children, who were in the lowest and highest DXA tertiles as 8-yr olds, remained in the lowest and highest DXA tertiles as adolescents. Reproduced from Bone, 44:752-7, Copyright (2009), with permission from Elsevier.

10.3.56 Peak lean tissue mass accrual precedes changes in bone strength indices at the proximal femur during the pubertal growth spurt
Jackowski SA, Faulkner RA, Farthing JP, Kontulainen SA, Beck TJ, Baxter-Jones AD
Bone 2009;44:1186-90

The authors examined the timing and magnitude of peak lean tissue mass accrual (PLTV) relative to the age and magnitude of two variables of bone strength [peak cross sectional area velocity (PCSAV), and peak section modulus velocity, (PZV)] at the proximal femur in 41 males and 42 females aged 8-18 years. There were no sex differences in the ages at which tissue peaks occurred when aligned by maturational age. There were differences between the age of PLTV and both PCSAV and PZV at the narrow neck (p=0.001) and femoral shaft (p=0.03), where the age of PLTV preceded both PCSAV and PZV when pooled by gender. PLTV was a predictor of the magnitude of both PCSAV and PZV at all sites (p<0.05).

10.3.57 Divergent effects of glucocorticoids on cortical and trabecular compartment BMD in childhood nephrotic syndrome
Wetzsteon RJ, Shults J, Zemel BS, Gupta PU, Burnham JM, Herskovitz RM, Howard KM, Leonard MB
J Bone Miner Res 2009;24:503-13

Tibia pQCT was used in 55 childhood steroid-sensitive nephrotic syndrome (SSNS) (age, 5-19 yr) and >650 controls. Z-scores for cortical area were greater (+0.37; 95% CI=0.09, 0.66; p=0.01), for cortical vBMD were greater (+1.17; 95% CI=0.89, 1.45; p<0.0001), and for trabecular vBMD were lower (-0.60; 95% CI = -0.89, -0.31; p<0.0001) compared with controls. Muscle area (+0.34; 95% CI=0.08, 0.61; p=0.01) and fat area (+0.56; 95% CI=0.27, 0.84; p<0.001) Z-scores were greater in SSNS, and adjustment for muscle area eliminated the greater cortical area in SSNS. Bone formation and resorption biomarkers were inversely associated with cortical vBMD in SSNS and controls and were lower in the 34 SSNS participants taking GCs. Lower bone biomarkers were associated with greater cortical vBMD. Studies are needed to determine the fracture implications of these varied effects.

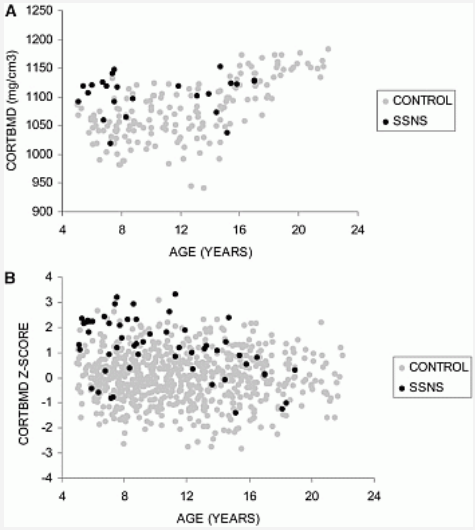

Fig. 10.3.57a Distributions of (A) absolute CortBMD (mg/cm^3) and (B) CortBMD Z-scores are shown relative to age in SSNS participants and healthy controls. The absolute CortBMD data in A are limited to white males, given race and sex effects

on CortBMD. The age-, sex-, and race-specific CortBMD Z-scores in B are shown for all SSNS and control participants. Absolute CortBMD values increase with age in the healthy controls, as expected. The age-specific CortBMD Z-scores do not increase with age in the healthy controls, as expected. Reproduced from J Bone Miner Res 2009;24:503-13 with permission of the American Society of Bone and Mineral Research.

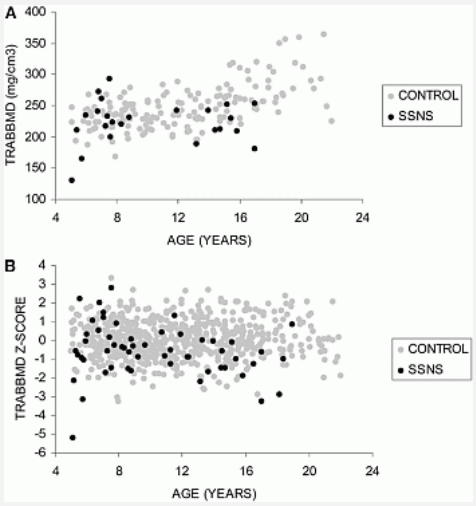

Fig. 10.3.57b Distributions of (A) absolute TrabBMD (mg/cm^3) and (B) TrabBMD Z-scores are shown relative to age in SSNS participants and healthy controls. The absolute TrabBMD data in A are limited to white males, given race and sex effects on TrabBMD. The age-, sex-, and race-specific TrabBMD Z-scores in B are shown for all SSNS and control participants. Absolute TrabBMD values increase with age in the healthy controls, as expected. The age-specific TrabBMD Z-scores do not increase with age in the healthy controls, as expected. Reproduced from J Bone Miner Res 2009;24:503-13 with permission of the American Society of Bone and Mineral Research.

10.3.58 Interaction of dietary zinc and intracellular binding protein metallothionein in postnatal bone growth
Fong L, Tan K, Tran C, Cool J, Scherer MA, Elovaris R, Coyle P, Foster BK, Rofe AM, Xian CJ
Bone 2009;44:1151-62

10.3.59 A delay in pubertal onset affects the covariation of body weight, estradiol, and bone size
Yingling VR
Calcif Tissue Int 2009;84:286-96

10.3.60 Evaluation of the femoral midshaft in children with cerebral palsy using magnetic resonance imaging
Modlesky CM, Kanoff SA, Johnson DL, Subramanian P, Miller F
Osteoporos Int 2009;20:609-15

10.3.61 Conjugated oral versus transdermal estrogen replacement in girls with Turner Syndrome: A pilot comparative study
Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.3.62 Do estrogens impact adolescent idiopathic scoliosis?
Leboeuf D, Letellier K, Alos N, Edery P, Moldovan F
Trends Endocrinol Metab 2009;20:147-52

10.3.63 Novel and unexpected functions of zebrafish CCAAT box binding transcription factor (NF-Y) B subunit during cartilages development
Chen Y-H, Lin Y-T, Lee G-H
Bone 2009;44:777-84

10.3.64 Morpholino-mediated knockdown in primary chondrocytes implicates Hoxc8 in regulation of cell cycle progression
Kamel S, Kruger C, Salbaum JM, Kappen C
Bone 2009;44:708-16

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Remodelling Markers

10.3.65 Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men
Kindblom JM, Ohlsson C, Ljunggren O, Karlsson MK, Tivesten A, Smith U, Mellstrom D
J Bone Miner Res 2009;24:785-91

Fasting plasma osteocalcin, plasma glucose, serum insulin, and lipids were analyzed in elderly men (75.3±3.2 yr of age) (n=1010; nondiabetic, n=857; diabetic, n=153) of the MrOS Sweden study. Diabetic subjects had lower plasma osteocalcin (-21.7%, p<0.001) than nondiabetic subjects. For both all subjects and nondiabetic subjects, plasma osteocalcin was inversely related BMI, fat mass, and plasma glucose (p<0.001), whereas it was not associated with height or lean mass. Plasma osteocalcin explained 6.3% of the variance in plasma glucose, whereas it associated moderately with serum insulin. Osteocalcin was an independent negative predictor of plasma glucose (p<0.001).

10.3.66 Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States
Glover SJ, Gall M, Schoenborn-Kellenberger O, Wagener M, Garnero P, Boonen S, Cauley JA, Black DM, Delmas PD, Eastell R
J Bone Miner Res 2009;24:389-97

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

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Bone Formation

10.3.67 Fetuin-A and BMD in older persons: The Health Aging and Body Composition (Health ABC) study
Ix JH, Wassel CL, Bauer DC, Toroian D, Tylavsky FA, Cauley JA, Harris TB, Price PA, Cummings SR, Shlipak MG
J Bone Miner Res 2009;24:514-21

Fetuin-A is a hepatic secretory protein that promotes bone mineralization in vitro. 3075 black and white persons 70-79 yr of age were studied. This cross-sectional study measured serum fetuin-A among 508 participants within sex and race strata. Among women (n=257), higher fetuin-A levels were associated with higher total hip (p=0.02), lumbar spine (p=0.03), and whole body BMD (p=0.01) in models adjusted for age, race, diabetes, alcohol and tobacco use, physical activity, BMI, C-reactive protein levels, calcium supplement, and estrogen use. For example, each SD (0.38 g/liter) higher level of fetuin-A was associated with 0.016 g/cm^2 higher total hip areal BMD. The association was of similar magnitude and direction for femoral neck BMD but did not reach statistical significance (p=0.11). In contrast, among men (n=251), fetuin-A had no significant associations with total hip (p=0.79), lumbar spine (p=0.35), whole body (p=0.46), or femoral neck BMD (p=0.54) in multivariable models. Higher fetuin-A is associated with higher BMD among older women not men.

10.3.68 Osteocyte-derived HB-GAM (pleiotrophin) is associated with bone formation and mechanical loading
Imai S, Heino TJ, Hienola A, Kurata K, Büki K, Matsusue Y, Väänänen HK, Rauvala H
Bone 2009;44:785-94

HB-GAM (also known as pleiotrophin) is a cell matrix-associated protein that is highly expressed in bone. It affects osteoblast function, and might therefore play a role in bone development and remodeling. The bones of HB-GAM deficient mice with an inbred mouse background were studied. MLO-Y4 osteocytes were subjected to fluid shear stress in vitro, and gene and protein expression were studied. The skeletal structure of the HB-GAM knockout mice developed normally. However, a growth retardation of the weight-bearing bones was observed by 2 months of age, suggesting a link to physical activity. Adult HB-GAM deficient mice were characterized by low bone formation and osteopenia, as well as resistance to immobilization-dependent bone remodeling. HB-GAM was localized around osteocytes and their processes in vivo and furthermore, osteocytic HB-GAM expression was upregulated by mechanical loading in vitro. HB-GAM did not affect on human osteoclast formation or resorption in vitro. HB-GAM is an osteocyte-derived factor that could participate in mediating the osteogenic effects of mechanical loading on bone.

10.3.69 Overexpression of cathepsin K accelerates the resorption cycle and osteoblast differentiation in vitro
Morko J, Kiviranta R, Mulari MT, Ivaska KK, Vaananen HK, Vuorio E, Laitala-Leinonen T
Bone 2009;44:717-28

Bone resorption is a multistep process including osteoclast attachment, cytoskeletal reorganization, formation of four distinct plasma membrane domains, and matrix demineralization and degradation followed by cell detachment. The present study describes the intracellular mechanisms by which overexpression of cathepsin K in osteoclasts results in enhanced bone resorption. Osteoclasts and bone marrow-derived osteoclast and osteoblast precursors were isolated from mice homozygous (UTU17(+/+)) and negative for the transgene locus. Cells cultured on bovine cortical bone slices were analyzed by fluorescence and confocal laser scanning microscopy, and bone resorption was studied by measurements of biochemical resorption markers, morphometry, and FESEM. Excessive cathepsin K protein and enzyme activity were microscopically observed in various intracellular vesicles and in the resorption lacunae of cathepsin K-overexpressing osteoclasts. The number of cathepsin K-containing vesicles in UTU17(+/+) osteoclasts was highly increased, and colocalization with markers for the biosynthetic and transcytotic pathways was observed throughout the cytoplasm. As a functional consequence of cathepsin K overexpression, biochemical resorption markers were increased in culture media of UTU17(+/+) osteoclasts. Detailed morphometrical analysis of the erosion in bone slices indicated that the increased biosynthesis of cathepsin K was sufficient to accelerate the osteoclastic bone resorption cycle. Cathepsin K overexpression also enhanced osteogenesis and induced the formation of exceptionally small, actively resorbing osteoclasts from their bone marrow precursors in vitro. The present study describes for the first time how enhancement in one phase of the osteoclastic resorption cycle also stimulates its other phases and further demonstrate that tight control and temporal coupling of mesenchymal and hematopoietic bone cells in this multistep process.

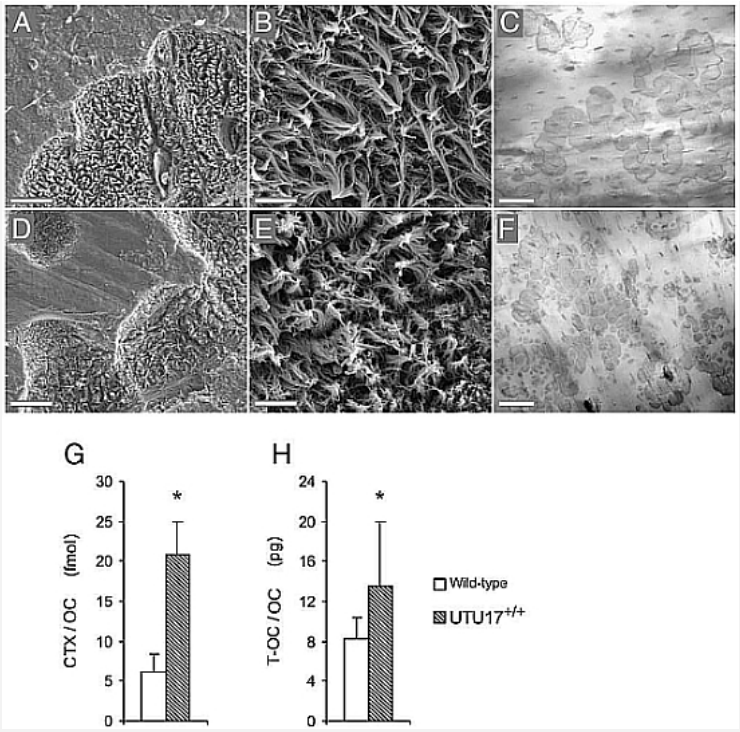

*Fig. 10.3.69a Resorption of bovine cortical bone slices exposed to control (A-C) and UTU17$^{+/+}$ mouse osteoclasts (D-F). Morphology of resorption lacunae was studied by FESEM (A, B, D and E) and conventional fluorescence microscopy afterWGA-lectin staining (C and F). The bars in panels A and D correspond to 25 µm; in panels B and E to 1 µm; and in panels C and F to 250 µm. The amount of C-terminal fragments of type I collagen (CTX in G) and bovine osteocalcin (T-OC in H) released into the culture medium were measured using ELISA assays. The results are shownas CTX (fmol) or T-OC (ng) per actively resorbing osteoclast, anddemonstrate the mean±SD. The total number of osteoclasts per bone slicewas 344±43 (wild-type) and 389±63 (UTU17$^{+/+}$). *p<0.05 (Mann-Whitney U test; n=4-5 in each study group). Reproduced from Bone, 44:717-28, Copyright (2009), with permission from Elsevier.*

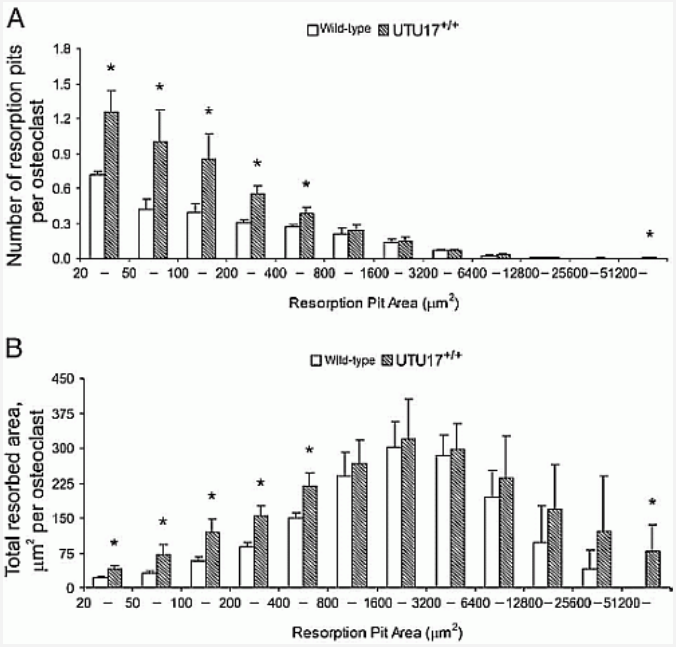

*Fig. 10.3.69b In vitro resorption capacity of cathepsin K-overexpressing osteoclasts. Area of resorption pits were microscopically analyzed and assorted according to their size followed by calculating their number (A) and total resorbed area (B) per osteoclast. Striped columns represent bone slices exposed to UTU17$^{+/+}$ osteoclasts, and open columns represent bone slices exposed to wildtype cells. The mean number of resorption pits per osteoclast was 2.5±0.2 µm^2 in wildtype and 4.5±0.6 µm^2 in UTU17$^{+/+}$ samples and total resorbed area per osteoclast was 1507±116 µm and 2096±345 µm, correspondingly. The total number of osteoclasts per bone slice was 344±43 (wild-type) and 389±63 (UTU17$^{+/+}$). *p<0.05 (Mann-Whitney U test; n=4-5 in each study group). Reproduced from Bone, 44:717-28, Copyright (2009), with permission from Elsevier.*

10.3.70 Glutaredoxin 5 regulates osteoblast apoptosis by protecting against oxidative stress

Linares GR, Xing W, Govoni KE, Chen S-T, Mohan S

Bone 2009;44:795-804

There is now increasing evidence which suggests an important role for reactive oxygen species (ROS) in the pathogenesis of osteoporosis. Glutaredoxin (Grx) 5, a protein expressed in bone was investigated. Osteoblasts were transfected with Grx5 siRNA and treated with hydrogen peroxide (H_2O_2). Grx5 siRNA treatment increased apoptosis while Grx5 overexpression protected MC3T3-E1 cells against H2O2 induced apoptosis and ROS formation. Grx5 deficiency results in impaired biogenesis of Fe-S cluster in yeast. Activity of mitochondrial aconitase, whose activity is dependent on Fe-S cluster, decreased in Grx5 siRNA treated cells. Since reduced formation of Fe-S cluster would lead to increased level of free iron, a competitive inhibitor of manganese superoxide dismutase (MnSOD), MnSOD activity was measured in Grx5 deficient osteoblasts and found

MnSOD activity was reduced. Long term inhibition of Grx5 on osteoblast apoptosis was evaluated using lentiviral shRNA technology. Grx5 shRNA cells exhibited higher caspase activity and cardiolipin oxidation in the presence of H_2O_2. MnSOD activity was rescued by the addition of MnCl2 to Grx5 shRNA osteoblasts in the presence of H_2O_2. Grx5 is a determinant of osteoblast apoptosis and acts via a molecular pathway that involves regulation of ROS production, cardiolipin oxidation, caspase activity, Fe-S cluster formation, and MnSOD activity.

10.3.71 Potential roles of growth factor PDGF-BB in the bony repair of injured growth plate
Chung R, Foster BK, Zannettino ACW, Xian CJ
Bone 2009;44:878-85

10.3.72 P2X7 nucleotide receptor plays an important role in callus remodeling during fracture repair
Li J, Meyer R, Duncan RL, Turner CH
Calcif Tissue Int 2009;84:405-12

10.3.73 miR-196a regulates proliferation and osteogenic differentiation in mesenchymal stem cells derived from human adipose tissue
Kim YJ, Bae SW, Yu SS, Bae YC, Jung JS
J Bone Miner Res 2009;24:816-25

10.3.74 Ebf1-dependent control of the osteoblast and adipocyte lineages
Hesslein DG, Fretz JA, Xi Y, Nelson T, Zhou S, Lorenzo JA, Schatz DG, Horowitz MC
Bone 2009;44:537-46

10.3.75 Galectin-9 accelerates transforming growth factor β3-induced differentiation of human mesenchymal stem cells to chondrocytes
Arikawa T, Matsukawa A, Watanabe K, Sakata K-m, Seki M, Nagayama M, Takeshita K, Ito K, Niki T, Oomizu S, Shinonaga R, Saita N, Hirashima M
Bone 2009;44:849-57

10.3.76 SOX9 directly binds CREB as a novel synergism with the PKA pathway in BMP-2-induced osteochondrogenic differentiation
Zhao L, Li G, Zhou GQ
J Bone Miner Res 2009;24:826-36

10.3.77 Zfp521 antagonizes Runx2, delays osteoblast differentiation in vitro, and promotes bone formation in vivo
Wu M, Hesse E, Morvan F, Zhang JP, Correa D, Rowe GC, Kiviranta R, Neff L, Philbrick WM, Horne WC, Baron R
Bone 2009;44:528-36

10.3.78 Wnt inhibitory factor (WIF)-1 inhibits osteoblastic differentiation in mouse embryonic mesenchymal cells
Cho SW, Yang JY, Sun HJ, Jung JY, Her SJ, Cho HY, Choi HJ, Kim SW, Kim SY, Shin CS
Bone 2009;44:1069-77

10.3.79 EP2 and EP4 receptors differentially mediate MAPK pathways underlying anabolic actions of prostaglandin E2 on bone formation in rat calvaria cell cultures
Minamizaki T, Yoshiko Y, Kozai K, Aubin JE, Maeda N
Bone 2009;44:1177-85

10.3.80 Long term oncostatin M treatment induces an osteocyte-like differentiation on osteosarcoma and calvaria cells
Brounais B, David E, Chipoy C, Trichet V, Ferre V, Charrier C, Duplomb L, Berreur M, Redini F, Heymann D, Blanchard F
Bone 2009;44:830-9

10.3.81 FGF2 stimulation of the pyrophosphate-generating enzyme, PC-1, in pre-osteoblast cells is mediated by RUNX2
Hatch NE, Li Y, Franceschi RT
J Bone Miner Res 2009;24:652-62

10.3.82 Calreticulin mediated glucocorticoid receptor export is involved in beta-catenin translocation and Wnt signalling inhibition in human osteoblastic cells
Olkku A, Mahonen A
Bone 2009;44:555-65

10.3.83 JNK activity is essential for Atf4 expression and late-stage osteoblast differentiation
Matsuguchi T, Chiba N, Bandow K, Kakimoto K, Masuda A, Ohnishi T
J Bone Miner Res 2009;24:398-410

10.3.84 The thyroid hormone receptor (TR) β-selective agonist GC-1 inhibits proliferation but induces differentiation and TR β mRNA expression in mouse and rat osteoblast-like cells

Beber EH, Capelo LP, Fonseca TL, Costa CC, Lotfi CF, Scanlan TS, Gouveia CH
Calcif Tissue Int 2009;84:324-33

10.3.85 Thrombin-stimulated growth factor and cytokine expression in osteoblasts is mediated by protease-activated receptor-1 and prostanoids
Pagel CN, Song S-J, Loh LH, Tudor EM, Murray-Rust TA, Pike RN, Mackie EJ
Bone 2009;44:813-21

10.3.86 Wnt signaling inhibits cementoblast differentiation and promotes proliferation
Nemoto E, Koshikawa Y, Kanaya S, Tsuchiya M, Tamura M, Somerman MJ, Shimauchi H
Bone 2009;44:805-12

10.3.87 ECM compliance regulates osteogenesis by influencing MAPK signaling downstream of RhoA and ROCK
Khatiwala CB, Kim PD, Peyton SR, Putnam AJ
J Bone Miner Res 2009;24:886-98

10.3.88 Use of rapidly mineralising osteoblasts and short periods of mechanical loading to accelerate matrix maturation in 3D scaffolds
Sittichockechaiwut A, Scutt AM, Ryan AJ, Bonewald LF, Reilly GC
Bone 2009;44:822-9

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Bone Resorption

10.3.89 Osteocyte apoptosis controls activation of intracortical resorption in response to bone fatigue
Cardoso L, Herman BC, Verborgt O, Laudier D, Majeska RJ, Schaffler MB
J Bone Miner Res 2009;24:597-605

Osteocytes surrounding microcracks undergo apoptosis and regions containing apoptotic osteocytes colocalize with areas resorbed by osteoclasts. In vivo fatigue loading of ulna from 4- to 5-mo-old Sprague Dawley rats treated with an apoptosis inhibitor (the pan-caspase inhibitor Q-VD-OPh). Intracortical remodeling and osteocyte apoptosis were assessed on day 14 after fatigue. Prolonged exposure to Q-VD-OPh blocked fatigue-induced apoptosis and activation of osteoclastic resorption, whereas short-term caspase inhibition during only the first 2 days after fatigue resulted in >50% reductions in osteocyte apoptosis and resorption. Osteocyte apoptosis is necessary to initiate intracortical remodeling in response to fatigue microdamage; a dose-response relationship exists between the two processes, and early apoptotic events after fatigue-induced microdamage may play a substantial role in determining tissue remodeling.

10.3.90 Quantitative evaluation of bone resorption activity of osteoclast-like cells by measuring calcium phosphate resorbing area using incubator-facilitated and video-enhanced microscopy
Morimoto Y, Hoshino H, Sakurai T, Terakawa S, Nagano A
Microsc Res Tech 2009;72:317-22

Osteoclasts, which were obtained from a coculture of ddy-mouse osteoblastic cells and bone marrow cells, were cultured on CP-coated quartz cover slips. The CP-free area increased constantly in the OCLs alone, whereas it did not increase after the addition of elcatonin. This study showed that analysis of the resorbed areas under the OCL body using this method enables the sequential quantitative evaluation of the bone resorption activity and the effect of several therapeutic agents on bone resorption in vitro.

10.3.91 Ablation of cathepsin k activity in the young mouse causes hypermineralization of long bone and growth plates
Boskey AL, Gelb BD, Pourmand E, Kudrashov V, Doty SB, Spevak L, Schaffler MB
Calcif Tissue Int 2009;84:229-39

10.3.92 Locally administered T cells from mice immunized with lipopolysaccharide (LPS) accelerate LPS-induced bone resorption
Ozaki Y, Ukai T, Yamaguchi M, Yokoyama M, Ayón Haro ER, Yoshimoto M, Kaneko T, Yoshinaga M, Nakamura H, Shiraishi C, Hara Y
Bone 2009;44:1169-76

10.3.93 Proteinase-activated receptor (PAR)-2 activation impacts bone resorptive properties of human osteoarthritic subchondral bone osteoblasts
Amiable N, Tat SK, Lajeunesse D, Duval N, Pelletier JP, Martel-Pelletier J, Boileau C
Bone 2009;44:1143-50

10.3.94 Atp6v0d2 is an essential component of the osteoclast-specific proton pump that mediates extracellular acidification in bone resorption
Wu H, Xu G, Li YP
J Bone Miner Res 2009;24:871-85

10.3.95 Inhibiting Dickkopf-1 (Dkk1) removes suppression of bone formation and prevents the development of osteolytic bone disease in multiple myeloma
Heath DJ, Chantry AD, Buckle CH, Coulton L, Shaughnessy JD, Jr., Evans HR, Snowden JA, Stover DR, Vanderkerken K, Croucher PI
J Bone Miner Res 2009;24:425-36

10.3.96 Collagenase expression and activity in the stromal cells from giant cell tumour of bone
Cowan RW, Mak IWY, Colterjohn N, Singh G, Ghert M
Bone 2009;44:865-71

10.3.97 Mathematical modeling of spatio-temporal dynamics of a single bone multicellular unit
Ryser MD, Nigam N, Komarova SV
J Bone Miner Res 2009;24:860-70

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Systemic Factors

10.3.98 Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: Global perspective

Kuchuk NO, van Schoor NM, Pluijm SM, Chines A, Lips P

J Bone Miner Res 2009;24:693-701

The study was performed in 7441 postmenopausal women from 29 countries participating in a clinical trial on bazedoxifene (selective estrogen receptor modulator), with BMD T-score at the femoral neck or lumbar spine ≤ -2.5 or one to five mild or moderate vertebral fractures. The prevalence of 25(OH)D <25, 25-50, 50-75, and >75 nM was 5.9%, 29.4%, 43.5%, and 21.2%, respectively, in winter and 3.0%, 22.2%, 47.2%, and 27.5% in summer. Worldwide, a negative correlation between 25(OH)D and latitude was observed. With increasing 25(OH)D categories of <25, 25-50, 50-75, and >75 nM, mean PTH, OC, and CTX were decreasing ($p<0.001$), whereas BMD of all sites was increasing ($p<0.001$). A threshold in the positive relationship between 25(OH)D and different BMD parameters was visible at a 25(OH)D level of 50 nM. Our study showed a high prevalence of low 25(OH)D in postmenopausal women with osteoporosis worldwide.

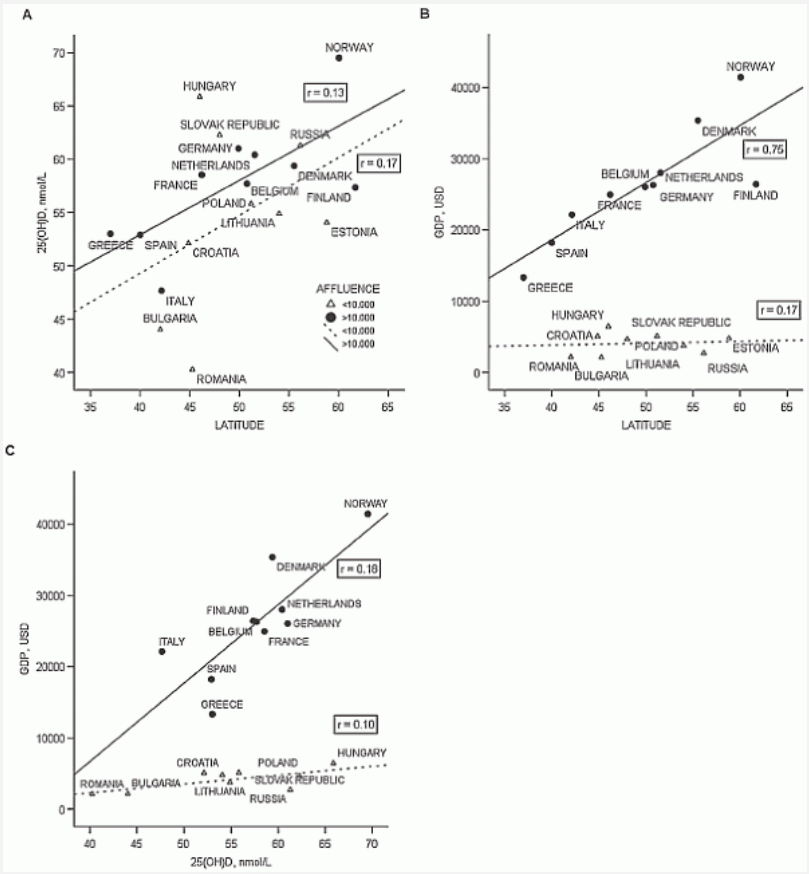

Fig. 10.3.98a Relationship between latitude, serum 25(OH)D, and gross domestic product per capita (GDP) in USD in Europe. (A) Latitude and serum 25(OH)D. (B) Latitude and GDP. (C) Serum 25(OH)D and GDP. Reproduced from J Bone Miner Res 2009;24:693-701 with permission of the American Society of Bone and Mineral Research.

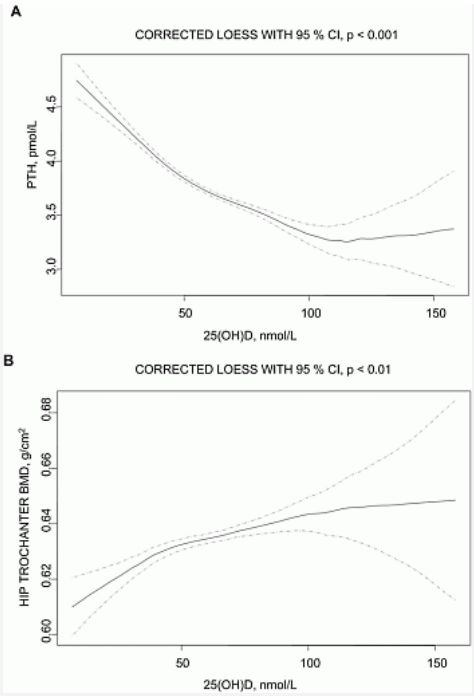

Fig. 10.3.98b Relationship of serum 25(OH)D with PTH and BMD. (A) With PTH, p<0.001. (B) With BMD of hip trochanter (p=0.01; dotted line represents 95% CI). *Similar shape was observed for the BMD of the femoral neck (p=0.19; data not shown). Reproduced from J Bone Miner Res 2009;24:693-701 with permission of the American Society of Bone and Mineral Research.*

10.3.99 Assessment of circulating Dickkopf-1 with a new two-site immunoassay in healthy subjects and women with breast cancer and bone metastases
Voorzanger-Rousselot N, Journe F, Doriath V, Body JJ, Garnero P
Calcif Tissue Int 2009;84:348-54

Serum Dkk-1 measurements were performed using a commercial sandwich ELISA in 150 healthy men, 175 healthy pre- and postmenopausal women (20-65 years), 22 women with BC and BM (mean age 63 years), and 16 women with BC and metastases at sites other than bone (mean age 53 years). The detection limit was determined to be 0.018 µg/L. In healthy women and men, Dkk-1 did not change with age. Serum Dkk-1 modestly correlated with serum bone alkaline phosphatase (r=0.19, P=0.013) and serum C-terminal crosslinking telopeptide of type I collagen (r=0.19, P=0.014) in women but not in men. Dkk-1 levels were higher in women with BC and BM (5.57±5.50 µg/L) than in healthy age-matched controls (3.47±1.47 µg/L, P<0.0001) and women with metastases at sites other than bone (3.57±1.66 µg/L, P=0.0003). In conclusion, serum Dkk-1 is stable with age in healthy women and men and increases in patients with BC and BM.

10.3.100 Testosterone, but not IGF-1, LH, prolactin or cortisol, may serve as antler-stimulating hormone in red deer stags (Cervus elaphus)
Bartos L, Schams D, Bubenik GA
Bone 2009;44:691-8

Eight 2-year-old red deer stags (Cervus elaphus), and 12 adult red deer stags were blood sampled and the length of their velvet antlers was measured in one week intervals during the period of antler growth. Antler growth per day was primarily dependent on changes in testosterone concentration per day in both groups of stags. Only in 2-year-old stags was a possible role of IGF-1 in the antler growth regulation. In addition to total antler length, only concentrations of testosterone and LH were higher in adult males in comparison to 2-year-old males.

10.3.101 Critical issues of PTH assays in CKD
Komaba H, Goto S, Fukagawa M
Bone 2009;44:666-70

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Local Factors

10.3.102 High cortical bone mass phenotype in betacellulin transgenic mice is EGFR dependent
Schneider MR, Mayer-Roenne B, Dahlhoff M, Proell V, Weber K, Wolf E, Erben RG
J Bone Miner Res 2009;24:455-67

Signaling through epidermal growth factor receptor (EGFR) by epidermal growth factor (EGF), transforming growth factor alpha (TGFA), and amphiregulin (AREG) effects skeletal growth. The role of betacellulin (BTC), another EGFR ligand, in skeletal development and bone metabolism is unknown. Transgenic mice overexpressing BTC ubiquitously under the control of the chicken beta-actin promoter (BTC-tg) exhibited stunted growth and disproportionately sized long bones. Osteoblastic cells from transgenic mice showed expression of BTC. In femurs of male and female BTC-tg mice, we found reduced longitudinal bone growth and a pronounced increase in total volumetric BMD. The increased femoral BMD was caused by augmented endocortical bone apposition. In contrast, vertebral BMD was reduced in BTC-tg mice. The increase in cortical bone in the appendicular skeleton of BTC-tg mice was blocked when they were crossed into the Egfr (Wa5) background characterized by a dominant negative EGFR.

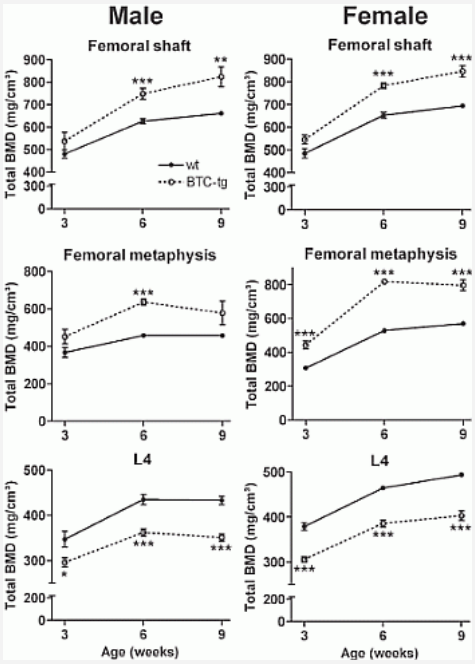
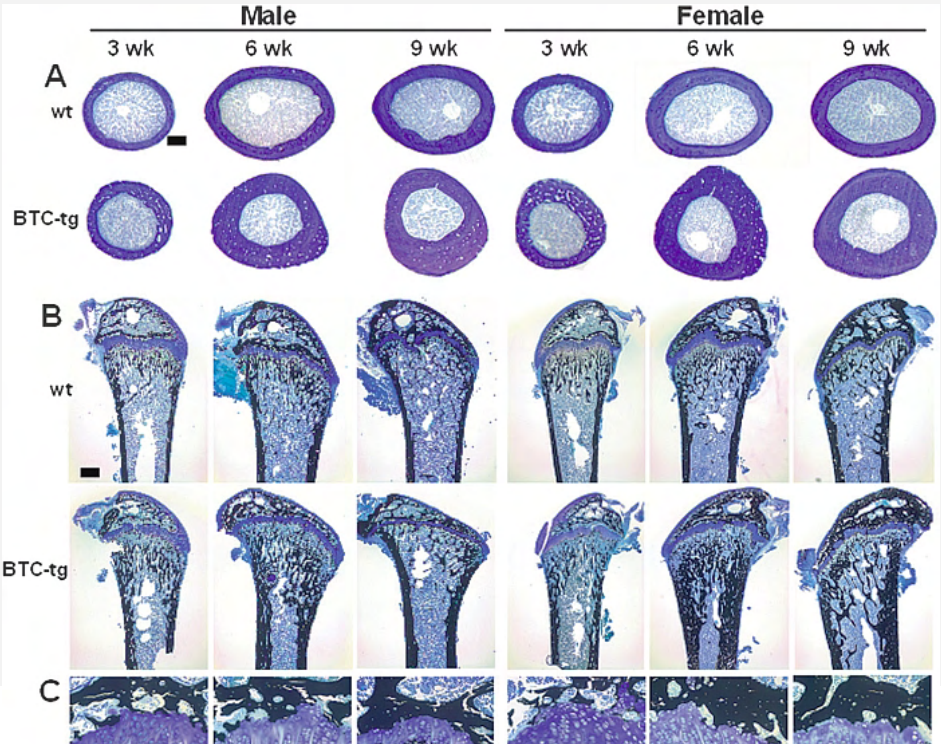


*Fig. 10.3.102a pQCT analysis of femurs and vertebral bodies. Total volumetric BMD at the femoral shaft (top panels), at the femoral metaphysis (middle panels), and in L4 lumbar vertebrae (bottom panels) of transgenic (BTC-tg) and age-matched wildtype (WT) mice. Each data point is the mean±SE of 5-10 animals. *p<0.05; **p<0.01; and ***p<0.001 vs. WT. Reproduced from J Bone Miner Res 2009;24:455-67 with permission of the American Society of Bone and Mineral Research.*



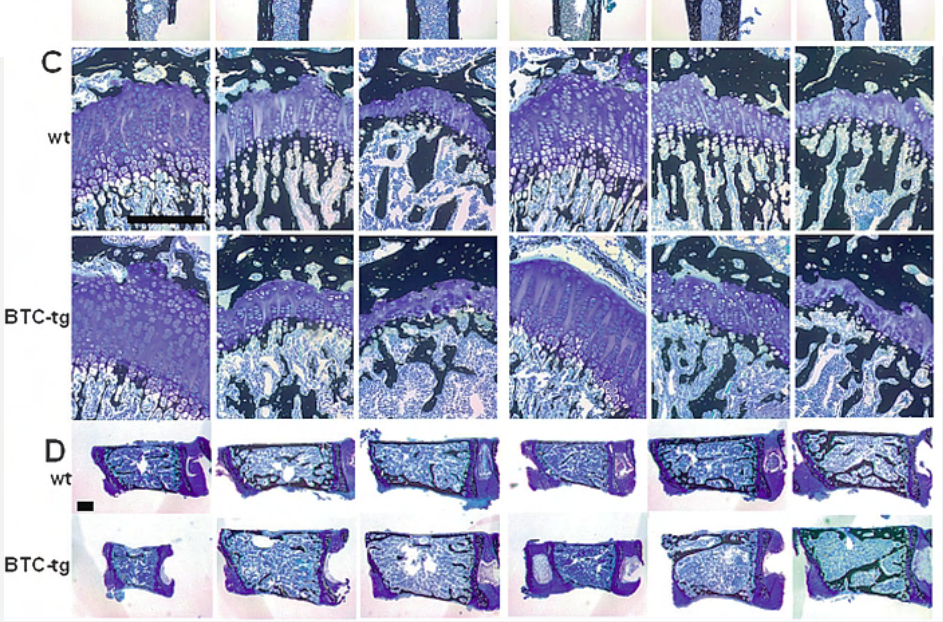


Fig. 10.3.102b Bone histology. Cross-sections of the femoral mid-diaphysis (A), longitudinal sections of distal femurs (B), distal femoral growth plates (C), and midsagittal sections of L1 vertebral bodies (D) from transgenic (BTC-tg) and wildtype (WT) males and females at the indicated ages. Note the smaller zone of hypertrophic chondrocytes in the growth plates of transgenic mice (C). 20-µm-thick microground sections (A) and 3-µm-thick microtome sections (B-D) from MMA-embedded bones stained with toluidine blue (A) or with von Kossa/McNeal's tetrachrome (B-D). Bar=0.5 mm. Reproduced from J Bone Miner Res 2009;24:455-67 with permission of the American Society of Bone and Mineral Research.

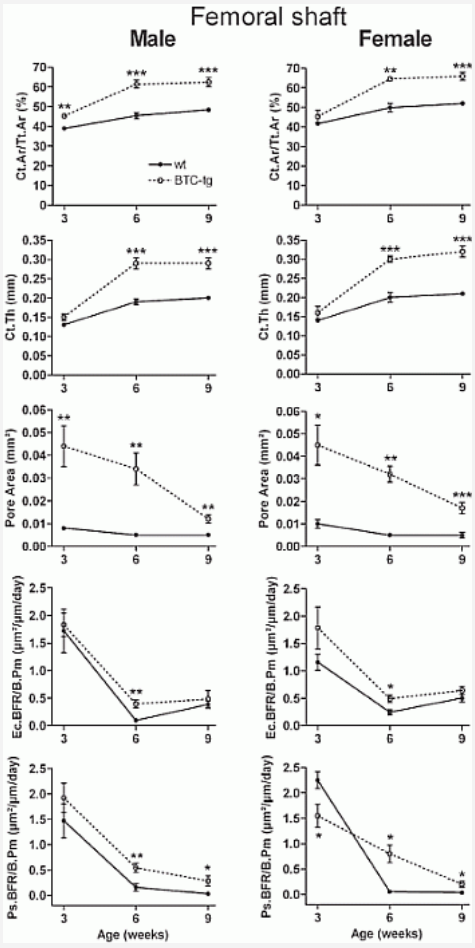


*Fig. 10.3.102c Cortical bone histomorphometry measured on crosssections of the femoral mid-diaphysis. Percent cortical area (Ct. Ar/Tt.Ar), cortical thickness (Ct.Th), intracortical pore area, endocortical (Ec.BFR/B.Pm), and periosteal (Ps.BFR/B.Pm) bone formation rate in male and female mice transgenic (BTC-tg) and wildtype (WT) mice at the indicated ages. Each data point is the mean±SE of 5-10 animals. *p<0.05; **p<0.01; and ***p<0.001 vs. WT. Reproduced from J Bone Miner Res 2009;24:455-67 with permission of the American Society of Bone and Mineral Research.*

10.3.103 Beta-Arrestin2 regulates RANKL and ephrins gene expression in response to bone remodeling in mice
Pierroz DD, Rufo A, Bianchi EN, Glatt V, Capulli M, Rucci N, Cavat F, Rizzoli R, Teti A, Bouxsein ML, Ferrari SL
J Bone Miner Res 2009;24:775-84

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Risk Factors

10.3.104 Vertebral fracture status and the world health organization risk factors for predicting osteoporotic fracture risk
Chen P, Krege JH, Adachi JD, Prior JC, Tenenhouse A, Brown JP, Papadimitropoulos E, Kreiger N, Olszynski WP, Josse RG, Goltzman D
J Bone Miner Res 2009;24:495-502

A randomly selected cohort of 2761 men and women ≥50 yr of age was enrolled in the Canadian Multicentre Osteoporosis Study (CaMOS) for 5 yr. In univariate analyses, age, BMD, and spine fracture status had the highest gradient of risk. A model considering these three risk factors captured almost all of the predictive information provided by a model considering spine fracture status plus the WHO risk factors and provided greater predictive information than a model considering the WHO risk factors alone. The use of spine fracture status along with age and BMD predicted future fracture risk with greater simplicity and higher prognostic accuracy than consideration of the risk factors included in the WHO tool.

10.3.105 Practical operationalizations of risk factors for fracture in older women: Results from two longitudinal studies
Pluijm SM, Steyerberg EW, Kuchuk NO, Rivadeneira FF, Looman CW, Van Schoor NM, Koes B, Mackenbach JP, Lips P, Pols HA
J Bone Miner Res 2009;24:534-42

4157 women of ≥60 yr of age with a median follow-up of 8.9 yr of the Rotterdam Study and 762 women of ≥65 yr of age with a median follow-up of 6.0 yr of the Longitudinal Aging Study Amsterdam (LASA) were assessed. In the Rotterdam Study, 399 fractures occurred during 31,472 person-years (PY). A prior fracture in the past 5 yr (chi^2=6; p=0.02), body weight <64 kg (versus ≥64 kg; chi^2=6.7; p=0.01), BMI <22 kg/m^2 (versus ≥22 kg/m(2); chi^2=8.7; p=0.003), and use of a walking aid (chi^2=7.5; p=0.004) were the most practical operationalizations of the risk factor categories, after adjustment for age and other risk factors. In LASA, 52 fragility fractures occurred during 3935 PY of follow-up. Associations were similar, except that low body weight and BMI were not associated with fragility fracture. None of the usual operationalizations of family history of hip fractures was independently associated with fragility fracture. Prior osteoporotic fracture, body weight <64 kg, a BMI <22 kg/m^2, and the use of a walking aid are practical operationalizations of risk factors for fragility fractures.

10.3.106 Sister's fracture history may be associated with perimenopausal bone fragility and modifies the predictability of fracture risk
Sirola J, Salovaara K, Tuppurainen M, Jurvelin JS, Alhava E, Kroger H
Osteoporos Int 2009;20:557-65

The study sample of 971 perimenopausal women was extracted from randomly selected Kuopio Osteoporosis Risk Factor and Prevention cohort and measured with DXA in femoral neck (FN) in baseline (1989-1991), in 5 years (1994-97), and in 10 years (1999-2001). All low-trauma energy fractures during the 10-year follow-up were recorded. There was a correlation between fathers' vs. brothers' and mothers' vs. sisters' fractures (p<0.01 in Pearson bivariate correlations). Sister's, but not mother's, father's, or brother's wrist and hip fractures were associated with lowered 10-year fragility fracture-free survival rate (HR=0.56, p=0.006). Sisters' or other relatives' fractures were not associated with FN bone loss rate or BMD in the follow-up measurements. Baseline FN T-score predicted fracture-free survival only among women without sisters' fracture history (HR=0.62, p<0.001 vs. women with sisters' fracture in Cox regression). Sisters' fracture history is associated with 10-year fracture-free survival in perimenopausal women but not with BMD or its changes.

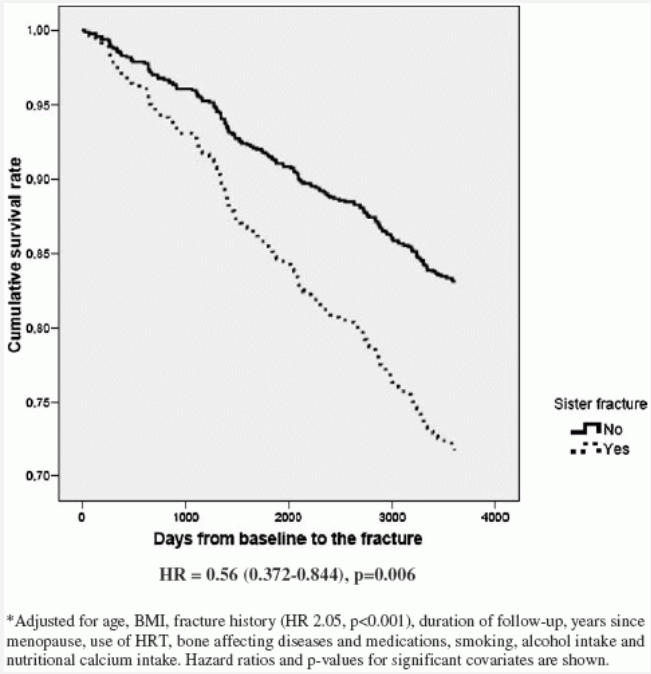


Fig. 10.3.106a Association of sister's fractures with perimenopausal fracture-free survival during the 15-year follow-up. Cox proportional hazards model adjusted for age, BMI, fracture history (HR=2.05, p<0.001), duration of follow-up, years since menopause, use of HRT, bone-affecting diseases and medications, smoking, alcohol intake, and nutritional calcium intake. Hazard ratios and p values for significant covariates are shown. HR=0.56 (0.372-0.844), p=0.006. Reproduced

from Osteoporos Int 2009;20:557-65 with permission from Springer.

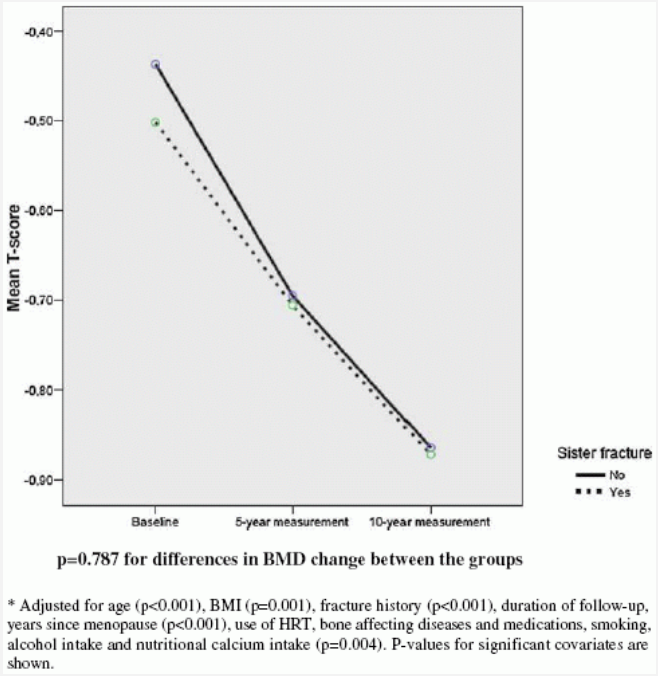


Fig. 10.3.106b Association of sister's fractures with perimenopausal BMD and its change. Analysis of co-variance adjusted for age (p<0.001), BMI (p=0.001), fracture history (p<0.001), duration of follow-up, years since menopause (p<0.001), use of HRT, bone-affecting diseases and medications, smoking, alcohol intake, and nutritional calcium intake (p=0.004). p values for significant covariates are shown. p=0.787 for differences in BMD change between the groups. Reproduced from Osteoporos Int 2009;20:557-65 with permission from Springer.

10.3.107 Genetic and environmental determinants on bone loss in postmenopausal Caucasian women: A 14-year longitudinal twin study
Zhai G, Andrew T, Kato BS, Blake GM, Spector TD
Osteoporos Int 2009;20:949-53

Postmenopausal female monozygotic (MZ) and dizygotic (DZ) twins aged 40 or above at baseline were selected from the Twins UK registry and followed up for an average of 8 years (range 5-14 years). A total of 712 postmenopausal Caucasian female twins (152 MZ and 204 DZ pairs) were included. Intraclass correlation coefficients for the bone loss at all sites were higher in MZ than DZ twin pairs (p=0.0045, 0.0003, and 0.0007 for femoral neck, lumbar spine, and forearm, respectively), indicating a significant genetic influence on bone loss at these sites. After adjustment for age at baseline and weight change during the follow-up, the heritability estimate was 47% (95% CI 27-63%) for bone loss at femoral neck, 44% (95% CI 27-58%) for lumbar spine, and 56% (95% CI 44-65%) for forearm.

10.3.108 Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: Results from the Women's Health Initiative
Chen Z, Maricic M, Aragaki AK, Mouton C, Arendell L, Lopez AM, Bassford T, Chlebowski RT
Osteoporos Int 2009;20:527-36

Postmenopausal women (N=146,959) from the Women's Health Initiative prospective cohort, who had no cancer history at baseline, were followed for up to 9 years and classified into no cancer, incident breast cancer (BC) and incident other cancer (OC) groups. While hip fracture risk before a cancer diagnosis was similar between the no cancer and cancer groups, hip fracture risk was higher after BC diagnosis (HR=1.55, CI=1.13-2.11) and the elevated risk was even more notable after OC diagnosis (HR=2.09, CI=1.65-2.65). Risk of falls also increased after BC (HR=1.15, CI=1.06-1.25) or OC diagnosis (HR=1.27, CI=1.18-1.36), but could not fully explain the elevated hip fracture risk. Incident clinical vertebral and total fractures were also significantly increased after OC diagnosis (p<0.05).

10.3.109 High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy
Crew KD, Shane E, Cremers S, McMahon DJ, Irani D, Hershman DL
J Clin Oncol 2009;27:2151-6

The study included 103 premenopausal women from the northeastern United States with stages I to III breast cancer who received adjuvant chemotherapy and participated in a one-year zoledronate intervention trial. All patients were prescribed vitamin D3 (cholecalciferol) 400 IU and calcium carbonate 1000 mg daily. At baseline, 74% of women were vitamin D deficient (median, 17 ng/mL). Vitamin D deficiency was slightly less common in white women (66%) compared with black (80%) and Hispanic (84%) women. After vitamin D supplementation for one year, less than 15% of white and Hispanic women, and no black women, achieved sufficient 25-OHD levels. Vitamin D levels did not correlate with baseline BMD and were not altered by chemotherapy or bisphosphonate use. Vitamin D deficiency is prevalent in women with breast cancer. The current recommended dietary allowance of vitamin D is too low to increase serum 25-OHD greater than 30 ng/mL. Optimal dosing for bone health and, possibly, improved survival has yet to be determined.

10.3.110 Vitamin D and mortality in older men and women
Pilz S, Dobnig H, Nijpels G, Heine RJ, Stehouwer CD, Snijder MB, van Dam RM, Dekker JM
Clin Endocrinol (Oxf) 2009;[Epub ahead of print]

Vitamin D deficiency is common among the elderly and may contribute to cardiovascular disease. To elucidate whether low serum levels of 25-hydroxyvitamin D [25(OH)D] are associated with an increased risk of all-cause and cardiovascular mortality a prospective population-based study among in 614 participants at the follow-up visit in 2000-2001 after 6.2 years, 51 participants died including 20 deaths due to cardiovascular causes. Unadjusted Cox proportional hazard ratios (with 95% CI) for all-cause and cardiovascular mortality in the first when compared to the upper three 25(OH)D quartiles were 2.24 (1.28-3.92; p=0.005) and 4.78 (1.95-11.69; p=0.001), respectively. Tthe hazard ratios remained significant for all-cause [1.97 (1.08-3.58; p=0.027)] and for cardiovascular mortality [5.38 (2.02-14.34; p=0.001)] after adjustments.

10.3.111 Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004
Ginde AA, Liu MC, Camargo CA, Jr.
Arch Intern Med 2009;169:626-32

In 18,883 participants in NHANES III and 13,369 participants in NHANES 2001-2004 mean serum 25(OH)D level was 30 (95% CI, 29-30) ng/mL during NHANES III and decreased to 24 (23-25) ng/mL during NHANES 2001-2004. Accordingly, the prevalence of 25(OH)D levels of less than 10 ng/mL increased from 2% (95% CI, 2%-2%) to 6% (5%-8%), and 25(OH)D levels of 30 ng/mL or more decreased from 45% (43%-47%) to 23% (20%-26%). The prevalence of 25(OH)D levels of less than 10 ng/mL in non-Hispanic blacks rose from 9% during NHANES III to 29% during NHANES 2001-2004, with a corresponding decrease in the prevalence of levels of 30 ng/mL or more from 12% to 3%. Differences by age strata (mean serum 25(OH)D levels ranging from 28-32 ng/mL) and sex (28 ng/mL for women and 32 ng/mL for men) during NHANES III equalized during NHANES 2001-2004 (24 vs. 24 ng/mL for age and 24 vs. 24 ng/mL for sex).

10.3.112 Effects of vitamin D insufficiency on bone mineral density in African American men
Akhter N, Sinnott B, Mahmood K, Rao S, Kukreja S, Barengolts E
Osteoporos Int 2009;20:745-50

The data for 112 African American (AA) males who had both 25-OHD levels and BMD of spine and hip were extracted and analyzed using SAS software. AA men were aged 38-85 years, with mean age of 62 years. Levels of 25-OHD ranged from 4-45 ng/ml, with mean 17.5 ng/ml, 24% and 89% of the subjects had 25-OHD below 10 and 30 ng/ml, respectively. In the overall group, there was no correlation between 25-OHD and BMD. In a subgroup analysis of subjects with 25-OHD ≤15 ng/ml, in multiple adjusted models, 25-OHD was positively associated with BMD of spine (r=0.26, p=0.05), total hip (r=0.27, p<0.05), Ward's triangle (r=0.25, p=0.05), and trochanter (r=0.30, p<0.05). The negative effect of vitamin D insufficiency on bone was observed only at very low levels of 25-OHD.

10.3.113 Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults
Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, Orav JE, Li R, Spiegelman D, Dietrich T, Willett WC
J Bone Miner Res 2009;24:935-42

4958 women and 5003 men ≥20 yr of age from the U.S. NHANES III population-based survey were studied. Standardized means for BMD by quartiles of sex-specific calcium intake for three 25(OH)D categories (<50, 50-74, and 75+ nM) among men and women showed a higher calcium intake was associated with higher BMD (p-value for trend: p=0.005) only for women with 25(OH)D status <50 nM, whereas calcium intake beyond the upper end of the lowest quartile (>566 mg/d) was not associated with BMD at 25(OH)D >50 nM. Among men, there was no association between a higher calcium intake beyond the upper end of the lowest quartile (626 mg/d) and BMD within all 25(OH)D categories. Among both sexes, BMD increased stepwise and with higher 25(OH)D (<50, 50-74, 75+ nM; p-value for trend: women<0.0001; men=0.0001). Among men and women, 25(OH)D status seems to be the dominant predictor of BMD relative to calcium intake. Only women with 25(OH)D concentrations <50 nM seem to benefit from a higher calcium intake.

10.3.114 Serum 25-hydroxyvitamin D status of vegetarians, partial vegetarians, and nonvegetarians: The Adventist Health Study-2
Chan J, Jaceldo-Siegl K, Fraser GE
Am J Clin Nutr 2009;89:1686S-92S

Food-frequency questionnaires and sun-exposure data were obtained from 199 black and 229 non-Hispanic white adults. No significant difference in s25(OH)D by vegetarian status for either white or black subjects. Among whites, dietary vitamin D intake and sun behavior were different between vegetarian groups, but there was no difference in skin type distribution. Among blacks, no significant differences were observed for any of these variables between vegetarian groups. The mean (±SD) s25(OH)D was higher in whites (77.1±10.33 nmol/L) than in blacks (50.7±27.4 nmol/L) (P<0.0001). s25(OH)D concentrations were not associated with vegetarian status. Other factors, such as vitamin D supplementation, degree of skin pigmentation, and amount and intensity of sun exposure have greater influence on s25(OH)D than diet.

10.3.115 Sex-specific association of serum vitamin D levels with physical function in older adults
Dam TT, von Muhlen D, Barrett-Connor EL
Osteoporos Int 2009;20:751-60

1065 community-dwelling men and women (mean age 74.6 years) with 25(OH)D levels and performance on timed up and go (TUG) and timed chair stand (TCS) were seen in 1997-1999; 769 (72%) returned for follow-up. 25(OH)D was higher in men than women, but the prevalence of vitamin D insufficiency (<75 nmol/L) was 14%. There were no baseline sex differences in TUG or TCS. However, after 2.5 years, decline in TCS and TUG was greater in women than men (11% vs. 3%; p<0.001). Women in the lowest 25(OH)D quartile (<80 nmol/L) compared to the highest quartile had an accelerated rate of functional decline on the TUG and TCS independent of covariates. No associations were seen in men.

10.3.116 High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease
Kuwabara A, Tanaka K, Tsugawa N, Nakase H, Tsuji H, Shide K, Kamao M, Chiba T, Inagaki N, Okano T, Kido S
Osteoporos Int 2009;20:935-42

70 patients with inflammatory bowel disease (IBD) were evaluated for their BMD; plasma levels of vitamin K; phylloquinone (PK), menaquinone-7 (MK-7), and 25OH-D; serum PTH, protein induced by vitamin K absence (PIVKA-II), and undercarboxylated osteocalcin (ucOC) levels; and their food intake. Compared with ulcerative colitis (UC) patients, CD patients had lower plasma vitamin K and 25OH-D; higher serum PTH, PIVKA-II, and ucOC; and lower BMD scores at almost all measurement sites. More IBD patients were vitamin K deficient in bone than in liver. Multiple regression analyses revealed that

low plasma concentrations of vitamin K and 25OH-D were independent risk factors for low BMD and that they were associated with the patients' fat intake, but not with their intake of these vitamins.

10.3.117 Nitrate use and changes in bone mineral density: The Canadian Multicentre Osteoporosis Study
Jamal SA, Goltzman D, Hanley DA, Papaioannou A, Prior JC, Josse RG
Osteoporos Int 2009;20:737-44

Among 1419 men 71 reported daily nitrate use and in 2587 women 97 reported daily nitrate use. Male nonusers had decreased hip BMD (-1.3%; 95% = -1.6 to -1.1) and increased spine BMD (2.8%; 95% CI = 2.5 to 3.1). Male nitrate users had increased hip BMD (1.4%; 95% CI = 0.1 to 2.8) and spine BMD (4.5%; 95% CI = 3.2 to 5.7). Among women, nonusers had decreased hip BMD (-1.9; 95% CI = -2.1 to -1.7) and increased spine BMD (2.1%; 95% CI = 1.9 to 2.4) whilst users had an increase in hip BMD (2.0%; 95% CI = 1.2 to 2.8) and spine BMD (4.1%; 95% CI = 3.4 to 4.9). Nitrate use is associated with increased BMD at the hip and spine in men and women.

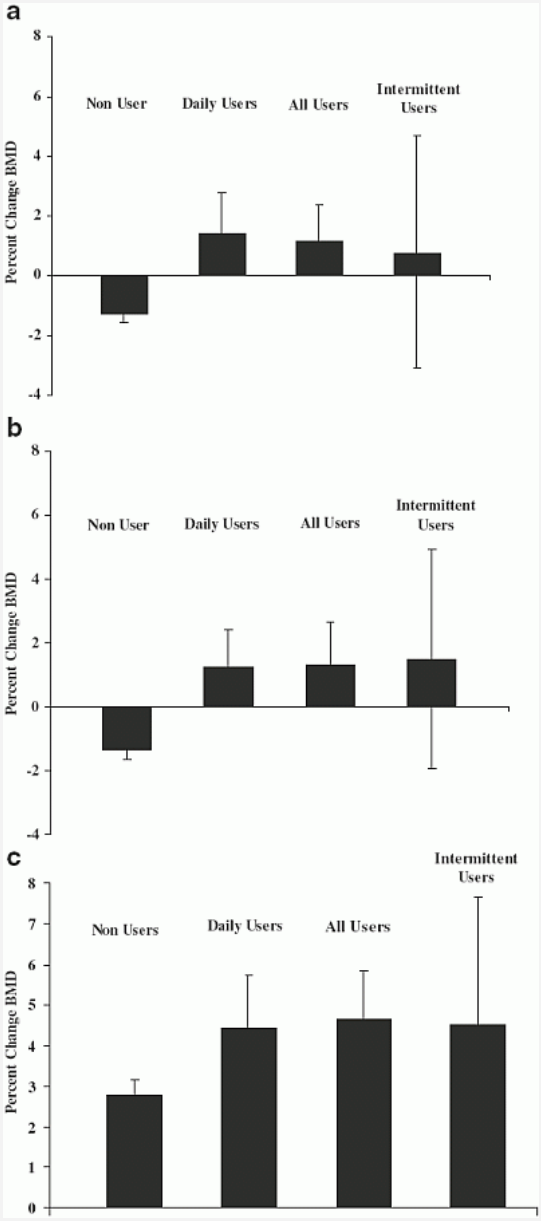


Fig. 10.3.117 a) Annualised percent change in total hip BMD in men, by nitrate use. b) Annualised percent change in femoral neck BMD in men, by nitrate use. c) Annualised percent change in lumbar spine BMD in men, by nitrate use. Total hip, femoral neck and lumbar spine BMD were adjusted for age, weight, baseline BMD, clinical centre and baseline differences (type 2 diabetes, self-rated health, kidney disease, vitamin D intake, caffeine intake, postsecondary education, sedentary hours per day and use of diuretics). Reproduced from Osteoporos Int 2009;20:737-44 with permission from Springer.

10.3.118 Vertebral fractures in patients with chronic obstructive pulmonary disease: The EOLO Study
Nuti R, Siviero P, Maggi S, Guglielmi G, Caffarelli C, Crepaldi G, Gonnelli S
Osteoporos Int 2009;20:989-98

In 3030 ambulatory COPD patients (1778 men and 1262 women) aged 50 years or over, we evaluated: COPD severity, presence of vertebral fractures on lateral chest X-ray and bone status by using a quantitative ultrasound device. In men there was a strong association between COPD severity and fractures ($p<0.001$), conversely in women the association between COPD severity and fractures was at limit ($p=0.049$). In men, but not in women, glucocorticoid treatment was associated with vertebral fractures. The patients with high or moderate risk of osteoporosis presented an increased risk of vertebral fracture (OR 2.71; 95% CI 2.04-3.60 and OR 1.54; 95% CI 1.26-1.88, respectively). Logistic regression analysis showed that COPD severity and glucocorticoid treatment, both inhaled and oral, were associated with increased risk of vertebral fractures.

10.3.119 Osteoarthritis and risk of fractures
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2009;84:249-56

The authors conducted a case-control study on the effects of osteoarthritis (OA) on the risk of fractures. There were 124,655 fracture cases and 373,962 age- and gender-matched controls. OA was associated with a decreased risk of any fracture and of hip, forearm, and spine fractures. The effect on fractures in areas rich in cortical bone such as the hip in general was larger than effects on skeletal sites rich in trabecular bone such as the spine. OA in the hip and knee, in general, was associated with a decreasing risk of fractures with time since diagnosis of OA, while this was not the case for OA in other locations. OA seems to be associated with a decreased risk of fractures at multiple skeletal sites as well as sites far from the location of OA. This may indicate systemic effects on bone strength, especially in areas rich in cortical bone.

10.3.120 Epidemiology of lumbar osteoporosis and osteoarthritis and their causal relationship – Is osteoarthritis a predictor for osteoporosis or vice versa? The Miyama study
Yoshimura N, Muraki S, Oka H, Mabuchi A, Kinoshita H, Yosihda M, Kawaguchi H, Nakamura K, Akune T
Osteoporos Int 2009;20:999-1008

From 1543 participants aged 40-79 years, 200 men and 200 women were selected and followed up for 10 years. The incidence of lumbar OP per 10,000 person-years for persons in their 40s, 50s, 60s, and 70s was 0, 0, 109.5, and 151.1 for men and 124.2, 384.0, 227.3, and 239.5 for women, respectively. The cumulative incidence of lumbar OA over 10 years aged 40-79 years was 25.8% in men and 45.2% in women. Cox's proportional hazards model showed no significant relationship between the presence of lumbar OA at the baseline and incidence of lumbar and femoral neck OP in both genders. A significant relationship was demonstrated between the presence of lumbar OP, not femoral neck OP, at the baseline and cumulative incidence of lumbar OA in women (odds ratio, 0.20; 95% CI, 0.05-0.80; P=0.02).

10.3.121 Nightshift work and fracture risk: The Nurses' Health Study
Feskanich D, Hankinson SE, Schernhammer ES
Osteoporos Int 2009;20:537-42

The study population was drawn from Nurses' Health Study participants who were working full- or part-time in nursing in 1988 and had reported their total number of years of rotating nightshift work. Through 2000, 1223 incident wrist and hip fractures involving low or moderate trauma were identified among 38,062 postmenopausal women. Compared with women who never worked night shifts, 20+ years of nightshift work was associated with a increased risk of wrist and hip fractures over 8 years of follow-up (RR=1.37, 95% CI, 1.04-1.80). This risk was strongest among women with a lower BMI (<24) who never used hormone replacement therapy (RR=2.36; 95% CI, 1.33-4.20). The elevated risk was no longer apparent with 12 years of follow-up after the baseline single assessment of nightshift work.

10.3.122 Maternal dietary patterns during pregnancy and childhood bone mass: A longitudinal study
Cole ZA, Gale CR, Javaid MK, Robinson SM, Law C, Boucher BJ, Crozier SR, Godfrey KM, Dennison EM, Cooper C
J Bone Miner Res 2009;24:663-8

198 pregnant women 17-43 yr of age and their offspring at 9 yr of age were studied. A high prudent diet score was characterized by elevated intakes of fruit, vegetables, and wholemeal bread, rice, and pasta and low intakes of processed foods. Higher prudent diet score in late pregnancy was associated with greater ($p<0.001$) whole body and lumbar spine BMC and areal BMD in the offspring, after adjustment.

10.3.123 Milk, rather than other foods, is associated with vertebral bone mass and circulating IGF-1 in female adolescents
Esterle L, Sabatier JP, Guillon-Metz F, Walrant-Debray O, Guaydier-Souquieres G, Jehan F, Garabedian M
Osteoporos Int 2009;20:567-75

Lumbar BMC, BMD and area, circulating IGF-1, markers of bone metabolism, and -13910 LCT (lactase gene) polymorphism; and intakes of milk, dairy products, calcium, phosphorus, magnesium, proteins, and energy were evaluated in 192 healthy adolescent girls. After menarche, BMC, BMD, serum IGF-1, and serum PTH were associated with milk consumption, but not with other calcium sources. All four parameters were also associated with phosphorus, magnesium, protein, and energy from milk, but not from other sources. Girls with milk intakes below 55 mL/day have lower BMD, BMC, and IGF-1 and higher PTH compared to girls consuming over 260 mL/day. Neither BMC, BMD, calcium intakes, nor milk consumption were associated with -13910 LCT polymorphism.

10.3.124 Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications
Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T
J Bone Miner Res 2009;24:702-9

Japanese T2DM patients (161 men >50 yr and 137 postmenopausal women) and non-DM controls (76 and 622, respectively) were studied. Logistic regression analysis adjusted for age, BMI, and L-BMD showed that the presence of T2DM was an independent risk factor for prevalent VFs in women (OR=1.86, $p=0.019$) and men (OR=4.73, $p<0.001$). BMD at any site, however, was not associated with VFs in T2DM patients, in contrast to the significant association in controls (at least $p=0.010$).

10.3.125 Poor glycemic control is associated with low BMD detected in premenopausal women with type 1 diabetes
Danielson KK, Elliott ME, LeCaire T, Binkley N, Palta M
Osteoporos Int 2009;20:923-33

Premenopausal women from the Wisconsin Diabetes Registry Study and matched controls were compared (n=75 pairs). Heel and forearm BMD were measured, and hip and spine BMD were measured in a subset. Markers of bone formation (osteocalcin) and resorption (NTx), and glycemic control (HbA1c) were determined. Among women with diabetes, mean disease duration was 16 years and current HbA1c was 8%. Compared to controls, women with diabetes had a high prevalence of previous fracture (37% vs. 24%) and low BMD for age (heel or forearm: 49% vs. 31%), low heel and forearm BMD, and low osteocalcin levels. Poor glycemic control was associated with low BMD at all bone sites except the spine, and with low osteocalcin and NTx levels.

10.3.126 Bone disease in thalassemia: A frequent and still unresolved problem

Vogiatzi MG, Macklin EA, Fung EB, Cheung AM, Vichinsky E, Olivieri N, Kirby M, Kwiatkowski JL, Cunningham M, Holm IA, Lane J, Schneider R, Fleisher M, Grady RW, Peterson CC, Giardina PJ
J Bone Miner Res 2009;24:543-57

Adults with beta thalassemia major have low BMD, fractures, and bone pain. Patients of all thalassemia syndromes in the Thalassemia Clinical Research Network, ≥6 yr of age, with no pre-existing condition participated. 361 subjects, 49% male, with a mean age of 23.2 yr (range, 6.1-75 yr), were studied. Spine and femur BMD Z-scores < -2 occurred in 46% and 25% of participants, respectively. Greater age, lower weight, hypogonadism, and increased bone turnover were independent predictors of low bone mass regardless of thalassemia syndrome. Peak bone mass was suboptimal. 33% had a history of fractures, and 34% reported bone pain. BMD was negatively associated with fractures. Nine percent had decreased height of several vertebrae by MXA, which was associated with the use of iron chelator deferoxamine before 6 yr of age. In patients with thalassemia, low BMD and fractures occur frequently and independently of the particular syndrome.

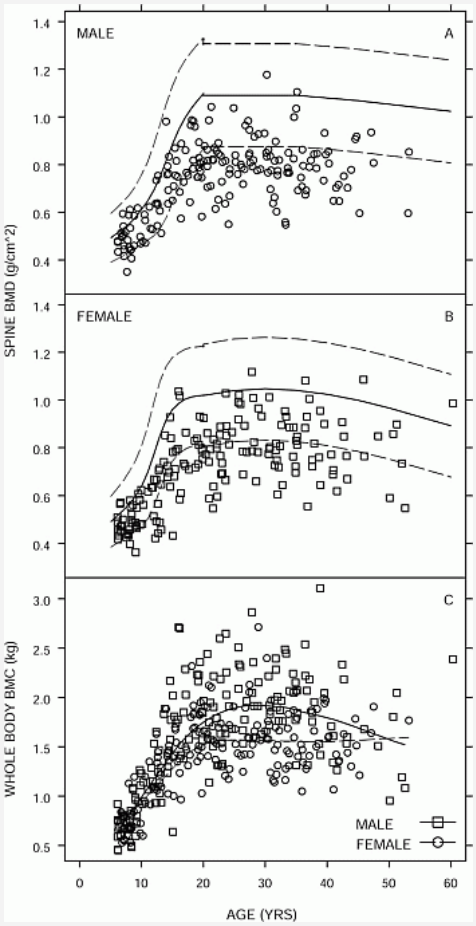


Fig. 10.3.126a Bone mass vs. age. (A and B) Spine BMD (g/cm^2) with age-dependent reference norms for whites (solid line) and ±2 SD (dashed lines) for males (A) and females (B). (C) Whole body BMC (kg) with locally weighted regressions for males (solid line) and females (dashed line). One individual age 75 yr is omitted (symbols: male, □; female, O). Reproduced from J Bone Miner Res 2009;24:543-57 with permission of the American Society of Bone and Mineral Research.

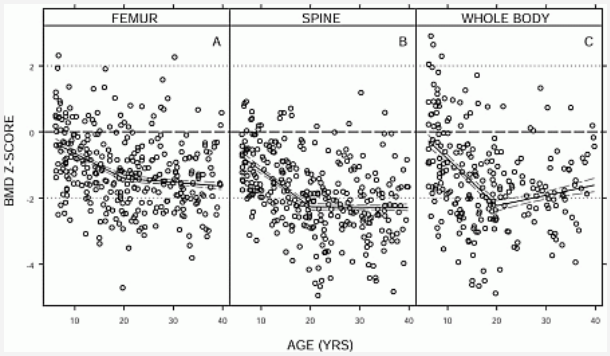


Fig. 10.3.126b Spine, femur, and total body BMD Z-scores with a partial-linear spline (solid line) and 95% CI (dashed lines). Individuals >40 yr of age are omitted. Reproduced from J Bone Miner Res 2009;24:543-57 with permission of the American Society of Bone and Mineral Research.

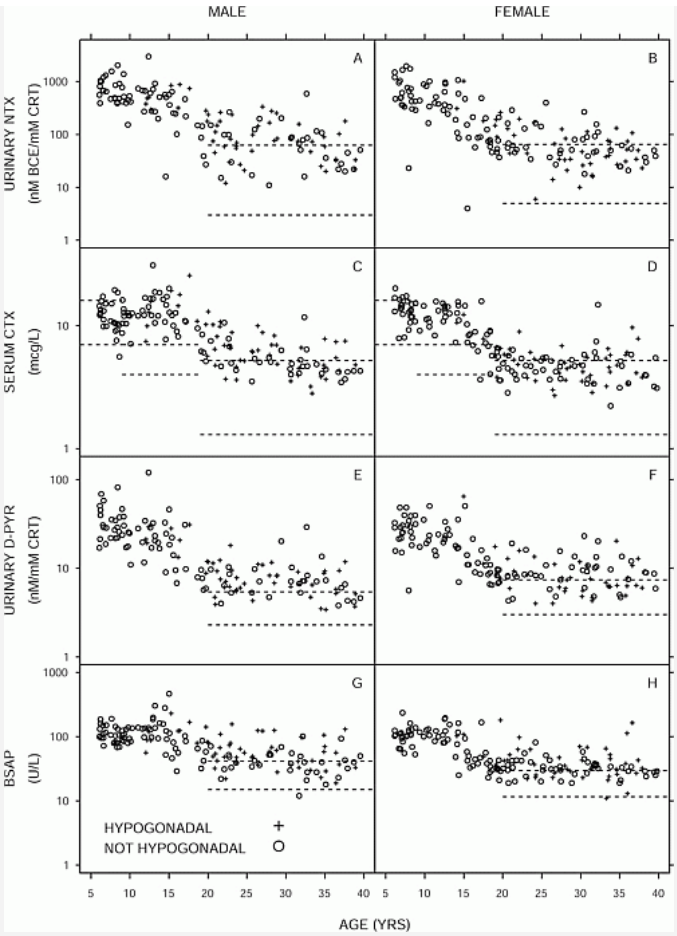


Fig. 10.3.126c Bone turnover markers vs. age stratified by sex and hypogonadal status (hypogonadal, +; not hypogonadal, O) with agedependent upper and lower limits of normal (dashed lines). One individual age 75 yr is omitted. Reproduced from J Bone Miner Res 2009;24:543-57 with permission of the American Society of Bone and Mineral Research.

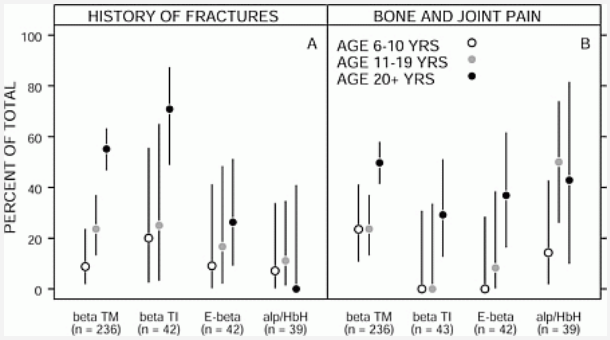


Fig. 10.3.126d Prevalence of history of fracture (A) and recent bone or joint pain (B) by thalassemia syndrome, stratified by age group (6-10 yr, O; 11-19 yr, ●; 20 or more yrs, ●). Point estimates and exact 95% confidence intervals are indicated. Reproduced from J Bone Miner Res 2009;24:543-57 with permission of the American Society of Bone and Mineral Research.

10.3.127 Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment
Rittweger J, Simunic B, Bilancio G, De Santo NG, Cirillo M, Biolo G, Pisot R, Eiken O, Mekjavic IB, Narici M
Bone 2009;44:612-8

Immobilization-induced bone loss is usually greater in the epiphyses than in the diaphyses. The larger fraction of trabecular bone in the epiphyses offers an explanation for this phenomenon. It suggests that immobilization-induced bone loss from the distal tibia epiphysis is mainly from the cortical compartment. During 5 weeks of immobilization 10 healthy male volunteers with mean age of 24.3 years (SD 2.6 years) underwent bed rest. Relative bone losses were largest at the patella, where they amounted to -3.2% (SD 1.8%, p<0.001) of the baseline values, and smallest at the tibia diaphysis, where they amounted to -0.7% (SD 1.0%, p=0.019). The relative losses were generally larger from cortical than from trabecular compartments (p=0.004), and whilst all skeletal sites depicted such cortical losses, substantial trabecular losses were found only from the proximal tibia epiphysis. Results confirm that the differential losses from the various skeletal sites cannot be explained on the basis of trabecular vs. cortical tissue composition differences, but that endocortical circumference can account for the different amounts of bone loss in the tibia. The subendocortical layer as a transitional zone, which can readily be transformed into trabecular bone in response to immobilization. The latter will lead to cortical thinning, a factor that has been associated with the risk of fracture and with osteoarthritis.

10.3.128 Beta-adrenergic blockade and leptin replacement effectively mitigate disuse bone loss
Baek K, Bloomfield SA
J Bone Miner Res 2009;24:792-9

Adult male rats were randomized into six groups: hind limb unloaded (HU) rats treated with vehicle (VEHHU), leptin analog (LEPHU), or beta-blocker (BBHU) during a 28-days and cage activity controls (CC) treated with the same agents and pair-fed.

The 20% decrease in cancellous vBMD observed in the VEHHU group was halved in BBHU rats and LEPHU rats. Bone formation rate (BFR) in BBHU rats, but not in LEPHU rats, was preserved. The 3-fold increase in resorption surface with HU was abolished by BB and LEP. The decrease in serum leptin after a 28-day HU was attenuated in BBHU and LEPHU rats and was predictive of the decrease in BFR with HU. Blocking sympathetic adrenergic signaling by beta-blocker during HU mitigates disuse-induced decreases in cancellous bone mass through stimulation of osteoblastic activity and suppression of osteoclastic activity. A direct effect of beta-adrenergic blockade on bone cells during HU may be enhanced by an indirect effect mitigating reductions in circulating leptin, possibly through disinhibition of leptin release from adipocytes.

10.3.129 High-fat diet decreases cancellous bone mass but has no effect on cortical bone mass in the tibia in mice
Cao JJ, Gregoire BR, Gao H
Bone 2009;44:1097-104

Six-wk-old male C57BL/6 mice (n=21) were assigned to a control (10 kcal% energy as fat) or high-fat diet (HFD, 45 kcal% energy as fat) for 14 weeks. Mice fed the HFD were 31% heavier (P<0.01) than those fed the control diet. There were more ALP positive colony forming units at d14 and calcium nodules at d28 of culture by BMSC from HFD mice than from control mice (P<0.01). Receptor activator of NF-κB ligand (RANKL) mRNA levels and the ratio of RANKL to osteoprotegerin expression in HFD animals was higher (P<0.01) than in control diet animals. Serum tartrate-resistant acid phosphatase levels were higher in HFD fed mice (P<0.05). There were no differences in tibial fat-free weight, length, and cortical parameters of midshaft between the two groups. Compared with control mice, tibial trabecular bone volume was reduced, and trabecular separation was increased in HFD mice. Trabecular number was lower (P<0.05) and connectivity density tended to be less (P=0.07) in HFD mice than in control mice.

10.3.130 Type 2 diabetic mice demonstrate slender long bones with increased fragility secondary to increased osteoclastogenesis
Kawashima Y, Fritton JC, Yakar S, Epstein S, Schaffler MB, Jepsen KJ, LeRoith D
Bone 2009;44:648-55

MKR mice exhibit muscle hypoplasia from birth with reduced mass by the prediabetic age of 3 weeks. A compensatory hyperplasia ensues during early (5 weeks) development; by 6-8 weeks muscle is normal in structure and function. The 8-week and 16-week, but not 3-week, male MKR had slender (i.e., narrow relative to length) femurs that were 20% weaker (p<0.05) relative to WT control femurs. Tissue-level mineral density was not affected. Impaired periosteal expansion during early diabetes resulted from 250% more, and 40% less of the cortical bone surface undergoing resorption and formation, respectively (p<0.05). Greater resorption persisted in adult MKR on both periosteal and endosteal surfaces. Differences were not limited to cortical bone as the distal femur metaphysis of 16 week MKR contained less trabecular bone and trabecular separation was greater than in WT by 60% (p<0.05). At all ages, MKR marrow-derived cultures demonstrated the ability for enhanced osteoclast differentiation in response to M-CSF and RANK-L. The MKR mouse model suggests that skeletal fragility in type 2 diabetes may arise from reduced transverse bone accrual and increased osteoclastogenesis during growth that is accelerated by the diabetic/ hyperinsulinemic milieu.

10.3.131 Thioredoxin-1 overexpression in transgenic mice attenuates streptozotocin-induced diabetic osteopenia: A novel role of oxidative stress and therapeutic implications
Hamada Y, Fujii H, Kitazawa R, Yodoi J, Kitazawa S, Fukagawa M
Bone 2009;44:936-41

To determine the role of oxidative stress in diabetic osteopenia, overexpression of thioredoxin-1 (TRX), a major intracellular antioxidant, was studied. TRX transgenic mice (TRX-Tg) carry the human TRX transgene. 8-week-old male TRX-Tg mice and wild type (WT) were intraperitoneally injected with streptozotocin or vehicle. Urinary 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage, was elevated in diabetic WT and attenuated in diabetic TRX-Tg. Immunohistochemical staining for 8-OHdG revealed intensity in the bone tissue of diabetic WT while staining was attenuated in diabetic TRX-Tg. TRX over expression partially restored reduced BMD and prevented the suppression of bone formation observed in diabetic WT. Increased oxidative stress in diabetic condition contributes to the development of diabetic osteopenia. Suppression of increased oxidative stress by TRX induction could be a potential therapeutic approach for diabetic osteopenia.

10.3.132 Bone matrix quality and plasma homocysteine levels
Blouin S, Thaler HW, Korninger C, Schmid R, Hofstaetter JG, Zoehrer R, Phipps R, Klaushofer K, Roschger P, Paschalis EP
Bone 2009;44:959-64

Femoral heads from 19 females, age range 70-95 years old with known homocysteine plasma levels were investigated. There was a significant correlation between plasma homocysteine levels and collagen crosslink ratio in areas of primary mineralized bone (p<0.0001), unlike the case of trabecular bone surfaces undergoing resorption (p>0.05). On the other hand there was no correlation in any of the BMDD parameters and plasma homocysteine levels (p>0.05). The results are consistent with the known effect of homocysteine on collagen posttranslational modifications.

10.3.133 The Osteoporosis Self-Assessment Tool versus alternative tests for selecting postmenopausal women for bone mineral density assessment: A comparative systematic review of accuracy
Rud B, Hilden J, Hyldstrup L, Hrobjartsson A
Osteoporos Int 2009;20:599-607

10.3.134 A simple risk score for the assessment of absolute fracture risk in general practice based on two longitudinal studies
Pluijm SM, Koes B, de Laet C, Van Schoor NM, Kuchuk NO, Rivadeneira F, Mackenbach JP, Lips P, Pols HA, Steyerberg EW
J Bone Miner Res 2009;24:768-74

10.3.135 Risk factors for severity and type of the hip fracture
Cauley JA, Lui LY, Genant HK, Salamone L, Browner W, Fink HA, Cohen P, Hillier T, Bauer DC, Cummings SR
J Bone Miner Res 2009;24:943-55

10.3.136 Physical tests for patient selection for bone mineral density measurements in postmenopausal women
Karkkainen M, Rikkonen T, Kroger H, Sirola J, Tuppurainen M, Salovaara K, Arokoski J, Jurvelin J, Honkanen R, Alhava E
Bone 2009;44:660-5

10.3.137 Low sit-to-stand performance is associated with low femoral neck bone mineral density in healthy women
Blain H, Jaussent A, Thomas E, Micallef JP, Dupuy AM, Bernard P, Mariano-Goulart D, Cristol JP, Sultan C, Rossi M, Picot MC
Calcif Tissue Int 2009;84:266-75

10.3.138 Association of unipedal standing time and bone mineral density in community-dwelling Japanese women
Sakai A, Toba N, Takeda M, Suzuki M, Abe Y, Aoyagi K, Nakamura T
Osteoporos Int 2009;20:731-6

10.3.139 BMD in population-based adult women is associated with socioeconomic status
Brennan SL, Henry MJ, Wluka AE, Nicholson GC, Kotowicz MA, Williams JW, Pasco JA
J Bone Miner Res 2009;24:809-15

10.3.140 Vitamin D, PTH and calcium levels in pregnant women and their neonates
Bowyer L, Catling-Paull C, Diamond T, Homer C, Davis G, Craig ME
Clin Endocrinol (Oxf) 2009;70:372-7

10.3.141 Behavioural and physical characteristics associated with vitamin D status in women
Pasco JA, Henry MJ, Nicholson GC, Brennan SL, Kotowicz MA
Bone 2009;44:1085-91

10.3.142 Estimation of the dietary requirement for vitamin D in free-living adults ≥64 y of age
Cashman KD, Wallace JM, Horigan G, Hill TR, Barnes MS, Lucey AJ, Bonham MP, Taylor N, Duffy EM, Seamans K, Muldowney S, Fitzgerald AP, Flynn A, Strain JJ, Kiely M
Am J Clin Nutr 2009;89:1366-74

10.3.143 Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers
Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R
Am J Clin Nutr 2009;89:1321-7

10.3.144 25-hydroxyvitamin D is not associated with carotid intima-media thickness in older men and women
Pilz S, Henry RM, Snijder MB, van Dam RM, Nijpels G, Stehouwer CD, Tomaschitz A, Pieber TR, Dekker JM
Calcif Tissue Int 2009;84:423-4

10.3.145 Serum 25-hydroxyvitamin D levels are not associated with subclinical vascular disease or C-reactive protein in the old order Amish
Michos ED, Streeten EA, Ryan KA, Rampersaud E, Peyser PA, Bielak LF, Shuldiner AR, Mitchell BD, Post W
Calcif Tissue Int 2009;84:195-202

10.3.146 Hypovitaminosis D and valvular calcification in patients with dilated cardiomyopathy
Dishmon DA, Dotson JL, Munir A, Nelson MD, Bhattacharya SK, D'Cruz I A, Davis RC, Weber KT
Am J Med Sci 2009;337:312-6

10.3.147 Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey
Ginde AA, Mansbach JM, Camargo CA, Jr.
Arch Intern Med 2009;169:384-90

10.3.148 Serum 25-hydroxyvitamin D as an independent determinant of 1-84 PTH and bone mineral density in non-diabetic predialysis CKD patients
Tomida K, Hamano T, Mikami S, Fujii N, Okada N, Matsui I, Nagasawa Y, Moriyama T, Ito T, Imai E, Isaka Y, Rakugi H
Bone 2009;44:678-83

10.3.149 Treatment and prevention of vitamin D insufficiency in cystic fibrosis patients: Comparative efficacy of ergocalciferol, cholecalciferol and UV light
Khazai NB, Judd S, Jeng L, Wolfenden L, Stecenko A, Ziegler TR, Tangpricha V
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.3.150 Dietary protein and calcium interact to influence calcium retention: A controlled feeding study
Hunt JR, Johnson LK, Fariba Roughead ZK
Am J Clin Nutr 2009;89:1357-65

10.3.151 Association between iron overload and osteoporosis in patients with hereditary hemochromatosis
Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L
Osteoporos Int 2009;20:549-55

10.3.152 Cysteine, homocysteine and bone mineral density: A role for body composition?
Elshorbagy AK, Gjesdal CG, Nurk E, Tell GS, Ueland PM, Nygard O, Tverdal A, Vollset SE, Smith AD, Refsum H
Bone 2009;44:954-8

10.3.153 A study of bone marrow and subcutaneous fatty acid composition in subjects of varying bone mineral density
Griffith JF, Yeung DK, Ahuja AT, Choy CW, Mei WY, Lam SS, Lam TP, Chen ZY, Leung PC
Bone 2009;44:1092-6

10.3.154 Association between decreased bone mineral density and severity of distal radial fractures
Clayton RA, Gaston MS, Ralston SH, Court-Brown CM, McQueen MM
J Bone Joint Surg Am 2009;91:613-9

10.3.155 The effect of bed rest on bone turnover in young women hospitalized for anorexia nervosa: A pilot study
DiVasta AD, Feldman HA, Quach AE, Balestrino M, Gordon CM
J Clin Endocrinol Metab 2009;94:1650-5

10.3.156 Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis
Ghozlani I, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, Bezza A, El Maghraoui A
Bone 2009;44:772-6

10.3.157 Neuropsychological features in primary hyperparathyroidism: A prospective study
Walker MD, McMahon DJ, Inabnet WB, Lazar RM, Brown I, Vardy S, Cosman F, Silverberg SJ
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.3.158 A preliminary investigation into the effects of X-ray radiation on superficial cranial vascularization
Desmons S, Heger M, Delfosse C, Falgayrac G, Sarrazin T, Delattre C, Catros S, Mordon S, Penel G
Calcif Tissue Int 2009;84:379-87

10.3.159 Experimental folate and vitamin B12 deficiency does not alter bone quality in rats
Herrmann M, Wildemann B, Wagner A, Wolny M, Schorr H, Taban-Shomal O, Umanskaya N, Ross S, Garcia P, Hubner U, Herrmann W
J Bone Miner Res 2009;24:589-96

10.3.160 Vitamin B(12) deficiency stimulates osteoclastogenesis via increased homocysteine and methylmalonic acid
Vaes BL, Lute C, Blom HJ, Bravenboer N, de Vries TJ, Everts V, Dhonukshe-Rutten RA, Muller M, de Groot LC, Steegenga WT
Calcif Tissue Int 2009;84:413-22

10.3.161 Dioxins interfere with differentiation of osteoblasts and osteoclasts
Korkalainen M, Kallio E, Olkku A, Nelo K, Ilvesaro J, Tuukkanen J, Mahonen A, Viluksela M
Bone 2009;44:1134-42

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Corticosteroid Therapy

10.3.162 Restoration of bone mass and strength in glucocorticoid-treated mice by systemic transplantation of CXCR4 and cbfa-1 co-expressing mesenchymal stem cells

Lien CY, Chih-Yuan Ho K, Lee OK, Blunn GW, Su Y

J Bone Miner Res 2009;24:837-48

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Falls

10.3.163 Heritability of impaired balance: A nationwide cohort study in twins
Wagner H, Melhus H, Pedersen NL, Michaelsson K
Osteoporos Int 2009;20:577-83

To evaluate the heritability and environmental influence on self-reported impaired balance in older men and women, data from 22,998 Swedish twins, 55-99 years of age showed impaired balance reported by 2890 (12.3%) of the twins. The tetrachoric correlation for impaired balance was only slightly lower for like-sex dizygotic twins (0.31) compared to monozygotic twins (0.36). These correlations indicate a modest familial (genetic and shared environmental) influence. Model fitting results indicate that the age- and sex-adjusted heritability for impaired balance was 0.27 (95% CI=0.01-0.45). Individual-specific environmental influences differed only slightly by sex and age. These results imply that a self-reported impaired balance, an independent risk factor for osteoporotic fractures, has a modestly heritable etiology in older subjects. Our observation can partly explain the previously observed modest heritability for osteoporotic fractures even though there is a high heritability for BMD.

10.3.164 Predictors of falls among postmenopausal women: Results from the National Osteoporosis Risk Assessment (NORA)
Barrett-Connor E, Weiss TW, McHorney CA, Miller PD, Siris ES
Osteoporos Int 2009;20:715-22

66,134 NORA participants who completed the baseline survey and three follow-up surveys over 6 years. More than one third (38.2%) of participants reported at least one fall since baseline. The largest predictor of fall risk was history of falls (OR=2.7). In the multivariate analysis, 17 additional risk factors were associated with incident falls (but with smaller OR), including age, college education, poor hearing, diabetes, personal or family history of fracture, hypothyroidism, and height loss. Of the 3346 women with zero fall risk factors, 22.6% reported falling compared to 84.3% of the 51 women with ≥11 risk factors.

10.3.165 The health-related quality of life and cost implications of falls in elderly women
Iglesias CP, Manca A, Torgerson DJ
Osteoporos Int 2009;20:869-78

Three datasets providing longitudinal data on fear of falling, HRQoL and a common set of baseline risk factors for fracture (smoking status, weight and age) were analysed. Multilevel random effects models were used to estimate the long-term impact on HRQoL associated with falls, fractures and fear of falling. Healthcare resource use primary data were collected to estimate falls and fractures cost. Older, low weight and smoking women reported lower HRQoL. The impact on HRQoL of a fracture was at least twice as large as that associated with falls. The largest negative effect on HRQoL was associated with self-reported fear of falling. The cost of falls was 1088 pounds. Similarly, the cost of falls leading to a fracture was 15,133 pounds, 2753 pounds, 1863 pounds, 1331 pounds and 3498 pounds for hip, wrist, arm, vertebral and other fractures, respectively. The main burden to morbidity is due to fear of falling. Interventions aimed at reducing fear of falling may produce larger gains in HRQoL.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Treatment

10.3.166 Estimates of the proportion of older white women who would be recommended for pharmacologic treatment by the new U.S. National Osteoporosis Foundation Guidelines
Donaldson MG, Cawthon PM, Lui LY, Schousboe JT, Ensrud KE, Taylor BC, Cauley JA, Hillier TA, Black DM, Bauer DC, Cummings SR
J Bone Miner Res 2009;24:675-80

The new U.S. National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis includes criteria for recommending pharmacologic treatment based on history of hip or vertebral fracture, femoral neck (FN), or spine BMD T-scores ≤ -2.5 and presence of low bone mass at the FN or spine plus a 10-yr risk of hip fracture ≥3% or of major osteoporotic fracture ≥20%. The proportion of women recommended for treatment by these guidelines is not known. Application of NOF guidelines to SOF data estimated that at least 72% of U.S. white women ≥65 yr of age and 93% of those ≥75 yr of age would be recommended for drug treatment.

10.3.167 Selective modification of bone quality by PTH, pamidronate, or raloxifene
Brennan TC, Rizzoli R, Ammann P
J Bone Miner Res 2009;24:800-8

Eight weeks after ovariectomy (OVX), 8-mo-old osteoporotic rats received pamidronate (APD; 0.6 mg/kg, 5 days/mo, SC), raloxifene (3 mg/kg, 5/7 days, tube feeding), PTH(1-34) (10 μg/kg, 5/7 days, SC), or vehicle for 16 wk, PTH induced greater maximal load than APD or raloxifene, as well as greater absorbed energy, BMD, and increased bone turnover markers. PTH increased trabecular bone volume and connectivity to values higher than sham. Animals treated with APD had BV/TV values higher than OVX but lower than sham, whereas raloxifene had no effect. Tissue hardness was identical in PTH-treated and OVX untreated controls. In contrast, APD reversed the decline in strength to levels not significantly different to sham, reduced bone turnover, and increased hardness. Raloxifene increased material level cortical hardness and elastic modulus. These results show the different mechanisms by which anticatabolics and bone anabolics reduce fracture risk. PTH influences microarchitecture, whereas bisphosphonates alter material-level bone properties, with probable opposite effects on remodeling space. Raloxifene primarily improved the material stiffness at the cortical level.

10.3.168 Bisphosphonate dose and incidence of fractures in postmenopausal osteoporosis
Makras P, Hamdy NAT, Zwinderman AH, Ballieux BEPB, Papapoulos SE
Bone 2009;44:766-71

In this retrospective analysis, the effect of different doses of intravenous pamidronate given at 3-monthly intervals on the incidence of fractures in 92 women with severe postmenopausal osteoporosis showed that the risk of sustaining a new vertebral fracture on treatment was increased by 32% for every prevalent vertebral fracture (OR: 1.32, CI: 1.05, 1.66; p=0.02). Patients with nonvertebral fractures received a lower dose of pamidronate and their risk for these fractures increased by 25% for every prevalent vertebral fracture at baseline (OR: 1.25, CI: 1.01, 1.53; p=0.03). Patients who received oral bisphosphonate before intravenous pamidronate had a higher incidence of nonvertebral fractures which, however, did not hold true after adjustment for baseline BMD and prevalent fractures. In patients with osteoporosis bone fragility during treatment with intravenous pamidronate is mainly determined by the severity of the disease, assessed by the presence and numbers of prevalent fractures, rather than the dose of the bisphosphonate or the rate of bone turnover.

10.3.169 The relation between bisphosphonate use and non-union of fractures of the humerus in older adults
Solomon DH, Hochberg MC, Mogun H, Schneeweiss S
Osteoporos Int 2009;20:895-901

In a nested case-control study among subjects who had experienced a humerus fracture, bisphosphonate exposure was assessed during the 365 days prior to the non-union among cases or the matched date for controls. From the cohort of 19,731 patients with humerus fractures, 81 (0.4%) experienced a non-union. Among the 81 cases, 13 (16.0%) were exposed to bisphosphonates postfracture, while 69 of the 810 controls (8.5%) were exposed in the postfracture interval. In fully adjusted multivariable regression models, bisphosphonate use in the postfracture period was associated with an increased odds of non-union (OR 2.37, 95% CI 1.13-4.96). Albeit limited by small sample sizes, the increased risk associated with bisphosphonate use persisted in the subgroup of patients without a history of osteoporosis or prior fractures (OR 1.91, 95% CI 0.75-4.83).

10.3.170 Unusual mid-shaft fractures during long term bisphosphonate therapy
Odvina CV, Levy S, Rao S, Zerwekh JE, Sudhaker Rao D
Clin Endocrinol (Oxf) 2009;[Epub ahead of print]

Of the 13 patients who sustained atraumatic mid-shaft fractures, 10 were on alendronate and 3 were on risedronate therapy before the fractures. In addition to bisphosphonates, 3 patients were on estrogen and 2 on tamoxifen concomitantly. Four patients with glucocorticoid-induced osteoporosis were on alendronate for 3-11 years along with glucocorticoid therapy. Bone histomorphometry showed suppression of turnover in 5 patients and low turnover in one patient. Long-term bisphosphonate therapy may increase the risk of unusual long bone mid-shaft fractures. This is likely due to prolonged suppression of bone turnover, which could lead to accumulation of microdamage and development of hypermineralized bone.

10.3.171 Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: The eValuation of IBandronate Efficacy (VIBE) database fracture study
Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, Silverman SL
Bone 2009;44:758-65

The eValuation of IBandronate Efficacy (VIBE) head-to-head database fracture study compared fracture rates between patients treated with monthly ibandronate and weekly oral bisphosphonates (BPs). This study included women ≥45 years old, newly prescribed monthly oral ibandronate or weekly oral alendronate or risedronate. The primary analysis included patients who were adherent to treatment during the first 90 days after the index date. The primary analysis included 7345 monthly ibandronate and 56,837 weekly BP patients. Fracture rates after the 12-month observational period were <2% and fracture risk was not different between patients receiving monthly ibandronate or weekly BPs for hip, nonvertebral or any clinical fracture (adjusted relative risk: hip=1.06, p=0.84; nonvertebral=0.88, p=0.255; any clinical fracture=0.82, p=0.052). Ibandronate patients had a lower risk of vertebral fracture than weekly BP patients (adjusted relative risk 0.36, 95% CI 0.18-0.75, p=0.006). In the secondary, "intent-to-treat" analysis, relative risks of fracture were not different between groups for any fracture type. This retrospective cohort study found that patients treated with oral monthly ibandronate or weekly BPs (alendronate and risedronate) had similar, low risks of hip fracture, nonvertebral fracture and any clinical fracture. Ibandronate patients had a lower relative risk of vertebral fracture than weekly BP patients.

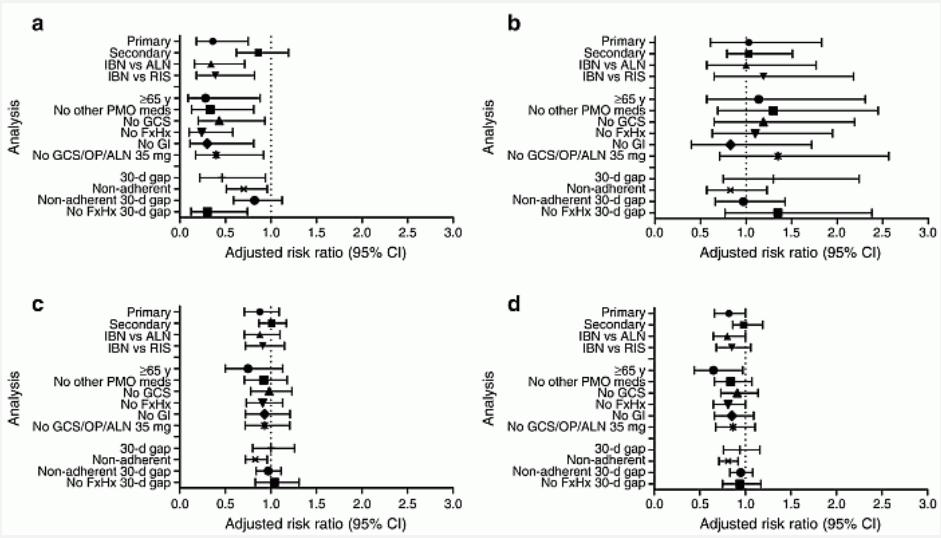
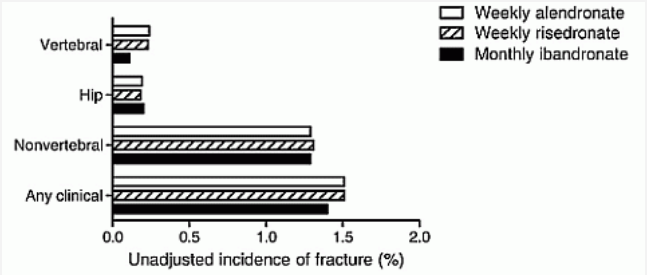


Fig. 10.3.171a Relative risk of fracture in primary, secondary and sensitivity analyses. a) Vertebral fracture, b) Hip fracture, c) Nonvertebral fracture, d) Any clinical fracture. GI, gastrointestinal; CI, confidence interval. Primary, primary analysis in patients adherent for N90 days. Secondary, secondary 'intent-to-treat' analysis. IBN vs ALN, monthly ibandronate vs weekly alendronate. IBN vs RIS, monthly ibandronate vs weekly risedronate. ≥65 years, including patients aged 65 years or older. No other PMO meds, excluding patients with estrogen, calcitonin or raloxifene prescribing during the pre-index period. No GCS, excluding patients with glucocorticoid medication prescribing during the pre-index period. No FxHx, excluding patients with a fracture during the pre-index period. No GI, excluding patients with GI medication prescribing during the pre-index period. No GCS/OP/ALN 35 mg, excluding patients with glucocorticoid medication prescribing during the pre-index period and/or osteopenia diagnosis code during the pre-index period and/or alendronate 35mg prescribing during the pre-index period or follow-up. 30-d gap, treatment discontinuation defined as a 30-day refill gap for both treatments, excluding patients who did not meet the adherence requirement in the first 90 days. Non-adherent, treatment discontinuation defined as a 45-day refill gap for monthly ibandronate and 30-day prescription gap for weekly BPs, including patients who did not meet the adherence requirement in the first 90 days. Non-adherent, 30-d gap, treatment discontinuation defined as a 30-day refill gap for both treatments, including patients who did not meet the adherence requirement in the first 90 days. No FxHx, 30-d gap, treatment discontinuation defined as a 30-day refill gap for both treatments, excluding patients with a fracture in the pre-index period. Reproduced from Bone, 44:758-65, Copyright (2009), with permission from Elsevier.



Analysis Fracture type	Unadjusted relative risk[a]	Adjusted relative risk (95% CI)[b]	*p*
Monthly ibandronate compared with weekly alendronate (monthly ibandronate *n*=7345, weekly alendronate *n*=35,865)			
Vertebral	0.44	0.34 (0.16–0.71)	0.004
Hip	1.05	1.00 (0.57–1.77)	0.999
Nonvertebral	0.97	0.88 (0.70–1.10)	0.255
Any clinical	0.90	0.80 (0.65–1.00)	0.045
Monthly ibandronate compared with weekly risedronate (monthly ibandronate *n*=7345, weekly risedronate *n*=20,972)			
Vertebral	0.46	0.39 (0.18–0.82)	0.014
Hip	1.11	1.19 (0.65–2.18)	0.570
Nonvertebral	0.98	0.91 (0.72–1.15)	0.418
Any clinical	0.92	0.85 (0.68–1.06)	0.143

Fig. 10.3.171b Fracture incidence and relative risk of fracture for monthly ibandronate compared with individual weekly bisphosphonates (monthly n=7345, weekly alendronate n=35,865, weekly risedronate n=20,972). CI, confidence interval. [a]Relative risk based on Cox regression model. [b]Relative risk based on Cox regression model, adjusted for baseline age; osteoporosis diagnosis; use of dual energy X-ray absorptiometry; fracture history; number of concomitant medications; use of estrogen; and number of outpatient visits in the pre-index period. Reproduced from Bone, 44:758-65, Copyright (2009), with permission from Elsevier.

10.3.172 Ten-year fracture probability identifies women who will benefit from clodronate therapy – Additional results from a double-blind, placebo-controlled randomised study

McCloskey EV, Johansson H, Oden A, Vasireddy S, Kayan K, Pande K, Jalava T, Kanis JA

Osteoporos Int 2009;20:811-7

Women aged 75 years or more were recruited to a randomised, double-blind controlled trial of 800 mg oral clodronate (Bonefos®) daily over 3 years. Baseline clinical risk factors were entered in the FRAX® model to compute the 10-year probability of major osteoporotic fractures with or without input of femoral neck BMD. In 3974 women, the interaction between fracture probability and treatment efficacy was significant when probability was assessed without BMD (p=0.043), but not when BMD was included (p=0.10). Efficacy was more evident in those deemed at highest risk. For example women lying at the 75th percentile of fracture probability in the absence of BMD (10-year probability 24%) treatment reduced fracture risk by 27% (HR 0.73, 95% CI 0.58-0.92). In those with a fracture probability of 30% (90th percentile), the fracture risk reduction was 38% (HR 0.62, 0.46-0.84). The estimation of an individual's 10-year probability of fracture by the FRAX® algorithm identifies patients at high risk of fracture who will respond to bisphosphonate therapy.

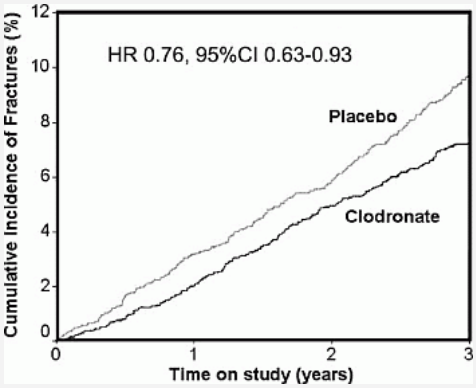


Fig. 10.3.172a Impact of clodronate on the incidence of osteoporotic fractures over 3 years of treatment in the 3974 women included in this analysis. Reproduced from Osteoporos Int 2009;20:811-7 with permission from Springer.

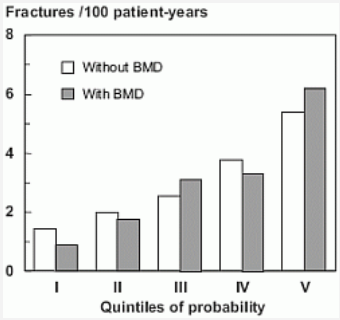


Fig. 10.3.172b Relationship in women assigned to the placebo arm of the study between 10-year probabilities of fracture (as quintiles) and observed fracture incidence (fractures/100 person-years) over 3 years with femoral neck excluded from (i.e., clinical risk factors alone) or included in the calculation of fracture probability. Reproduced from Osteoporos Int 2009;20:811-7 with permission from Springer.

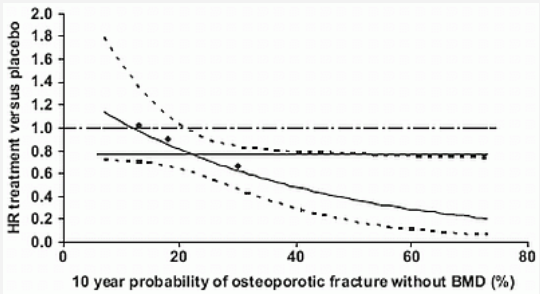


Fig. 10.3.172c Relationship between 10-year probabilities of major osteoporotic fracture, calculated with clinical risk factors alone (i.e., without femoral neck BMD) and the efficacy of clodronate to reduce fracture risk (hazard ratio with 95% confidence intervals). The solid horizontal line represents the overall treatment efficacy (HR 0.77) and the dashed horizontal line a hazard ratio of 1. The diamonds correspond to the 10th, 50th and 90th percentiles of probability in the population studied. Reproduced from Osteoporos Int 2009;20:811-7 with permission from Springer.

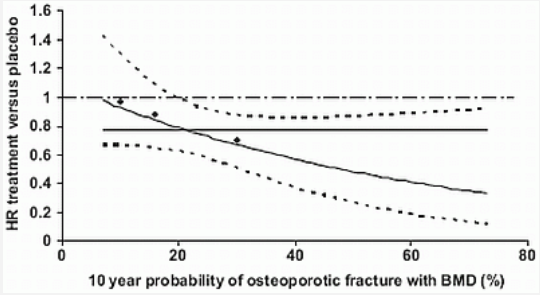


Fig. 10.3.172d Relationship between 10-year probabilities of fracture, calculated with clinical risk factors combined with femoral neck BMD, and the efficacy of clodronate to reduce fracture risk (hazard ratio with 95% confidence intervals). The solid horizontal line represents the overall treatment efficacy (HR 0.77) and the dashed horizontal line a hazard ratio of 1. The diamonds correspond to the 10th, 50th and 90th percentiles of probability in the population studied. Reproduced from Osteoporos Int 2009;20:811-7 with permission from Springer.

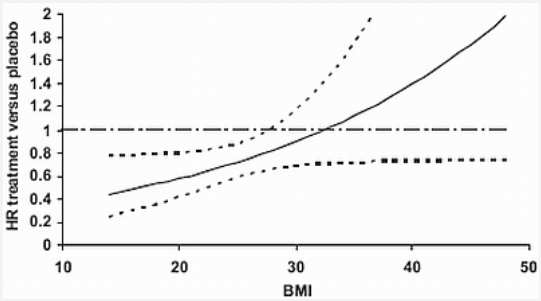


Fig. 10.3.172e Relationship between the treatment efficacy of clodronate (hazard ratio with 95% confidence intervals) and BMI at entry to the study. The dashed horizontal line represents a hazard ratio of 1. The significant interaction suggests a stronger treatment effect in those women with lower BMI at entry. Reproduced from Osteoporos Int 2009;20:811-7 with permission from Springer.

10.3.173 RisedronatE and ALendronate Intervention over Three Years (REALITY): Minimal differences in fracture risk reduction
Curtis JR, Westfall AO, Cheng H, Saag KG, Delzell E
Osteoporos Int 2009;20:973-8

Using claims data from a U.S. healthcare organization, the authors identified new, adherent users of weekly alendronate or risedronate and assessed subsequent fractures. Fracture incidence rate differences and ratios between the two agents were calculated. There were no significant differences in fracture rates between alendronate users (n=12,956) and risedronate users (n=6107) at one year. Using all available data, the rate of hip fracture was higher among risedronate users compared to alendronate users (absolute rate difference approximately 5 per 1000 person-years). Risedronate users had a higher relative rate of hip fracture (RR=1.77, 95% CI 1.15-2.74) and similar rates of clinical vertebral and nonvertebral fractures compared to alendronate users.

10.3.174 Phase III randomized, placebo-controlled, double-blind trial of risedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer
Hines SL, Mincey BA, Sloan JA, Thomas SP, Chottiner E, Loprinzi CL, Carlson MD, Atherton PJ, Salim M, Perez EA
J Clin Oncol 2009;27:1047-53

Premenopausal women undergoing chemotherapy for breast cancer were treated with oral calcium 600 mg and vitamin D 400 U daily and randomly assigned to receive oral risedronate 35 mg weekly or placebo, with all these therapies beginning within a month of the start of chemotherapy. Most chemotherapy regimens included anthracyclines, taxanes, or cyclophosphamide. A total of 216 women enrolled; 170 women provided BMD data at one year. There was no difference in the mean change or percent change in LS BMD between groups, with a loss of 4.3% in the risedronate arm and 5.4% for placebo at 1 year (P=0.18). Loss of BMD at the femoral neck and total hip were also similar between treatment groups. Risedronate did not prevent bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer.

10.3.175 Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate
Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D
Osteoporos Int 2009;20:887-94

Using a canine animal model (n=12), saline vehicle (VEH), alendronate (ALN 0.20, 1.00 mg/kg) or risedronate (RIS 0.10, 0.50 mg/kg) for one year accumulated AGEs at high treatment doses (+49 to +86%; p<0.001), but not at doses equivalent to those used for the treatment of postmenopausal osteoporosis. Likewise, postyield work-to-fracture of the tissue was reduced at these high doses (-28% to -51%; p<0.001). AGE accumulation inversely correlated with postyield work-to-fracture (r^2=0.45; p<0.001).

10.3.176 Effect of alendronate in elderly patients after low trauma hip fracture repair
Cecilia D, Jodar E, Fernandez C, Resines C, Hawkins F
Osteoporos Int 2009;20:903-10

239 patients (81±7 years; 79.8% women) were randomized to calcium (500 mg/daily) and vitamin D(3) (400 IU/daily; Ca-Vit D group) or alendronate (ALN, 70 mg/week) plus calcium and vitamin D3 (ALN + Ca-Vit D group). 147 (61.5%) patients completed the trial. Alendronate increased proximal femoral BMD in the intention-to-treat analysis; total hip 2.57% (0.67; 4.47); trochanteric 2.96% (0.71; 5.20), intertrochanteric 2.32% (0.36; 4.29), but the differences were not significant in the BMD of the femoral neck (0.47%; (-2.03; 2.96)) and the lumbar spine (0.69%; (-0.86; 2.23)). Bone turnover markers decreased during alendronate treatment.

10.3.177 The anabolic action of intermittent PTH in combination with cathepsin K inhibitor or alendronate differs depending on the remodeling status in bone in ovariectomized mice
Yamane H, Sakai A, Mori T, Tanaka S, Moridera K, Nakamura T
Bone 2009;44:1055-62

C57/BL/6J mice were OVX and treated with cathepsin K inhibitor, alendronate, or a vehicle (daily, for 8 weeks) after 6 weeks, with or without PTH (1-34) (5 times/week, for the last 4 weeks). CatK inhibitor and alendronate increased the BMD and the bone volume of the primary and secondary spongiosa with a reduction in urinary CTX that increased by OVX, respectively. CatK inhibitor augmented the anabolic action of PTH on the BMD and bone volume, while alendronate had the same effect on the BMD

and bone volume only at the primary spongiosa. CatK inhibitor did not decrease serum osteocalcin with or without PTH, while alendronate did. CatK inhibitor did not decrease osteoclast number or bone formation rate with or without PTH, while alendronate decreased those values and increased osteoclast apoptosis. The combination of PTH and CatK inhibitor increased alkaline phosphatase-positive CFU-F formation and c-fos, osterix, and osteocalcin mRNA expressions of bone marrow cells as well as PTH alone, while the combination of PTH and alendronate decreased those values. This study demonstrated that alendronate enhances the anabolic action of PTH at the primary spongiosa, but blunts it in the remodeling trabecular bone, while CatK inhibitor enhances the action at both sites in OVX mice.

10.3.178 Marked reduction of bone turnover by alendronate attenuates the acute response of bone resorption marker to endogenous parathyroid hormone
Zikan V, Stepan JJ
Bone 2009;44:634-8

40 women (age, 55-80 years) with postmenopausal osteoporosis (treated with ALN, RIS and RLX or untreated-control group) were given infusions of sodium ethylenediaminetetraacetic acid (EDTA; 10 mg/kg of body weight). In all women, decrease in serum iCa following the EDTA load resulted in an acute increase in serum PTH. Between 60 and 180 min, plasma PTH in the ALN and RIS treated women remained higher than in the control group. The integrated β-CTX responses (area under curves, AUCs) to peaks of PTH were lower in the ALN treated women than in those treated with RIS, RLX or control group. There was no difference in β-CTX AUC response to PTH between RIS, RLX and control women. Women with postmenopausal osteoporosis treated with ALN, a substantial reduction of bone turnover blunts the acute bone resorbing effect of endogenous PTH.

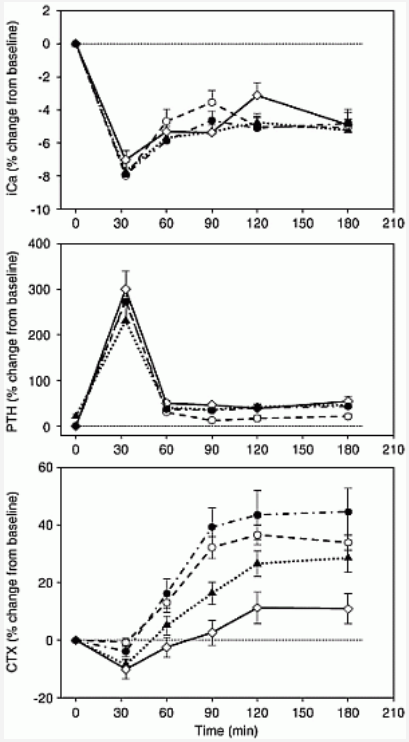


Fig. 10.3.178a Serum ionized calcium (S-iCa; upper panel), plasma intact parathyroid hormone (PTH; mid panel) and serum β C-terminal telopeptide of type I collagen (β-CTX; lower panel) responses to EDTA-infusions in ALN (◇), RIS (▲) and RLX (●) treated women and in control group (○). The values are mean±SE. Significances are shown in the next Figure. Reproduced from Bone, 44:634-8, Copyright (2009), with permission from Elsevier.

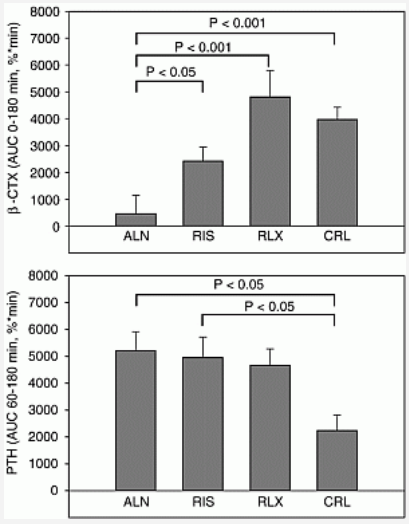


*Fig. 10.3.178b The areas under the curve (AUC, %*min) for the serum β-CTX concentrations between 0 and 180 min (upper panel) and for the plasma PTH concentrations between 60 and 180 min (lower panel) after EDTA-infusions in treated women (ALN, RIS and RLX) and in control group (CRL). Significance of difference between the study groups (ANOVA, Tukey test for multiple comparisons). Results shown are mean±SE. Reproduced from Bone, 44:634-8, Copyright (2009), with permission from Elsevier.*

10.3.179 Alendronate/vitamin D3 70 mg/2800 IU with and without additional 2800 IU vitamin D3 for osteoporosis: Results from the 24-week extension of a 15-week randomized, controlled trial
Binkley N, Ringe JD, Reed JI, Ljunggren O, Holick MF, Minne HW, Liu M, Lamotta A, West JA, Santora AC
Bone 2009;44:639-47

A once-weekly (OW) alendronate (ALN) preparation that includes 2800 IU of vitamin D3 in a single combination tablet (ALN+D2800) is available for treating patients and ensuring intake of vitamin D that is consistent with existing guidelines. This randomized, double-blind study extension was conducted to evaluate the safety and tolerability of ALN+D2800 and ALN+D2800 plus an additional 2800 IU vitamin D3 single tablet supplement (ALN+D5600) for 24 weeks in men and postmenopausal women with osteoporosis previously treated OW for 15 weeks with either ALN or ALN+D2800. Hypercalciuria incidence (4.2% [ALN +D5600] vs. 2.8% [ALN+D2800]), did not differ between groups. No participants developed hypercalcemia. Among the participants with vitamin D insufficiency at the week 0 baseline, the prevalence of insufficiency at the end of the study was reduced by 92% in the ALN+D5600 group and by 86% in the ALN+D2800 group. In subjects previously treated with ALN+D2800 for 15 weeks, the addition of 2800 IU D3 for 24 weeks did not produce hypercalcemia nor increase the risk of hypercalciuria.

10.3.180 A double-blinded head-to-head trial of minodronate and alendronate in women with postmenopausal osteoporosis
Hagino H, Nishizawa Y, Sone T, Morii H, Taketani Y, Nakamura T, Itabashi A, Mizunuma H, Ohashi Y, Shiraki M, Minamide T, Matsumoto T
Bone 2009;44:1078-84

270 postmenopausal osteoporotic women ≥45 years of age were randomized into the minodronate (n=135) or alendronate (n=135). Each subject received 1 mg minodronate or 5 mg alendronate once a day for 12 months. After one year ent, the lumbar spine BMD increased by 5.86% and 6.29% in the minodronate and alendronate groups, respectively, and the total hip BMD increased by 3.47% and 3.27%, respectively. Bone turnover markers were rapidly reduced within one month in both treatment groups. Urine DPD was significantly lower in the minodronate group than in the alendronate group at 6 months, and urine NTX was significantly lower in the minodronate group than in the alendronate group at 1 and 9 months.

10.3.181 Assessment of vertebral fracture risk and therapeutic effects of alendronate in postmenopausal women using a quantitative computed tomography-based nonlinear finite element method
Imai K, Ohnishi I, Matsumoto T, Yamamoto S, Nakamura K
Osteoporos Int 2009;20:801-10

QCT-based finite element method (QCT/FEM) can predict vertebral compressive strength ex vivo. This study aimed to assess vertebral fracture risk and alendronate effects on osteoporosis in vivo using QCT/FEM. Vertebral strength in 104 postmenopausal women was analyzed, and the discriminatory power for vertebral fracture was assessed cross-sectionally. Alendronate effects were also prospectively assessed in 33 patients with postmenopausal osteoporosis treated with alendronate for one year. On the age and body weight adjusted logistic regression, vertebral strength had stronger discriminatory power for vertebral fracture (OR per SD change: 6.71) than areal BMD and volumetric BMD. The optimal point for the vertebral fracture threshold was 1.95 kN with 75.9% sensitivity and 78.7% specificity. At 3 months, vertebral strength increased by 10.2% from baseline. The minimum principal strain distribution showed that the area of high fracture risk decreased. At one year, the density of the inner cancellous bone increased by 8.3%, while the density of the juxta-cortical area increased by 13.6%. QCT/FEM had higher discriminatory power for vertebral fracture than BMD and detected alendronate effects at 3 months. Alendronate altered density distributions, thereby decreasing the area with a high fracture risk, resulting in increased vertebral strength.

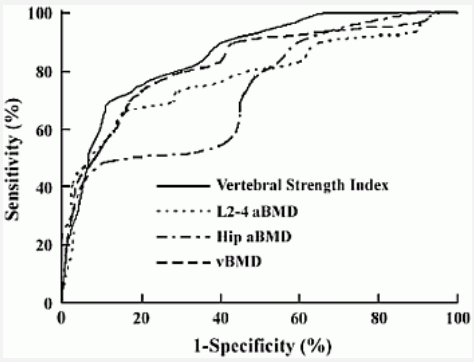


Fig. 10.3.181a ROC curves showing 1-specificity (false-positive rate) vs. sensitivity (true positive rate) for the vertebral strength index, L2-4 aBMD, hip aBMD, and vBMD. Reproduced from Osteoporos Int 2009;20:801-10 with permission from Springer.

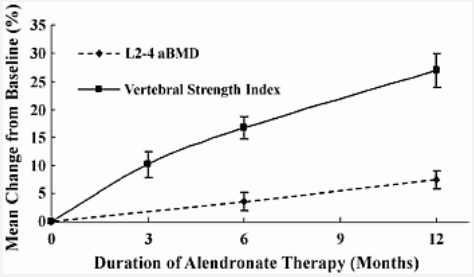


Fig. 10.3.181b Mean (±SE of mean) changes from baseline values in L2-4 aBMD measured by DXA and L2 vertebral strength index analyzed by QCT/FEM in women with postmenopausal osteoporosis receiving alendronate therapy for 12 months. Reproduced from Osteoporos Int 2009;20:801-10 with permission from Springer.

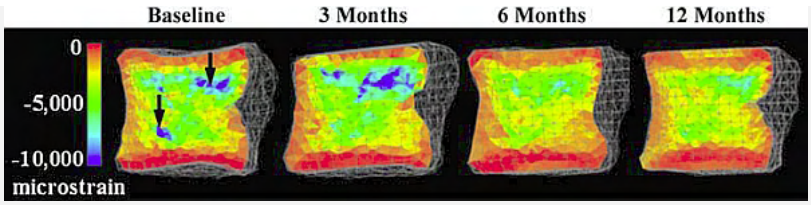


Fig. 10.3.181c Distribution of minimum principal strain at the midsagittal section with an applied load of 1 kN as analyzed by QCT/FEM. The area displaying less than -10,000 microstrain of minimum principal strain at baseline (arrows), with high risk of fracture, is decreased after 6 and 12 months of alendronate therapy. Reproduced from Osteoporos Int 2009;20:801-10 with permission from Springer.

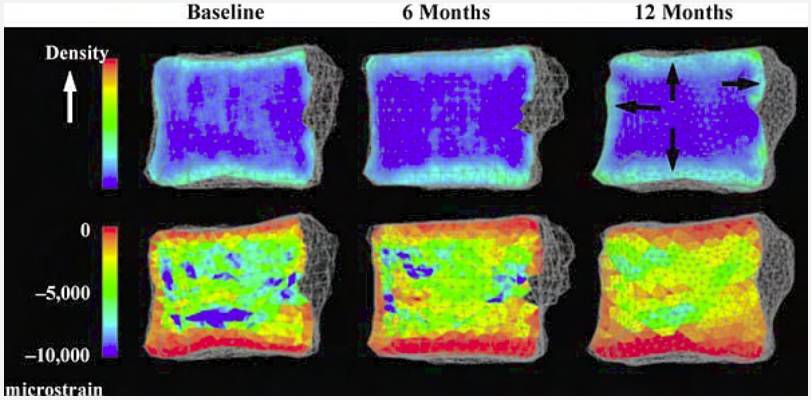


Fig. 10.3.181d Distribution of density and minimum principal strain. The density distribution shows an increased density in the juxta-cortical region (arrows). The area with a large negative value (for example, less than -10,000 microstrain) of the minimum principal strain narrowed after 12 months of alendronate therapy compared with the same area at baseline. Reproduced from Osteoporos Int 2009;20:801-10 with permission from Springer.

10.3.182 Alendronate treatment results in similar levels of trabecular bone remodeling in the femoral neck and vertebra
Diab T, Allen MR, Burr DB
Osteoporos Int 2009;20:647-52

Bone turnover suppression in sites that already have a low surface-based remodeling rate may lead to oversuppression. Dynamic histomorphometric parameters were assessed in trabecular bone of the femoral neck and lumbar vertebrae obtained from skeletally mature beagles treated with saline (1 ml/kg/day) or alendronate (ALN 0.2 or 1.0 mg/kg/day). Alendronate resulted in similar absolute levels of bone turnover in the femoral neck and vertebrae, although the femoral neck had 33% lower pretreatment surface-based remodeling rate than the vertebra ($p<0.05$). Additionally, the high dose of alendronate (ALN 1.0) suppressed bone turnover to similar absolute levels as the low dose of alendronate (ALN 0.2) in both sites. Alendronate may result in a lower limit of trabecular bone turnover suppression, suggesting that sites of low pretreatment remodeling rate are not more susceptible to oversuppression than those of high pretreatment remodeling rate.

10.3.183 Optimal increase in bone mass by continuous local infusion of alendronate during distraction osteogenesis in rabbits
Abbaspour A, Takahashi M, Sairyo K, Takata S, Yukata K, Inui A, Yasui N
Bone 2009;44:917-23

Since bone resorption, as well as regeneration, is stimulated in the distracted segment, bisphosphonate can be a beneficial agent for distraction osteogenesis. The left tibia of Japanese White rabbits subjected to slow distraction. At the beginning of the consolidation phase, alendronate (7 μg/kg/day) was infused into the lengthened segment for 14 days using an osmotic pump. Controls were infused with phosphate buffered saline (PBS). In PBS-infused control animals, BMC around the lengthened segment began to decrease after the first week of consolidation phase, forming a tubular bone structure with thin cortex. Infusion of alendronate increased peak BMC around the lengthened segment. At the end of the experiment, volumetric BMD, CBT and mechanical strength of the lengthened segment of the treatment group were twice controls. Alendronate infused in this manner prevented the osteopenia that began early in the consolidation phase.

10.3.184 Alendronate treatment of the brtl osteogenesis imperfecta mouse improves femoral geometry and load response before fracture but decreases predicted material properties and has detrimental effects on osteoblasts and bone formation
Uveges TE, Kozloff KM, Ty JM, Ledgard F, Raggio CL, Gronowicz G, Goldstein SA, Marini JC
J Bone Miner Res 2009;24:849-59

Brtl and wildtype mice were given alendronate (Aln; 0.219 mg/kg/wk, SC) for 6 or 12 wk and compared treated and untreated femora of both genotypes. Mutant and wildtype bone had similar responses to Aln. Femoral areal BMD and cortical volumetric BMD increased after 12 wk, but femoral length and growth curves were unaltered. Aln improved Brtl diaphyseal cortical thickness and trabecular number after 6 wk and cross-sectional shape after 12 wk. Mechanically, Aln increased stiffness in wildtype femora and load to fracture in both genotypes after 12 wk. However, predicted material strength and elastic modulus were negatively impacted by 12 wk of Aln in both genotypes, and metaphyseal remnants of mineralized cartilage also increased. Brtl femoral brittleness was unimproved. Brtl osteoclast and osteoblast surface were unchanged by treatment. However, decreased mineral apposition rate and bone formation rate/bone surface and the flattened morphology of Brtl osteoblasts suggested that Aln impaired osteoblast function and matrix synthesis. Aln improves Brtl femoral geometry and load to fracture but decreases bone matrix synthesis and predicted material modulus and strength, with retention of mineralized cartilage.

10.3.185 Bone structure and remodelling in stroke patients: Early effects of zoledronate
Poole KE, Vedi S, Debiram I, Rose C, Power J, Loveridge N, Warburton EA, Reeve J, Compston J

Bone 2009;44:629-33

Patients with acute stroke were randomly assigned to a single intravenous dose of zoledronate 4 mg or placebo within 5 weeks of stroke. Biopsies from 14 patients (3 females, 11 males, mean age 71±11) were suitable for analysis. These were taken at mean 10 weeks (±2) post-stroke, and included 5 patients who had received zoledronate. The eroded surface in cancellous bone (ES/BS) was higher in stroke patients than controls (5.7% vs. ref 1.6%, p<0.0001). Although ES/BS did not differ between zoledronate and placebo-treated groups, there were fewer osteoclasts and their precursors in zoledronate-treated individuals (p=0.023). Bone formation indices (osteoid surface, OS/BS and mineralising surface, MS/BS) were lower in stroke patients than controls and although OS/BS was higher in the zoledronate group than the placebo group (p=0.033), MS/BS was not different. There were no differences between hemiplegic and unaffected sides for any histomorphometric parameter despite asymmetric reductions in hip BMD (p=0.013). Stroke patients had higher resorption indices and lower bone forming surfaces than controls, consistent with uncoupling of bone remodelling. Zoledronate therapy was associated with a reduction in osteoclastic cell numbers consistent with its known mode of action in bone.

10.3.186 Pulse treatment with zoledronic acid causes sustained commitment of bone marrow derived mesenchymal stem cells for osteogenic differentiation
Ebert R, Zeck S, Krug R, Meissner-Weigl J, Schneider D, Seefried L, Eulert J, Jakob F
Bone 2009;44:858-64

Zoledronic acid (ZA) inhibits protein farnesylation and geranylgeranylation inhibiting osteoclast function and apoptosis. ZA in vitro causes inhibition of proliferation and induction of apoptosis in hMSC, an effect rescued by 10 µM geranylgeranyl pyrophosphate (GGPP). However, pulse stimulation for 3 and 6 h with these concentrations and subsequent culture for up to 2 weeks under osteogenic conditions exerts sustained regulation of osteogenic marker genes in hMSC. The effect on gene regulation translates into marked enhancement of mineralization, as shown by alizarin red and alkaline phosphatase staining after 4 weeks of osteogenic culture. ZA, when applied as a pulse stimulus, might therefore also stimulate osteogenic differentiation in vivo, since µM plasma concentrations can be achieved by intravenous application of 5 mg in patients.

10.3.187 Large osteoclasts in pediatric osteogenesis imperfecta patients receiving intravenous pamidronate
Cheung MS, Glorieux FH, Rauch F
J Bone Miner Res 2009;24:669-74

Measurement of osteoclast parameters in paired iliac bone specimens before and after 2-4 yr of cyclical intravenous pamidronate therapy in 44 pediatric OI patients (age range: 1.4-17.5 yr; 21 girls) revealed during pamidronate, average osteoclast diameter and the mean number of nuclei per osteoclast increased by 18% (p=0.02) and 43% (p<0.001), respectively. The number of samples containing large osteoclasts (LOcs, diameter >50 µm) increased from 6 (14%) before treatment to 23 (52%) after pamidronate (p<0.001). Post-treatment samples containing LOcs had a greater core width (p=0.04) and a higher cancellous bone volume per tissue volume (p<0.001), because cancellous bone volume had increased more during pamidronate (p<0.001). Osteoclast number and surface were higher in samples with LOcs, but there was no difference in cancellous bone formation parameters. In conclusion, this study did not show any indication that LOcs during pamidronate treatment are indicative of toxicity.

10.3.188 Effect of zoledronic acid on oral fibroblasts and epithelial cells: A potential mechanism of bisphosphonate-associated osteonecrosis
Scheper MA, Badros A, Chaisuparat R, Cullen KJ, Meiller TF
Br J Haematol 2009;144:667-76

Osteonecrosis of the jaw is assumed to be a bone disease. This study investigated the effects of ZA on soft tissues using oral mucosal cells as an in vitro model. Human gingival fibroblast and keratinocyte cell lines were exposed to different concentrations of ZA (0.25-3 µmol/l), using 1 µmol/l as the expected baseline concentration. A dose-response effect on apoptosis and cell proliferation was observed with increasing ZA concentrations; both reversed using siRNA against caspase 3 or 9. Gene expression analysis using RT(2) Profiler polymerase chain reaction Arrays demonstrated the differential expression of multiple genes involved in apoptosis including those that encode TNF, BCL-2, Caspase, IAP, TRAF and Death Domain families. Western blot analysis confirmed the presence of activated forms of caspase 3 and 9 and underexpression of survivin protein expression. This study demonstrated that low concentrations of ZA rapidly and directly affected the oral mucosal tissues though the induction of a gene-regulated apoptotic process. These findings support the potential for soft tissue injury as an initiating/potentiating event for osteonecrosis.

10.3.189 Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX®
Kanis JA, Johansson H, Oden A, McCloskey EV
Bone 2009;44:1049-54

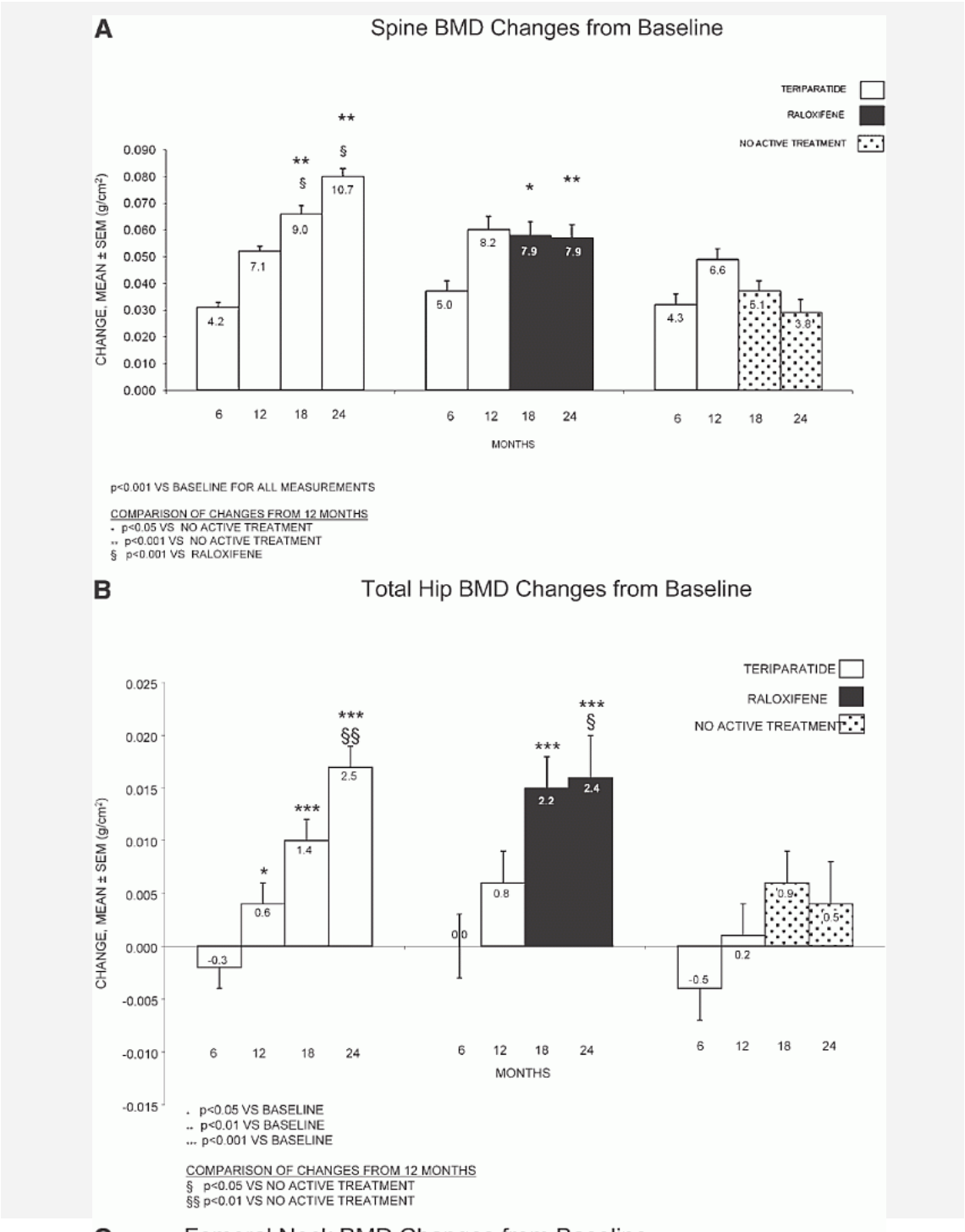
This was a double-blind, placebo- and raloxifene-controlled randomised 3-year study of 7492 women. For this analysis, women taking raloxifene were excluded (n=1849). The risk of a major osteoporotic fracture was assessed using region specific FRAX® algorithms. Bazedoxifene was associated with a 39% decrease in incident morphometric vertebral fractures (HR=0.61; 95% CI=0.43-0.86; p=0.005) and a nonsignificant 16% decrease in all clinical fractures (HR=0.84; 95% CI=0.67-1.06; p=0.14). Hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability. In patients with 10-year fracture probabilities at or above 16%, bazedoxifene decreased the risk of all clinical fractures. The 16% probability threshold corresponded to the 80th percentile of the study population. Hazard ratios for the effect of bazedoxifene on morphometric vertebral fractures also decreased with increasing fracture probability. In patients with 10-year fracture probabilities above 6.9% (corresponding to the 41st percentile), bazedoxifene decreased risk of morphometric vertebral fractures. At equivalent fracture probability percentiles, the effect of bazedoxifene was greater on vertebral fracture risk than on the risk of all clinical fractures. For example, at the 90th percentile of FRAX® probability, bazedoxifene reduced risk by 33% (95% CI=7-51%) for all clinical fractures and 51% (95% CI=21-69%) for morphometric vertebral fractures. Bazedoxifene (20 and 40 mg doses combined) decreased the risk of all clinical fractures and morphometric vertebral fractures in women at or above a FRAX® based fracture probability threshold. These results, consistent with the previous subgroup analysis, suggest that bazedoxifene should be targeted preferentially to women at high fracture risk.

10.3.190 Relationship between duration of teriparatide therapy and clinical outcomes in postmenopausal women with osteoporosis
Lindsay R, Miller P, Pohl G, Glass EV, Chen P, Krege JH
Osteoporos Int 2009;20:943-8

Postmenopausal women with osteoporosis were randomized to once-daily subcutaneous injection with placebo (N=544), teriparatide 20 µg (TPTD20; N=541), or teriparatide 40 µg (TPTD40; N=552) plus calcium and vitamin D supplementation. Compared with placebo, the relative hazard for nonvertebral fragility fractures decreased by 7.3% for each additional month of TPTD20 [HR=0.927, 95% CI (0.876 to 0.982), p=0.009] and by 7.6% for each additional month of TPTD40 [HR=0.924, 95% CI (0.871 to 0.981), p=0.009]. Clinical vertebral fractures appeared to increase over time in the placebo group and occurred primarily in the first time interval in the teriparatide treatment groups. Compared with placebo, the relative hazard of back pain was decreased by 8.3% for each additional month of TPTD20 [hazard ratio=0.920, 95% CI (0.902 to 0.939), p<0.001] and 8.7% for each additional month of TPTD40 [hazard ratio=0.917, 95% CI (0.898 to 0.935), p<0.001]. These findings suggest increased nonvertebral fracture protection, reduced back pain, and reduced occurrence of side effects with longer duration of teriparatide therapy.

10.3.191 Sequential treatment of severe postmenopausal osteoporosis after teriparatide: Final results of the randomized, controlled European Study of Forsteo (EUROFORS)
Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J, Audran M, Boonen S, Brixen K, Gomes JM, Obermayer-Pietsch B, Avramidis A, Sigurdsson G, Gluer CC
J Bone Miner Res 2009;24:726-36

In a prospective, randomized, controlled, 2-yr study, the investigators compared BMD and clinical safety of teriparatide, raloxifene, or no treatment after one year of teriparatide. Postmenopausal women with osteoporosis and a recent fragility fracture received open-label teriparatide (20 µg/d) for 12 mo before they were randomized (3:1:1) to continue teriparatide (n=305), switch to raloxifene 60 mg/d (n=100), or receive no treatment for the second year (n=102). All received calcium and vitamin D. Daily teriparatide for 2 yr increased spine BMD by 10.7%. Patients receiving raloxifene in year 2 had no further change in spine BMD from year 1 (change from baseline, 7.9%), whereas patients receiving no treatment had a BMD decrease of 2.5% in year 2 (change from baseline, +3.8%). At the total hip, BMD increases from baseline at 2 yr were 2.5% with teriparatide, 2.3% with raloxifene, and 0.5% with no treatment; the respective changes at the femoral neck were 3.5%, 3.1%, and 1.3%. The study had insufficient power to assess antifracture efficacy.



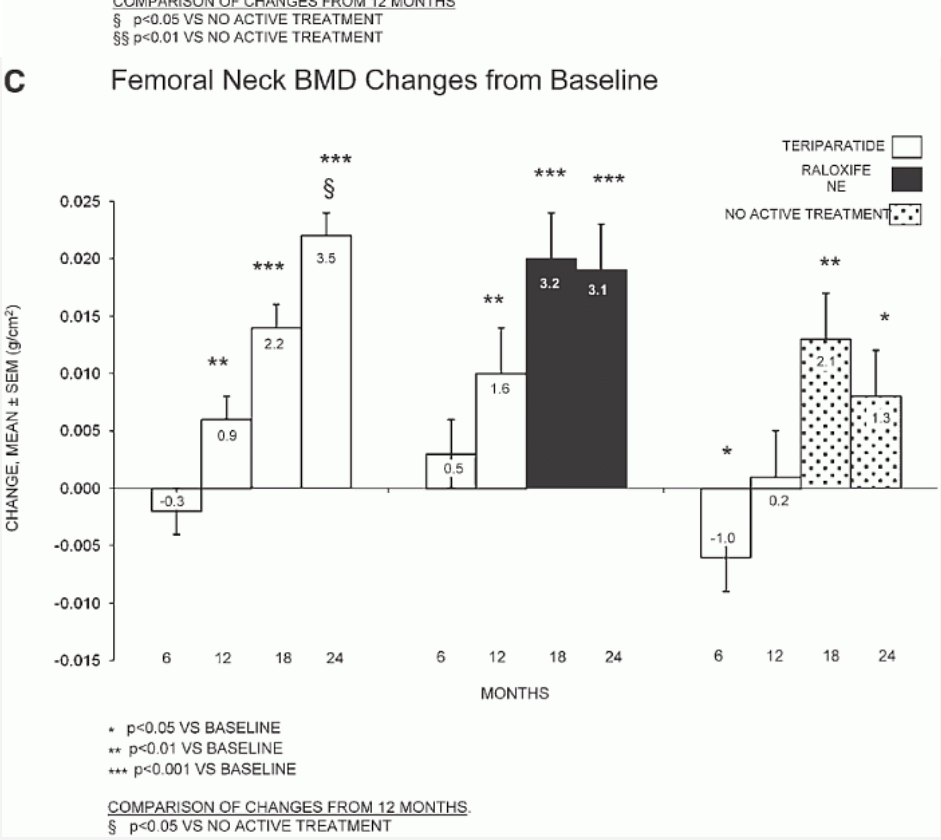


Fig. 10.3.191 BMD changes from baseline in EUROFORS substudy 1 participants. Absolute changes in BMD (g/cm^2) from baseline after 6, 12, 18, and 24 mo of treatment in (A) the lumbar spine, (B) total hip, and (C) femoral neck (full analysis population). Numbers at the top of the columns are estimates of percentage change in BMD from baseline. Reproduced from J Bone Miner Res 2009;24:726-36 with permission of the American Society of Bone and Mineral Research.

10.3.192 Persistence with teriparatide in postmenopausal osteoporosis; impact of a patient education and follow-up program: The French experience
Briot K, Ravaud P, Dargent-Molina P, Zylberman M, Liu-Leage S, Roux C
Osteoporos Int 2009;20:625-30

Since the launch of teriparatide in France in September 2004, 5413 postmenopausal women (mean age 72.3±14.5 years) with osteoporosis and vertebral fractures (mean 3.9±2) have participated in a persistence program. The persistence rate at 15 months was 81.5%, and a majority of patients completed the 18-month treatment. The main reason for discontinuation was adverse events (46.7%). Postmenopausal osteoporotic women treated by teriparatide and enrolled in an education and follow-up program have a high persistence rate.

10.3.193 No difference between strontium ranelate (SR) and calcium/vitamin D on bone turnover markers in women with established osteoporosis previously treated with teriparatide: A randomized controlled trial
Anastasilakis AD, Bhansali A, Ahluwalia J, Chanukya GV, Behera A, Dutta P
Clin Endocrinol (Oxf) 2009;70:522-6

22 postmenopausal Caucasian women (aged 65.7±1.7 years) with established osteoporosis previously treated with TPTD 20 µg daily for 18 months were randomly assigned to receive either SR (SR group, n=11) or calcium and vitamin D (control group, n=11). Serum P1NP, CTx and total ALP increased after TPTD treatment and decreased at the end of the study in both SR and control groups, with no difference between them. SR following TPTD administration acts predominantly as an antiresorptive agent with no evidence of additional osteoanabolic action. In this setting, SR is not more effective than Ca/vitamin D as far as bone turnover markers are concerned.

10.3.194 Strontium ranelate treatment of human primary osteoblasts promotes an osteocyte-like phenotype while eliciting an osteoprotegerin response
Atkins GJ, Welldon KJ, Halbout P, Findlay DM
Osteoporos Int 2009;20:653-64

Adult human primary osteoblasts (NHBC) were exposed to SR under mineralizing conditions in long-term cultures. SR increased osteoblast replication. SR time- and dose-dependently induced an osteocyte-like phenotype, as determined by cell surface alkaline phosphatase and STRO-1 expression. SR at 5 mM or greater increased in vitro mineralization. In parallel, mRNA levels of dentin matrix protein (DMP)-1 and sclerostin were higher under SR, suggestive of the presence of osteocytes. SR also increased the OPG/RANKL ratio throughout the culture period. This study suggests that SR can promote osteoblast maturation and an osteocyte-like phenotype.

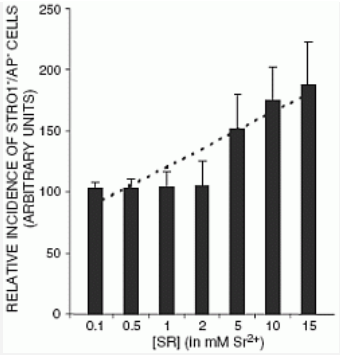


Fig. 10.3.194a SR increases the proportion of STRO-1⁻/AP⁻ (osteocyte-like) cells. The STRO-1 and AP reactivity of NHBC cultured for 14 days in the presence of SR (0-15 mM) was determined by flow cytometry. The %STRO-1⁻/AP⁻ cells were determined for each SR treatment and were normalized to the zero SR control, which was assigned the arbitrary value 100. Data shown are means±SD pooled from three different donors' cells. Differences between individual treatment groups were not statistically different (one-way ANOVA) due to large variance at the highest SR concentrations used. Spearman Rank correlation (dotted line) indicated a dose-dependent increase in %STRO-1⁻/AP⁻ cells (r^2=0.66, p=0.0012). Reproduced from Osteoporos Int 2009;20:653-64 with permission from Springer.

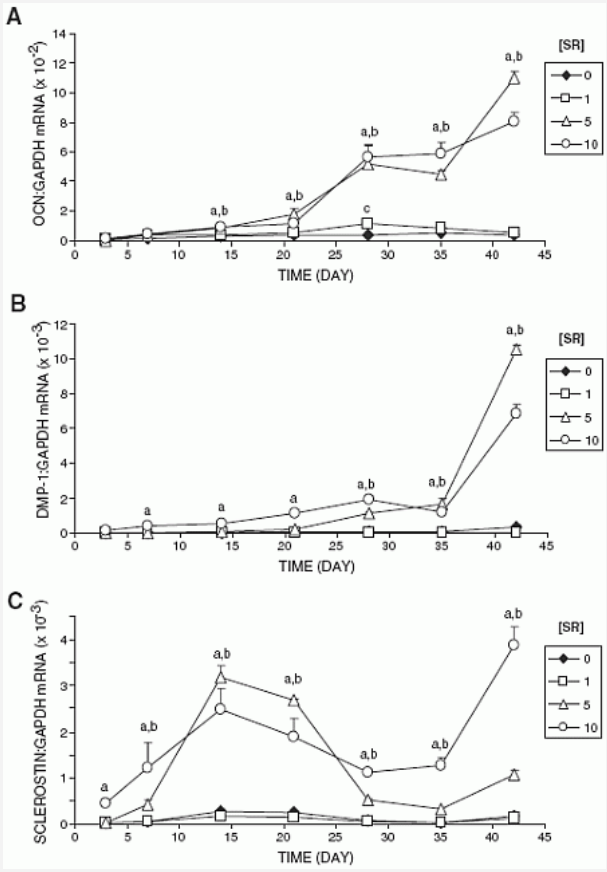


Fig. 10.3.194b SR increases NHBC expression of osteocalcin, sclerostin, and DMP-1. NHBC were cultured for up to 42 days under mineralizing conditions in the added presence of SR at 1, 5, or 10 mM. Total RNA was prepared at the times indicated, and real-time RT-PCR was performed for (a) OCN, (b) DMP-1, and (c) sclerostin. Data shown are means±SD of triplicate reactions. Statistical difference in expression to the control (absence of SR) is indicated; a, b Significant differences (p<0.01) for 10 mM and 5 mM SR treatments, respectively. Similar results were obtained for cells from five different donors. Reproduced from Osteoporos Int 2009;20:653-64 with permission from Springer.

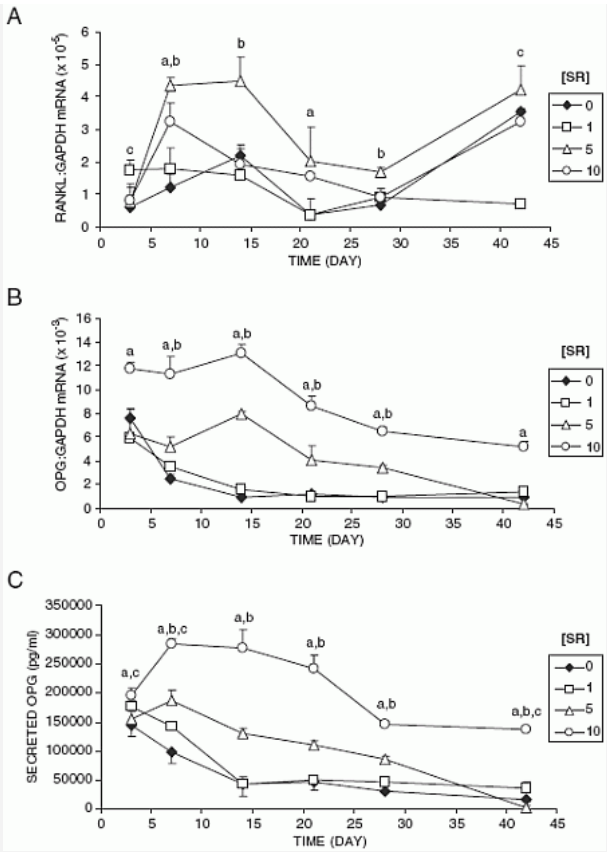


Fig. 10.3.194c Effect of SR on RANKL and OPG expression. NHBC were cultured for up to 42 days under mineralizing conditions in the added presence of SR at 1, 5, or 10 mM. Total RNA was prepared at the times indicated, and real-time RT-PCR performed for (a) RANKL and (b) OPG. (c) Supernatants from each of the treatments at each time point were tested for OPG protein content by enzyme-linked immunosorbent assay (ELISA), as described. Note that the OPG protein content in each case is that which had accumulated in the 3 days prior to sampling. For both PCR and ELISA, data shown are means±SD of triplicate reactions. Statistical difference in expression to the control (absence of SR) is indicated; a, b, and c denote significant differences (p<0.01) for 10, 5, and 1 mM SR treatments, respectively. Similar results were obtained for cells from two other donors. Reproduced from Osteoporos Int 2009;20:653-64 with permission from Springer.

10.3.195 Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates

Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, Gao G, Wu L, Sohn W, Jun S

J Clin Oncol 2009;27:1564-71

Eligible patients had histologically confirmed malignancy, ≥1 bone metastases, and uNTx higher than 50 nmol/L nine despite IV BPs. They were stratified by tumor type and screening uNTx levels (50-100 or >100 nmol/L BCE/mM creatinine), and randomly assigned to continue IV BPs every 4 weeks or receive subcutaneous denosumab 180 mg every 4 weeks or every 12 weeks. Among 111 patients accrued, the primary end point of uNTx levels lower than 50 nmol/L BCE/mM creatinine (uNTx <50) at week 13 was achieved by 49 (71%) of 69 patients in the denosumab arms, compared with 10 (29%) of 35 patients in the IV BP arm (P<0.001). The proportion of patients with uNTx lower than 50 was maintained at week 25 (64% denosumab arms; 37% IV BP arm; P=0.01). The incidence of SREs was 6 (8%) of 73 and 6 (17%) of 35 in the denosumab group and IV BP group, respectively. Rates of adverse events were similar between treatment groups. Among patients with elevated uNTx despite ongoing IV BP therapy, denosumab normalized uNTx levels more frequently than the continuation of IV BP. Fewer patients receiving denosumab experienced on-study SREs than those receiving IV BPs.

10.3.196 Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis

Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J, Gao Y, Shalhoub V, Tipton B, Haldankar R, Chen Q, Winters A, Boone T, Geng Z, Niu QT, Ke HZ, Kostenuik PJ, Simonet WS, Lacey DL, Paszty C

J Bone Miner Res 2009;24:578-88

6-month-old female rats were ovariectomized and left untreated for 1 yr at which point Scl-AbII was administered for 5 wk increased bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. This not only resulted in complete reversal, at several skeletal sites, but also further increased bone mass and strength to levels greater than those found in nonovariectomized control rats.

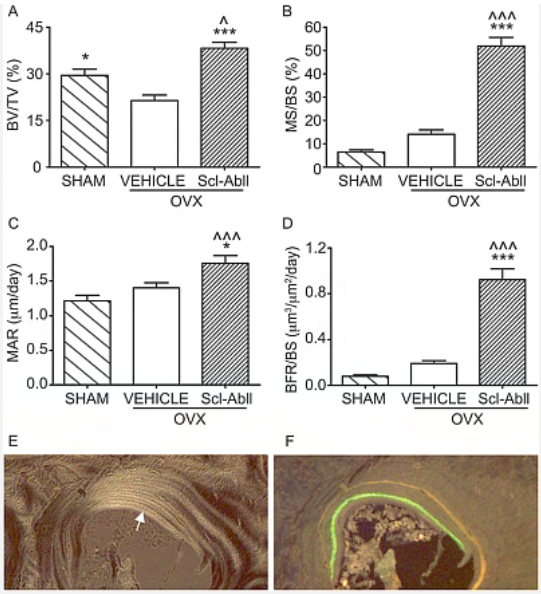


*Fig. 10.3.196a Scl-AbII treatment increases trabecular bone volume and bone formation in lumbar vertebrae as assessed by histomorphometric analysis. (A) Bone volume (BV/TV). (B) Mineralizing surface (MS/BS). (C) Mineral apposition rate (MAR). (D) Bone formation rate (BFR/BS). (E) Normal lamellar structure of newly formed bone in Scl-AbII–treated OVX rats as determined by polarized light microscopy (3200). White arrow indicates region of newly formed bone as delineated by tetracycline and calcein labels in F. (F) Fluorescent micrograph of the same trabecular bone section showing the tetracycline (orange/yellow) and calcein (green) labels. Unlabeled bone between the two labels was formed during the 7-day period between label injections. Data represent mean±SE for 8 rats/group. *p<0.05 and ***p<0.001 vs. OVX+vehicle. ^^p<0.01 and ^^^p<0.001 vs. Sham +vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.*

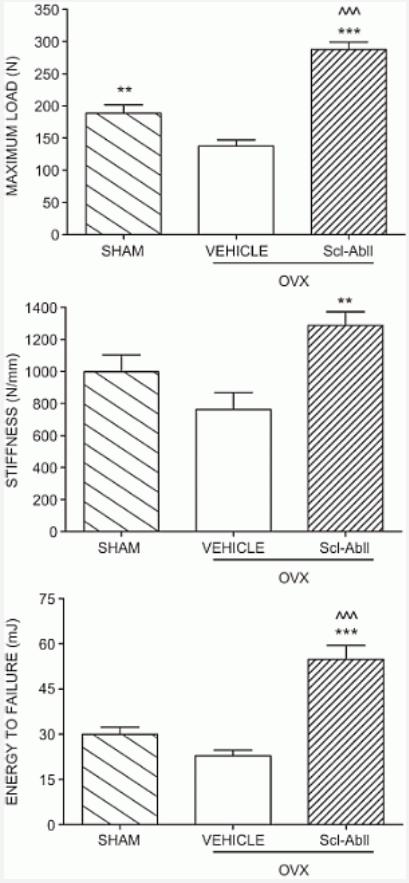


*Fig. 10.3.196b Scl-AbII treatment increases bone strength at lumbar vertebrae. The fourth and fifth lumbar vertebrae were subjected to compression testing. Maximum load, stiffness, and energy to failure are parameters of bone strength. Data represent mean±SE for 12 rats/group. **p<0.01 and ***p<0.001 vs. OVX+vehicle. ^^^p<0.001 vs. Sham+vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.*

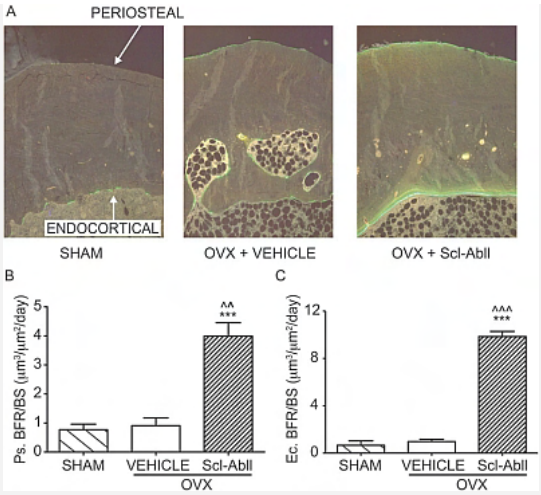


*Fig. 10.3.196c Scl-AbII treatment increases periosteal (Ps) and endocortical (Ec) bone formation at the femoral midshaft. (A) Fluorescent micrographs of cortical bone sections (3100). Scl-AbII–treated OVX rats had extensive tetracycline (yellow) and calcein (green) labels on periosteal and endocortical surfaces of femoral midshaft. (B) Periosteal bone formation rate (Ps. BFR/BS). (C) Endocortical bone formation rate (Ec.BFR/BS). Data represent mean±SE for 9-12 rats/group. ***p<0.001 vs. OVX+vehicle; ^^^p<0.001 vs. Sham+vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.*

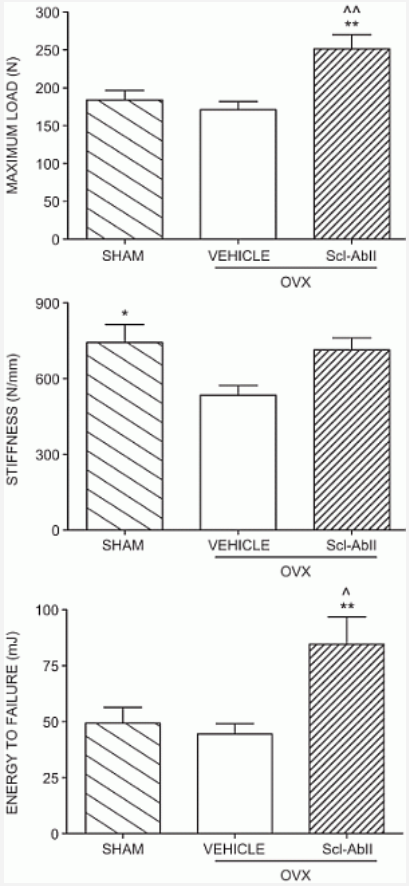


*Fig. 10.3.196d Scl-AbII treatment increases bone strength at the femoral midshaft. Maximum load, stiffness, and energy to failure were measured by subjecting femurs to a four-point bending test. Data represent mean±SE for 11-12 rats/group. *p<0.05 and **p<0.01 vs. OVX+vehicle. ^p<0.05 and ^^p<0.01 vs. Sham+vehicle. Reproduced from J Bone Miner Res 2009;24:578-88 with permission of the American Society of Bone and Mineral Research.*

10.3.197 Prevention of nonvertebral fractures with oral vitamin D and dose dependency: A meta-analysis of randomized controlled trials

Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J
Arch Intern Med 2009;169:551-61

12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures (n=42,279) and 8 RCTs for hip fractures (n=40,886) compared oral vitamin D, with or without calcium, with calcium or placebo. To incorporate adherence, the authors multiplied the dose by the percentage of adherence to estimate the mean received dose (dose x adherence) for each trial. The pooled relative risk (RR) was 0.86 (0.77-0.96) for nonvertebral fractures and 0.91 (0.78-1.05) for hip fractures, but with heterogeneity for both end points. Including all trials, antifracture efficacy increased with a higher dose and higher achieved 25-hydroxyvitamin D for both end points. Pooling trials with a higher dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (0.72-0.89; n=33 265 subjects, 9 trials) for nonvertebral fractures and 0.82 (0.69-0.97; n=31 872 subjects, 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (-29%) and institutionalized older individuals (-15%) independent of calcium supplementation. Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

10.3.198 Vitamin D supplementation during Antarctic winter
Smith SM, Gardner KK, Locke J, Zwart SR
Am J Clin Nutr 2009;89:1092-8

This study was designed to evaluate the effectiveness of 3 doses of vitamin D to raise and maintain 25(OH)D to a concentration >80 nmol/L in persons with limited ultraviolet B light exposure. This was a 5-mo, prospective, randomized, double-blind study of vitamin D supplementation. It was conducted during winter in Antarctica at the McMurdo Station, when ultraviolet B radiation levels are essentially zero. The 55 subjects were randomly divided into 3 groups for vitamin D supplementation: 2000 IU/d (n=18), 1000 IU/d (n=19), and 400 IU/d (n=18). An additional 7 subjects did not take supplements or took supplements of their own choosing. Blood samples were collected about every 2 mo during the winter. About 5 mo after supplementation started, 25(OH)D increased to 71±23 nmol/L in the 2000 IU/d group, 63±25 nmol/L in the 1000 IU/d group, and 57±15 nmol/L in the 400 IU/d group and decreased to 34±12 nmol/L in the group not taking supplements.

10.3.199 Effect of 1,25-dihydroxy vitamin D3 on fracture healing and bone remodeling in ovariectomized rat femora
Fu L, Tang T, Miao Y, Hao Y, Dai K
Bone 2009;44:893-8

Female Sprague Dawley rats of 6-mo-old were allocated into two groups after ovariectomy. Bilateral midshaft femoral osteotomy was performed 12 weeks postovariectomy. Treatment was begun at the second day after osteotomy and continued until sacrifice at 6 and 16 weeks postfracture with middle chain triglyceride vehicle and 1,25(OH)2D3 at 0.1 μg/kg/day by oral gavage. Soft X-ray radiography, at 6 weeks postfracture, showed a less distinct fracture line in the 1,25(OH)2D3 group, however, the fracture line was invisible in both groups at 16 weeks postfracture. MicroCT based histomorphometric data, at 6 weeks postfracture, showed that the total volume of callus (TV) was 23% higher in the 1,25(OH)2D3 group (P<0.001), and the new bone volume (BV), BV/TV, the trabecular number (Tb.N), and density of TV also showed the same trend. At 16 weeks postfracture, the increment still existed as shown by Tb.Th and density of TV (P<0.001, vs. control). Biomechanical testing data, at 6 weeks postfracture, showed that the ultimate load at failure and energy absorption of the 1,25(OH)2D3 group were nearly one-fold higher vehicle group. At 16 weeks postfracture, the ultimate load and energy absorption were also higher with the treatment. Fracture callus in the 1,25(OH)2D3 group was remodeled better compared to the control.

10.3.200 Quantification of bone tissue regeneration employing beta-tricalcium phosphate by three-dimensional non-invasive synchrotron micro-tomography – A comparative examination with histomorphometry
Stiller M, Rack A, Zabler S, Goebbels J, Dalugge O, Jonscher S, Knabe C
Bone 2009;44:619-28

This study presents a novel approach to evaluate the validity of two-dimensional histomorphometric measurements of a bone biopsy specimen after sinus floor elevation by means of high contrast, high resolution, 3-D and nondestructive synchrotron microtomography (SCT). Unilateral sinus grafting was carried out in two patients using beta-tricalcium phosphate (beta-TCP) and autogenous bone chips. For the first patient a beta-TCP with 35% porosity and in the second with 60% porosity was used. At implant placement, 6 months after grafting, a cylindrical specimen was biopsied from the augmented area. Subsequent to the histological embedding in resin the specimens were imaged using a SCT facility resulting in 3-D images with approximately 4 μm spatial resolution (1.5 μm pixel size. Bone area fractions determined by 2-D quantitative histomorphometry and by analysis of the corresponding 2-D slice from the SCT volume data were similar. For the first biopsy (beta-TCP with 35% porosity), the bone area fractions were 53.3% and 54.9% as derived by histomorphometry and by analyzing a SCT slice, respectively. For the second specimen (beta-TCP with 60% porosity) the bone area fractions were 38.8% and 39%, respectively. Although the agreement between the 2-D methods was excellent, the area fractions were higher than the volume fractions computed by 3-D image analysis on the entire SCT volume data set. The volume fractions were 48.8% (first biopsy) and 36.3% (second biopsy). Although the agreement between the 2-D methods is excellent in terms of computing the area fractions, the structural 3-D insight which can be derived from classical 2-D methods, including histomorphometric analysis is limited.

10.3.201 Phytotherapy versus hormonal therapy for postmenopausal bone loss: A meta-analysis
Xu M, Qi C, Deng B, Deng PX, Mo CW
Osteoporos Int 2009;20:519-26

The objective of this meta-analysis was to compare the efficacy and safety of phytotherapy with hormonal therapy. 14 randomized controlled trials involving 780 patients that met the inclusion criteria, and four trials were graded as high quality (score 3-5). There was no significant difference in lumbar, femoral or forearm BMD values between subjects treated with phytotherapy and those treated with hormonal therapy (P>0.05), but the incidence of uterine bleeding and breast pain was significantly lower in those treated with phytotherapy than in those treated with hormonal therapy (P=0.002 and P=0.01). Phytotherapy may not show effects beyond hormonal therapy but may be safer than hormonal therapy in the treatment of postmenopausal bone loss.

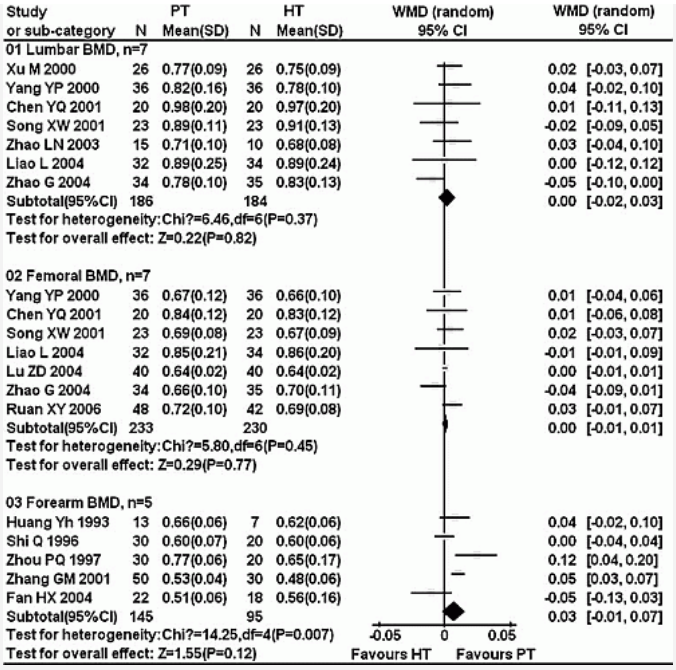


Fig. 10.3.201a Meta-analyses of efficacy (PT vs. HT). Reproduced from Osteoporos Int 2009;20:519-26 with permission from Springer.

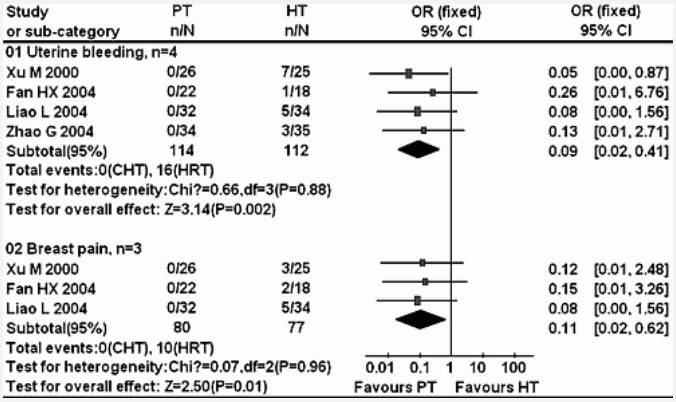


Fig. 10.3.201b Meta-analyses of safety (PT vs. HT). Reproduced from Osteoporos Int 2009;20:519-26 with permission from Springer.

10.3.202 Effect of long-term intervention of soy isoflavones on bone mineral density in women: A meta-analysis of randomized controlled trials

Liu J, Ho SC, Su YX, Chen WQ, Zhang CX, Chen YM

Bone 2009;44:948-53

In 10 RCTs of 896 women a mean dose of 87 mg soy isoflavones for at least one year did not affect BMD. The mean (95% CI) differences in BMD changes (in mg/cm^2/year) were 4.1 (-1.6, 9.8) (0.4%) at the lumbar spine, -1.5 (-7.2, 4.3) (-0.3%) at the femoral neck under random-effects model, and 2.5 (-0.5, 5.4) (0.2%) at the total hip by fix-effects model, respectively. Similar results were obtained in subgroup analyses by isoflavone sources (soy protein vs. isoflavone extract), ethnic differences (Asian vs. Western). Larger dose (≥80 mg/d), but not lower dose (<80 mg/d), of isoflavone intervention tended to have a weak beneficial effect on spine BMD (p=0.08 vs. p=0.94).

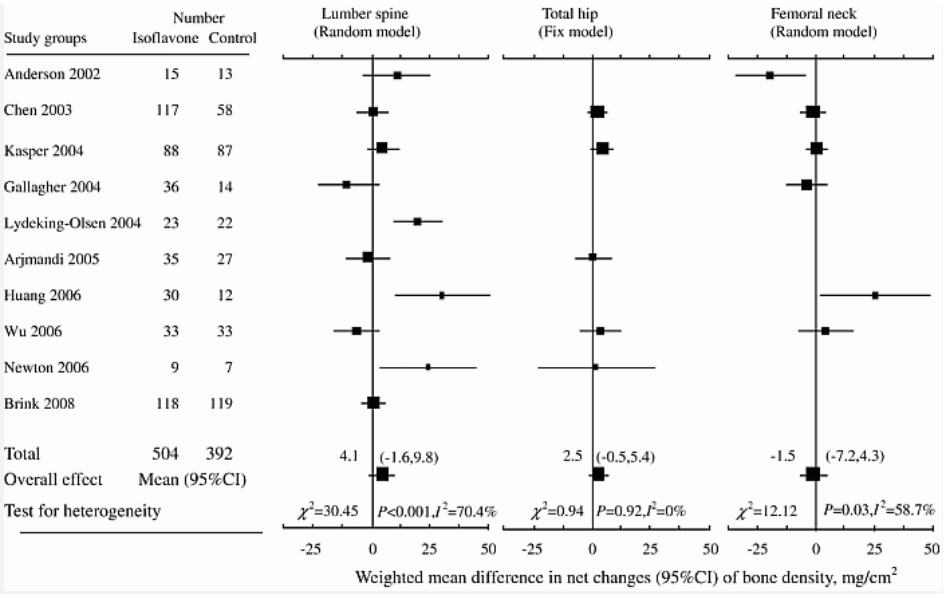


Fig. 10.3.202 Effects of soy isoflavone on bone mineral density. The horizontal lines denote the 95% CIs, some of which extend beyond the limits of the scales. Reproduced from Bone, 44:948-53, Copyright (2009), with permission from Elsevier.

10.3.203 Change in the use of hormone replacement therapy and the incidence of fracture in Oslo
Meyer HE, Lofthus CM, Sogaard AJ, Falch JA
Osteoporos Int 2009;20:827-30

Between the late 1970s and the late 1990s, the incidence of hip fracture and distal forearm fracture decreased in younger postmenopausal women in Oslo, but not in elderly women or in men. The purpose of this report is to evaluate whether the decreased incidence was coherent with trends in use of hormone replacement therapy (HRT). The sale of all estrogens increased 22 times from 1979 to 1999, and the subcategory estradiol combined with progestin increased 35 times. In the corresponding period the incidence of distal forearm fracture in women aged 50-64 years decreased by 33% and hip fracture by 39%. Based on differences in BMD between users and nonusers of HRT, half of this decline might be due to HRT.

10.3.204 Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone
Weiss EP, Shah K, Fontana L, Lambert CP, Holloszy JO, Villareal DT
Am J Clin Nutr 2009;89:1459-67

In year 1, a randomized trial was conducted in which men (n=55) and women (n=58) aged 65-75 y took 50 mg/d oral DHEA supplements or placebo. In year 2, all participants took open-label DHEA (50 mg/d). During both years, all participants received vitamin D (16 μg/d) and calcium (700 mg/d) supplements. In men, no difference between groups occurred in any BMD measures or in bone turnover markers during year 1 or year 2. The free testosterone index and estradiol increased in the DHEA group only. In women, spine BMD increased by 1.7±0.6% (P=0.0003) during year 1 and by 3.6 ±0.7% after 2 y of supplementation in the DHEA group; however, in the placebo group, spine BMD was unchanged during year 1 but increased to 2.6±0.9% above baseline during year 2 after the crossover to DHEA. Hip BMD did not change. Testosterone, estradiol, and insulin-like growth factor 1 increased in the DHEA group only. In both groups, serum concentrations of bone turnover markers decreased during year 1 and remained low during year 2, but did not differ between groups. DHEA supplementation in older women, but not in men, improves spine BMD when co-administered with vitamin D and calcium.

10.3.205 Estrogen action on bone marrow osteoclast lineage cells of postmenopausal women in vivo
Clowes JA, Eghbali-Fatourechi GZ, McCready L, Oursler MJ, Khosla S, Riggs BL
Osteoporos Int 2009;20:761-9

In bone marrow aspirates from 34 early postmenopausal women randomly assigned to receive 4 weeks of treatment (100 μg/day of transdermal 17β-estradiol) or no treatment, osteoclast differentiation and surface receptors showed that E treatment decreased (P<0.05) the proportion of marrow mononuclear cells (BMMNCs) expressing the calcitonin receptor (CTR), a late osteoclast phenotype marker. There was an increase in c-Fms concentration in osteoclast lineage cells (P<0.05) and in the proportion of BMMNCs expressing TNFR2 (P<0.05), but there were no effects on other surface receptors for proresorptive factors (RANK, TNFR1, TREM2, or OSCAR). Changes in serum CTx and TRAP 5b, markers for bone resorption, correlated directly (P<0.05) with the proportion of BMMNCs expressing CTR and, for TRAP 5b only, TNFR2 and inversely with c-Fms concentration (all P<0.05). E reduces bone resorption, in part, by decreasing differentiation of BMMNCs into mature osteoclasts. This action cannot be explained by decreased concentrations of surface receptors for proresorptive factors.

10.3.206 A small molecule inhibitor of the Wnt antagonist secreted frizzled-related protein-1 stimulates bone formation
Bodine PV, Stauffer B, Ponce-de-Leon H, Bhat RA, Mangine A, Seestaller-Wehr LM, Moran RA, Billiard J, Fukayama S, Komm BS, Pitts K, Krishnamurthy G, Gopalsamy A, Shi M, Kern JC, Commons TJ, Woodworth RP, Wilson MA, Welmaker GS, Trybulski EJ, Moore WJ
Bone 2009;44:1063-8

Deletion of the Wnt antagonist secreted frizzled-related protein (sFRP)-1 in mice activates canonical signaling in bone and increases trabecular bone formation in aged animals. The authors developed small molecules that bind to and inhibit sFRP-1 in vitro and demonstrate robust anabolic activity in an ex vivo organ culture assay. A diarylsulfone sulfonamide, bound to sFRP-1 with a K(D) of 0.35 μM in a tryptophan fluorescence quenching assay. This compound also selectively inhibited sFRP-1 with an EC(50) of 3.9 μM in the cell-based functional assay. Optimization of this high throughput screening hit for binding and functional potency as well as metabolic stability and other pharmaceutical properties led to improved lead compounds. One of these leads (WAY-316606) bound to sFRP-1 with a K(D) of 0.08 μM and inhibited it with an EC(50) of 0.65 μM. Moreover, this compound increased total bone area in a murine calvarial organ culture assay at concentrations as low as 0.0001 μM.

10.3.207 Single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women

Ruckle J, Jacobs M, Kramer W, Pearsall AE, Kumar R, Underwood KW, Seehra J, Yang Y, Condon CH, Sherman ML
J Bone Miner Res 2009;24:744-52

ACE-011 results in a sustained increase in biomarkers of bone formation and reduction in markers of bone resorption. The activin type IIA receptor (ActRIIA) is the high-affinity receptor for activin. ACE-011 is a dimeric fusion protein consisting of the extracellular domain of the human ActRIIA linked to the Fc portion of human IgG1. ACE-011 binds to activin, preventing activin from binding endogenous receptors. A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety and tolerability of ACE-011. 48 healthy, postmenopausal women were randomized to ACE-011 or placebo and were followed for 4 mo. The PK of ACE-011 was linear over the dose range studied, with a mean half-life of 24-32 days. The absorption after subcutaneous dosing was complete. ACE-011 caused a rapid and sustained dose-dependent increase in serum BSALP and a dose-dependent decrease in CTX and TRACP-5b. There was also a dose-dependent decrease in serum FSH levels consistent with inhibition of activin.

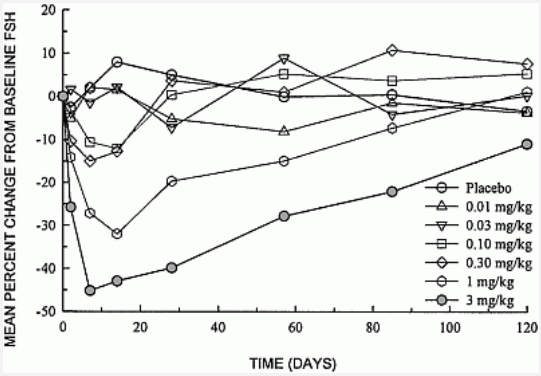


Fig. 10.3.207 Mean percent change from baseline in serum concentrations of FSH after intravenous administration of single doses of ACE-011 to healthy postmenopausal female volunteers. Mean data from IV cohorts are expressed over time. Dosing occurred on day 1. There were five active subjects in each cohort, except in the 0.01 mg/kg cohort after day 29, in which there were four active subjects, and six subjects in the placebo IV group. Reproduced from J Bone Miner Res 2009;24:744-52 with permission of the American Society of Bone and Mineral Research.

10.3.208 Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: A population-based cohort study

Mudano AS, Bian J, Cope JU, Curtis JR, Gross TP, Allison JJ, Kim Y, Briggs D, Melton ME, Xi J, Saag KG
Osteoporos Int 2009;20:819-26

A population-based retrospective cohort study using data from a large regional health insurer. Among 48 treated (51% vertebroplasty, 49% kyphoplasty) and 164 comparison patients, treated patients had a greater risk of secondary VCFs than comparison patients for fractures within 90 days of the procedure or comparison group time point [adjusted OR=6.8; 95% CI 1.7-26.9] and within 360 days (adjusted OR=2.9; 95% CI 1.1-7.9). Patients who had undergone vertebroplasty/kyphoplasty had a greater risk of new VCFs compared to patients with prior VCFs who did not undergo either procedure.

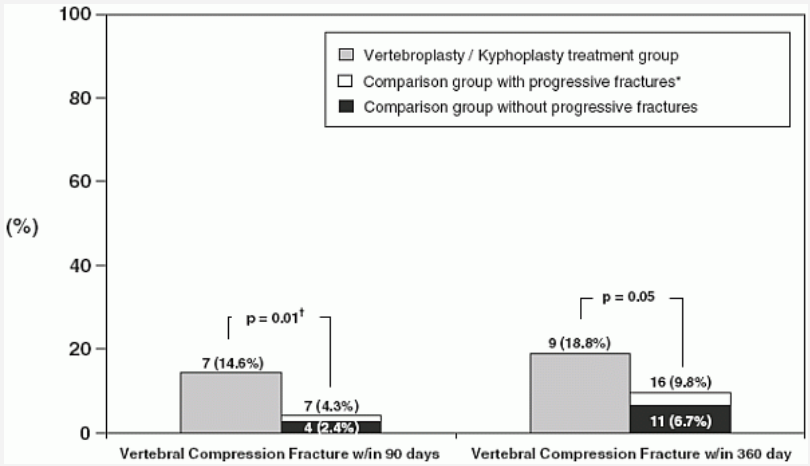


Fig. 10.3.208 Proportion of vertebroplasty/kyphoplasty treatment (n=48) and comparison (n=164) group patients with secondary fractures. Reproduced from Osteoporos Int 2009;20:819-26 with permission from Springer.

10.3.209 DXA-based hip structural analysis of once-weekly bisphosphonate-treated postmenopausal women with low bone mass

Bonnick SL, Beck TJ, Cosman F, Hochberg MC, Wang H, de Papp AE
Osteoporos Int 2009;20:911-21

10.3.210 Theoretical analysis of alendronate and risedronate effects on canine vertebral remodeling and microdamage

Wang X, Erickson AM, Allen MR, Burr DB, Martin RB, Hazelwood SJ
J Biomech 2009;42:938-44

10.3.211 The bisphosphonate zoledronic acid decreases tumor growth in bone in mice with defective osteoclasts
Hirbe AC, Roelofs AJ, Floyd DH, Deng H, Becker SN, Lanigan LG, Apicelli AJ, Xu Z, Prior JL, Eagleton MC, Piwnica-Worms D, Rogers MJ, Weilbaecher K
Bone 2009;44:908-16

10.3.212 Intravenous pamidronate in osteogenesis imperfecta type VII
Cheung MS, Glorieux FH, Rauch F
Calcif Tissue Int 2009;84:203-9

10.3.213 PTH(1-34) replacement therapy in a child with hypoparathyroidism caused by a sporadic calcium receptor mutation
Theman TA, Collins MT, Dempster DW, Zhou H, Reynolds JC, Brahim JS, Roschger P, Klaushofer K, Winer KK
J Bone Miner Res 2009;24:964-73

10.3.214 Parathyroid hormone enhances bone morphogenetic protein activity by increasing intracellular 3', 5'-cyclic adenosine monophosphate accumulation in osteoblastic MC3T3-E1 cells
Nakao Y, Koike T, Ohta Y, Manaka T, Imai Y, Takaoka K
Bone 2009;44:872-7

10.3.215 PTH and PTH antagonist induce different conformational changes in the PTHR1 receptor
Thomas BE, Sharma S, Mierke DF, Rosenblatt M
J Bone Miner Res 2009;24:925-34

10.3.216 Decreased bone turnover despite persistent secondary hyperparathyroidism during prolonged treatment with imatinib
O'Sullivan S, Horne A, Wattie D, Porteous F, Callon K, Gamble G, Ebeling P, Browett P, Grey A
J Clin Endocrinol Metab 2009;94:1131-6

10.3.217 Green tea polyphenols mitigate deterioration of bone microarchitecture in middle-aged female rats
Shen CL, Yeh JK, Stoecker BJ, Chyu MC, Wang JS
Bone 2009;44:684-90

10.3.218 Demineralized dentin matrix acts as a scaffold for repair of articular cartilage defects
Yagihashi K, Miyazawa K, Togari K, Goto S
Calcif Tissue Int 2009;84:210-20

10.3.219 Effects of cod bone gelatin on bone metabolism and bone microarchitecture in ovariectomized rats
Han X, Xu Y, Wang J, Pei X, Yang R, Li N, Li Y
Bone 2009;44:942-7

10.3.220 A local bone anabolic effect of rhFGF2-impregnated gelatin hydrogel by promoting cell proliferation and coordinating osteoblastic differentiation
Kodama N, Nagata M, Tabata Y, Ozeki M, Ninomiya T, Takagi R
Bone 2009;44:699-707

10.3.221 Effect of oral erythromycin therapy in patients with aseptic loosening of joint prostheses
Ren W, Blasier R, Peng X, Shi T, Wooley PH, Markel D
Bone 2009;44:671-7

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 3, 2009

Exercise

10.3.222 Maintenance of exercise-induced benefits in physical functioning and bone among elderly women
Karinkanta S, Heinonen A, Sievanen H, Uusi-Rasi K, Fogelholm M, Kannus P
Osteoporos Int 2009;20:665-74

Maintenance of exercise-induced benefits in physical functioning and bone structure was assessed one year after cessation of 12-month randomized controlled exercise intervention. 149 women 70-78 years of age participated in the 12-month exercise RCT and 120 (81%) completed follow-up. Exercise increased dynamic balance by 7% in the combination resistance and balance-jumping training group (COMB). At the follow-up, a 4% (95% CI: 1-8%) gain compared with the controls was still seen, while the exercise-induced isometric leg extension force and self-rated physical functioning benefits disappeared. During the intervention, at least twice a week trained COMB subjects obtained a 2% benefit in tibial shaft bone strength index compared to the controls. A half of this benefit seemed to be maintained at the follow-up.

10.3.223 Addition of aerobic exercise to a weight loss program increases BMD, with an associated reduction in inflammation in overweight postmenopausal women
Silverman NE, Nicklas BJ, Ryan AS
Calcif Tissue Int 2009;84:257-65

This was a nonrandomized controlled trial. 86 overweight and obese postmenopausal women (50-70 years of age; BMI, 25-40 kg/m^2) participated in a weight loss (WL; n=40) or weight loss plus walking (WL+AEX; n=46) program. Weight decreased in the WL ($p<0.001$) and WL+AEX ($p<0.001$) groups. VO(2) max increased ($p<0.001$) after WL+AEX. There was a 2% increase in femoral neck BMD in the WL+AEX group ($p=0.001$), which was different from the WL group. The change in sTNFR1 was associated with the change in femoral neck BMD ($p<0.05$). The change in VO(2) max was an independent predictor of the change in femoral neck BMD.

10.3.224 An assessment of the osteogenic index of therapeutic exercises for stroke patients: Relationship to severity of leg motor impairment
Lau RW, Pang MY
Osteoporos Int 2009;20:979-87

Sixty stroke patients were categorized into group 1 (moderate to severe leg motor impairment) and group 2 (mild to moderate impairment). Each subject performed five exercises in random order: walking at self-selected speed, walking at maximal speed, stepping onto a 6-in. riser, sit-to-stand, and jumping. The peak ground reaction force (GRF) on the hemiparetic side and the number of loading cycles achieved in 1 min were determined. The osteogenic index (OI) was computed for each exercise, based on the formula: OI=Peak GRF (in body weight) x In (number of loading cycles + 1). For group 1, stepping had higher OI than other exercises ($p<0.001$). For group 2, both walking at maximal speed and stepping had significantly higher OI than other exercises ($p<0.001$).

10.3.225 Minimum level of jumping exercise required to maintain exercise-induced bone gains in female rats
Ooi FK, Singh R, Singh HJ, Umemura Y
Osteoporos Int 2009;20:963-72

Twelve groups of 12-week old rats (n=10 rats per group) were given either no exercise for 8 (8S) or 32 weeks (32S), or received 8 weeks of standard training program (8STP) that consisted of 200 jumps per week, given at 40 jumps per day for 5 days per week, followed by 24 weeks of exercise at loads of either 40 or 20 or 10 jumps per day, for either 5, or 3, or 1 day/week. Bone mass, strength, midshaft periosteal perimeter and cortical area were ($p<0.05$) higher in the rats given 8STP than that in the 8S group. The minimal level of exercise required to maintain the bone gains was 31, 36, 25, and 21 jumps per week for mass, strength, periosteal perimeter and cortical area, respectively.

10.3.226 Short-term exercise in mice increases tibial post-yield mechanical properties while two weeks of latency following exercise increases tissue-level strength
Wallace JM, Ron MS, Kohn DH
Calcif Tissue Int 2009;84:297-304

Beginning at 8 weeks of age, exercise consisted of running on a treadmill (30 min/day, 12 m/min, 5° incline) for 21 consecutive days. At the end of running and 2 weeks later, in the cortical bone of the tibial mid-diaphyses of B6; 129 male mice, changes due to exercise and latency following exercise were assayed by mechanical tests and analyses of cross-sectional geometry. Exercise increased structural post-yield deformation compared with control mice, without changes in bone size or shape, suggesting that exercised-induced changes in pre-existing bone quality were responsible. Over the 2-week latency period, no growth-related changes were noted in control mice, but exercise-induced changes resulted in increased tissue stiffness and strength vs. mice sacrificed immediately after exercise ended. Exercise followed by latency can alter strength, stiffness, and ductility of bone independent of changes in size or shape, suggesting that exercise may be a practical way to increase the quality of the bone extracellular matrix.

10.3.227 Olympic fencers: Adaptations in cortical and trabecular bone determined by quantitative computed tomography
Chang G, Regatte RR, Schweitzer ME
Osteoporos Int 2009;20:779-85

10.3.228 The polycystic kidney disease 1 (Pkd1) gene is required for the responses of osteochondroprogenitor cells

to midpalatal suture expansion in mice
Hou B, Kolpakova-Hart E, Fukai N, Wu K, Olsen BR
Bone 2009;44:1121-33

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Men

10.3.229 Once-weekly risedronate in men with osteoporosis: Results of a 2-year, placebo-controlled, double-blind, multicenter study
Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD
J Bone Miner Res 2009;24:719-25

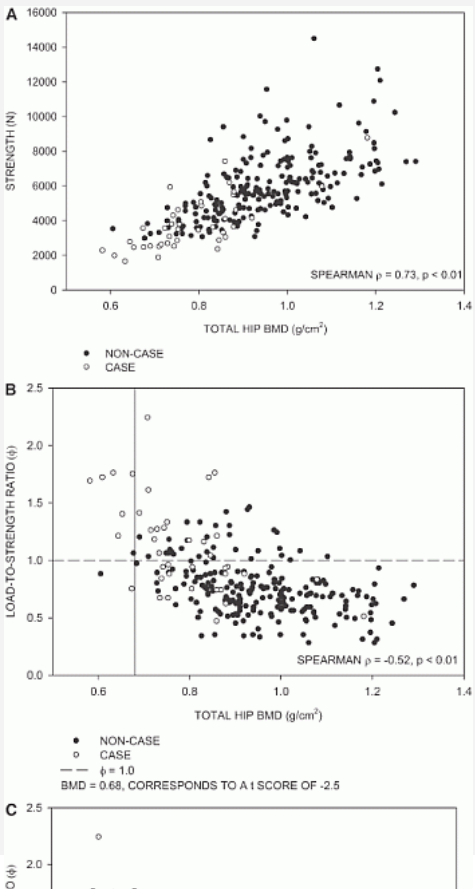
This multinational, 2-yr, randomized, double-blind, placebo-controlled study was conducted to determine the efficacy and safety of 35 mg once-a-week risedronate in men with osteoporosis. Patients had to be men ≥30 yr old, with lumbar spine T-score ≤ -2.5 and femoral neck T-score ≤ -1 SD or lumbar spine T-score ≤ -1 and femoral neck T-score ≤ -2 SD. Patients were randomized 2:1 to risedronate 35 mg once a week or placebo for 2 yr; all took 1000 mg calcium and 400-500 IU vitamin D daily. There were 284 men enrolled. Treatment increased spine BMD compared with placebo (4.5%; 95% CI: 3.5%, 5.6%; p<0.001). There was a (p<0.01) reduction from baseline in BTMs for the risedronate group compared with placebo at all time points. Risedronate therapy was well tolerated and was rapidly effective as indicated by BTM decreases at month 3 and BMD increases at month 6.

10.3.230 LRP5 polymorphisms and response to risedronate treatment in osteoporotic men
Kruk M, Ralston SH, Albagha OM
Calcif Tissue Int 2009;84:171-9

In 249 osteoporotic or osteopenic men who participated in a 24-month randomized double blind placebo-controlled trial of risedronate, V667M (rs4988321) and A1330V (rs3736228) regions were assessed and the latter was association with hip BMD at baseline. Subjects with the 1330 Val/Val genotype had 8.4% higher total-hip BMD compared with the other genotype groups (P=0.009), and similar associations were observed at the femoral neck (P=0.01) and trochanter (P=0.002). There was no association between A1330V and spine BMD, however, or between the V667M polymorphism and BMD at any site. The difference in hip BMD between A1330V genotype groups remained significant throughout the study, but there was no evidence of a genotype-treatment interaction in either risedronate- or placebo-treated patients.

10.3.231 Finite element analysis of the proximal femur and hip fracture risk in older men
Orwoll ES, Marshall LM, Nielson CM, Cummings SR, Lapidus J, Cauley JA, Ensrud K, Lane N, Hoffmann PR, Kopperdahl DL, Keaveny TM
J Bone Miner Res 2009;24:475-83

Low aBMD is associated with risk of hip fracture. Finite element (FE) analysis of QCT scans provides a measure of hip strength. A prospective case-cohort study of all first hip fractures (n=40) and a random sample (n=210) of nonfracture cases from 3549 community-dwelling men ≥65 yr of age used baseline QCT scans of the hip (mean follow-up, 5.6 yr). Both femoral strength (HR per SD change=13.1; 95% CI: 3.9-43.5) and the load-to-strength ratio (HR=4.0; 95% CI: 2.7-6.0) were associated with hip fracture risk, as was aBMD (HR=5.1; 95% CI: 2.8-9.2). After adjusting for age, BMI, and study site, the associations remained (femoral strength HR=6.5, 95% CI: 2.3-18.3; load-to-strength ratio HR=4.3, 95% CI: 2.5-7.4; aBMD HR=4.4, 95% CI: 2.1-9.1). When adjusted additionally for aBMD, the load-to-strength ratio remained associated with fracture (HR=3.1, 95% CI: 1.6-6.1).



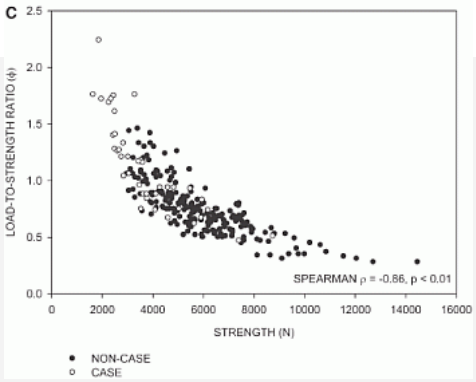


Fig. 10.3.231a Correlations between baseline measures of the hip. (A) Femoral strength vs. total hip aBMD. (B) Load-to-strength ratio vs. aBMD. (C) Load-to-strength ratio vs. femoral strength. Reproduced from J Bone Miner Res 2009;24:475-83 with permission of the American Society of Bone and Mineral Research.

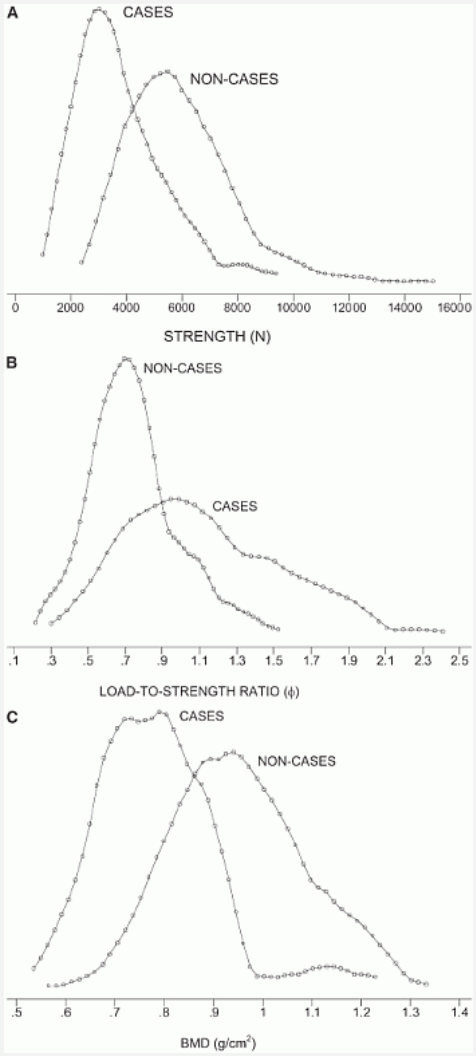


Fig. 10.3.231b The distributions of the hip measurements at baseline using Kernel density estimate curves in men with subsequent hip fractures and nonfractured men. Kernel estimators can be regarded as nonparametric histogram smoothers and are used here to compare the distributions of baseline hip measures in the two groups. (A) Femoral strength. (B) Load-to-strength ratio. (C) Total hip aBMD by DXA. Reproduced from J Bone Miner Res 2009;24:475-83 with permission of the American Society of Bone and Mineral Research.

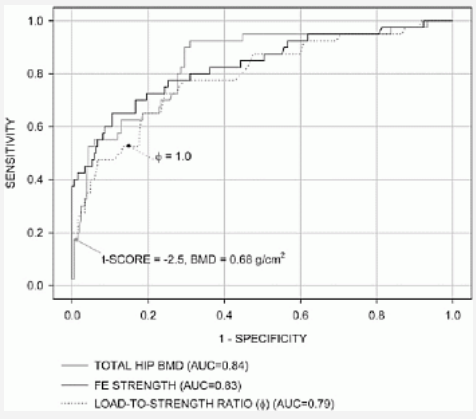


Fig. 10.3.231c ROC curves for hip fracture prediction using the three baseline hip measures. Conventional cut-offs of hip fracture

risk, a total hip DXA T-score of T=–2.5 (male reference), and the theoretical cut point of Φ=1:0 for the load-to-strength ratio, are indicated. Reproduced from J Bone Miner Res 2009;24:475-83 with permission of the American Society of Bone and Mineral Research.

10.3.232 Mapping the prescriptiome to fractures in men – A national analysis of prescription history and fracture risk
Abrahamsen B, Brixen K
Osteoporos Int 2009;20:585-97

In a nationwide population-based case-control study collecting fracture data from the Danish National Hospital Discharge Register and prescriptions from the National Prescriptions Database (1995-2000), 15,716 men and age- and sex-matched controls (n=47,149) were studied: 3.2 million redemptions of prescriptions for 1073 different drugs were obtained. The analysis confirmed associations between fracture risk and use of sedatives, anti-epileptics, antipsychotics, anxiolytics, SSRI, opioids and other analgesics, loop diuretics, and glucorticoids. New associations were also found. We observed an odds ratio (OR [95% CI] for any fracture) for fracture in users of dopaminergic agents (1.6 [1.3-1.9]) and iron compounds (1.2 [1.1-1.5]). The largest impact on fracture risk at population level was exerted by loop diuretics and analgesics.

10.3.233 Age-related changes in sex steroid levels influence bone mineral density in healthy Indian men
Venkat K, Desai M, Arora MM, Singh P, Khatkhatay MI
Osteoporos Int 2009;20:955-62

Total testosterone (TT), estradiol (E(2)), sex hormone-binding globulin (SHBG), PTH, osteocalcin (OC), and C-terminal telopeptide (CTX) were measured in 330 men aged 20-55 years and correlated with BMD measured by DXA. Both Bio-T (1% per year) and Bio-E(2) (0.8% per year) levels decreased in ageing men, whereas TT (0.4% per year) and E(2) (0.3% per year) levels decreased only marginally. SHBG (1.4% per year) and PTH (1% per year) levels increased with age. Serum TT (r=0.19, p=0.01) and Bio-T (r=0.2, p=0.01) levels were associated positively with BMD at spine, whereas E(2) and Bio-E(2) levels were associated with BMD at spine [E (2) (r=0.31, p<0.0001); Bio-E(2) r=0.37, p<0.0001] and femur (E(2) r=0.26, p=0.001; Bio-E (2) r=0.27, p=0.001). Men in the lowest quartile of Bio-E(2) were associated with lower BMD and higher bone turnover. Age-related decrease in bioavailable sex steroid levels is associated with BMD in healthy Indian men. Bio-E(2) was found to be an independent predictor of BMD.

10.3.234 Bone mineral density of the spine and femur in a group of healthy Moroccan men
El Maghraoui A, Ghazi M, Gassim S, Mounach A, Ghozlani I, Nouijai A, Achemlal L, Bezza A, Dehhaoui M
Bone 2009;44:965-9

A cross-sectional study of 592 Moroccan men aged between 20 and 79 years. Moroccan men showed the expected decline in BMD with age after peaking at 20-29 years age group. Every anatomical region has a different rate of bone loss: lumbar spine (0.3% per year) femoral neck (0.6%), trochanter (0.3%), and total hip (0.4%). The lumbar spine and femoral subregions BMD exhibited increases from 0.3 to 0.5% per kilogram of body weight. In the spine, the US/European Lunar reference values classified a larger proportion of men as osteoporotic (18.1% vs. 7.4%) while using the Arabic Lunar reference values, only 7.8% were classified as osteoporotic. However, using Arabic curve for the femurs resulted in underdiagnosis of osteoporosis (1.8% vs. 6.0%), whereas the US/European Lunar reference values classified men as osteoporotic in 3.9% and 5.3%, respectively.
In comparison with the other Countries, the spine BMD of Moroccan men were slightly lower than Iranian's, Europeans and Brazilians but higher than the Saudi and Lebanese males. We found BMD values taken at the lumbar spine to be around 4% lower than European values between ages 50 and 59 years, and 10% lower for older subjects. These values were 4-6% higher than Saudis/Lebanese values between ages 20-39. For older subjects, Moroccan values were more than 10% higher than Saudis and almost similar to Lebanese. Femoral neck BMD values were 8% higher in young adults (age 20-39 years) to US/Saudis/ Lebanese values, but about 10% lower in ages over 60 to US values, whereas it was similar to Saudis and Lebanese values.

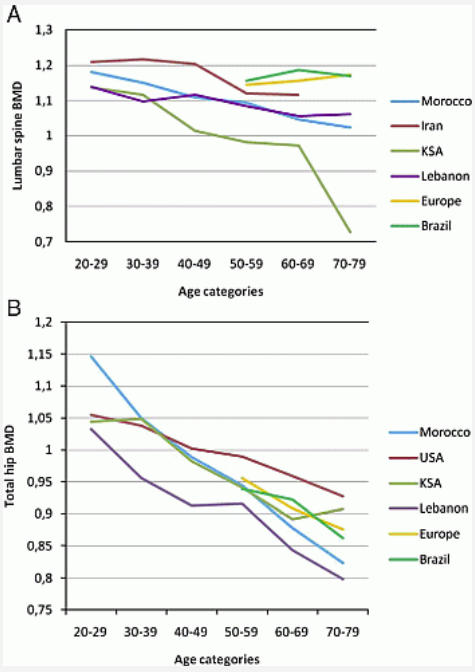


Fig. 10.3.234 BMD (g/cm^2) of Moroccan men at the spine (A) and femur (B) compared with other men from different countries. Reproduced from Bone, 44:965-9, Copyright (2009), with permission from Elsevier.

10.3.235 Mineralization and bone resorption are regulated by the androgen receptor in male mice
Chiang C, Chiu M, Moore AJ, Anderson PH, Ghasem-Zadeh A, McManus JF, Ma C, Seeman E, Clemens TL, Morris HA, Zajac

JD, Davey RA
J Bone Miner Res 2009;24:621-31

Deleted androgen receptor (AR) from terminally differentiated, mineralizing osteoblasts had decreased femoral trabecular bone volume because of a reduction in trabecular number at 6, 12, and 24 wk of age, indicative of increased bone resorption. The effects of AR inactivation in mineralizing osteoblasts was most marked in the young mutant mice at 6 wk of age when rates of bone turnover are high, with a 35% reduction in trabecular bone volume, decreased cortical thickness, and abnormalities in the mineralization of matrix, characterized by increased unmineralized bone matrix and a decrease in mineralizing surface. This impairment in bone architecture persisted throughout adulthood despite a compensatory increase in osteoblast activity. Androgens act through the AR in mineralizing osteoblasts to maintain bone by regulating bone resorption and the coordination of bone matrix synthesis and mineralization.

10.3.236 Risk factors for low BMD in healthy men age 50 years or older: A systematic review
Papaioannou A, Kennedy CC, Cranney A, Hawker G, Brown JP, Kaiser SM, Leslie WD, O'Brien CJ, Sawka AM, Khan A, Siminoski K, Tarulli G, Webster D, McGowan J, Adachi JD
Osteoporos Int 2009;20:507-18

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Reviews

General

10.3.237 Targeting bone remodeling for the treatment of osteoporosis: Summary of the proceedings of an ASBMR workshop
Bilezikian JP, Matsumoto T, Bellido T, Khosla S, Martin J, Recker RR, Heaney R, Seeman E, Papapoulos S, Goldring SR
J Bone Miner Res 2009;24:373-85

10.3.238 Local communication on and within bone controls bone remodeling
Henriksen K, Neutzsky-Wulff AV, Bonewald LF, Karsdal MA
Bone 2009;44:1026-33

10.3.239 Wnt signaling and osteoarthritis
Luyten FP, Tylzanowski P, Lories RJ
Bone 2009;44:522-7

Remodelling Markers

10.3.240 Bone turnover markers: Understanding their value in clinical trials and clinical practice
Civitelli R, Armamento-Villareal R, Napoli N
Osteoporos Int 2009;20:843-51

10.3.241 Use of bone turnover markers in the real world: Are we there yet?
Meier C, Seibel MJ, Kraenzlin ME
J Bone Miner Res 2009;24:386-8

Bone Formation

10.3.242 Role of the osteoblast lineage in the bone marrow hematopoietic niches
Wu JY, Scadden DT, Kronenberg HM
J Bone Miner Res 2009;24:759-64

Bone Resorption

10.3.243 Role of RANKL in bone diseases
Anandarajah AP
Trends Endocrinol Metab 2009;20:88-94

Risk Factors

10.3.244 FRAX® and its applications to clinical practice
Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E
Bone 2009;44:734-43

10.3.245 Bone loss without the loss of bone mineral material? A new perspective on anorexia nervosa
Bolotin HH
Bone 2009;44:1034-42

10.3.246 Alcohol and recommendations for bone health: Should we still exercise caution?
Macdonald HM
Am J Clin Nutr 2009;89:999-1000

Treatment

10.3.247 From randomized controlled trials to observational studies
Silverman SL
Am J Med 2009;122:114-20

10.3.248 Selecting patients for osteoporosis therapy
Silverman S
J Bone Miner Res 2009;24:765-7

10.3.249 Impact of osteoporosis treatment adherence on fracture rates in North America and Europe
Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL
Am J Med 2009;122:S3-13

10.3.250 Comparing non-vertebral fracture risk reduction with osteoporosis therapies: Looking beneath the surface
Sebba A
Osteoporos Int 2009;20:675-86

10.3.251 Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence
Inderjeeth CA, Foo AC, Lai MM, Glendenning P
Bone 2009;44:744-51

10.3.252 Treatment of osteoporosis with parathyroid hormone and teriparatide
Pleiner-Duxneuner J, Zwettler E, Paschalis E, Roschger P, Nell-Duxneuner V, Klaushofer K
Calcif Tissue Int 2009;84:159-70

10.3.253 Efficacy of bisphosphonates in reducing fracture risk in postmenopausal osteoporosis
Bilezikian JP
Am J Med 2009;122:S14-21

10.3.254 Safety of bisphosphonates in the treatment of osteoporosis
Recker RR, Lewiecki EM, Miller PD, Reiffel J
Am J Med 2009;122:S22-32

10.3.255 Osteonecrosis of the jaw and the role of bisphosphonates: A critical review
Silverman SL, Landesberg R
Am J Med 2009;122:S33-45

10.3.256 Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw
Baim S, Miller PD
J Bone Miner Res 2009;24:561-74

10.3.257 Inhibiting the inhibitor: A new route to bone anabolism
Jilka RL
J Bone Miner Res 2009;24:575-7

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Campaign Description

Campaign Vision

The IOF Invest in Your Bones campaign vision is of a world without osteoporotic fractures through increasing awareness and understanding of osteoporosis. The emphasis is also on improving quality of life and on the healthcare budget. In addition, the Invest in Your Bones campaign aims to sensitise health professionals, including general practitioners, radiologists and orthopaedic surgeons.

About the Campaign

In 2002, IOF inaugurated the first phase of the Invest in Your Bones Campaign. The campaign, now in its fourth phase (beginning in 2008), supports projects aimed at improving access to, and reimbursement of, diagnosis and proven therapies in individuals at high risk of fragility fracture. It has a geographic focus on France, Germany, Italy, Spain and the UK.

The campaign also helps the IOF to support the 'Call for Action' at the EU, through various policy and lobbying activities, including support to the European Parliament Osteoporosis Interest Group and EU Osteoporosis Consultation Panel.

Other key ongoing projects supported by the campaign include the Osteoporosis Education Program to Improve the Recognition and Reporting of Vertebral Fractures by Radiologists; an initiative involving orthopaedic surgeons aimed at optimizing the care of fragility fracture patients; the development of health economics studies in osteoporosis; and support to the development of new guidelines for assessing fracture risk in individuals.

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Recent Campaign Activities

France (en français)

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France

Interview du Professeur Christian Roux, **Université Paris-Descartes, Hôpital Cochin, Paris, France**

Question au Professeur Roux: Que penser du FRAX ® tool?

Le FRAX ® est un outil disponible sous forme d'algorithme accessible sur internet, développé par les experts de l'OMS à partir d'un très grand nombre de sujets issus de cohortes internationales, afin d'établir une valeur absolue de probabilité de fractures. Il utilise les facteurs de risque de fracture les plus pertinents, partant du constat que :

- la mesure de la densité minérale osseuse est un outil excellent dans la prédiction du risque fracturaire, mais peu sensible, un grand nombre de fractures survenant chez des sujets ayant une densité osseuse normale ou peu diminuée.
- certains facteurs de risque, indépendants de la densité osseuse, sont importants pour l'évaluation du risque fracturaire.

Le développement du FRAX ® ayant inclus des données françaises, il est applicable à la population française. C'est un outil simple d'utilisation, permettant de définir un risque absolu de fracture à 10 ans pour un individu donné. Validé chez des sujets sans traitement anti-ostéoporotique, il est important de rappeler que le FRAX ® ne doit pas être utilisé pour évaluer la réduction du risque fracturaire sous traitement.

Son intérêt pédagogique est indéniable, permettant de mettre en perspective l'importance des facteurs de risque clinique et la nécessité de la densitométrie. Il présente néanmoins certaines limites : l'absence de prise en compte de la durée et de la dose de corticothérapie, du nombre et du type de fractures prévalentes, de la densité osseuse rachidienne alors qu'il n'est pas rare que les valeurs soient abaissées au rachis et normales ou subnormales au col ; on peut dire que ces situations représentent une contre-indication à l'usage du FRAX ® , en sous-estimant le risque fracturaire. Enfin, la mesure de densité osseuse prise en compte est celle du col fémoral, site de loin le plus difficile à mesurer et siège du plus grand nombre d'erreurs en pratique courante. Ainsi, on peut proposer l'utilisation du FRAX ® dans les situations pour lesquelles la prise de décision thérapeutique est difficile, et chez les femmes les plus jeunes afin de confirmer la faiblesse du risque et étayer l'absence d'indication thérapeutique.

Si le FRAX ® va permettre de comparer la sévérité des populations des différentes études, son usage à visée thérapeutique en pratique courante nécessite encore de définir un seuil de décision, qui n'est pas consensuel à ce jour et qui potentiellement peut varier en fonction de l'âge. Si on considère la valeur du FRAX ® donnant une probabilité de fracture équivalente à celle des essais thérapeutiques, on peut proposer des seuils décisionnels de 15 à 20% pour les fractures majeures et 5 à 7% pour le col fémoral. Cette proposition ne tient que jusqu'à la validation des seuils français.

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International Osteoporosis Foundation

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Invest In Your Bones Campaign

- Campaign Description

IOF News

IOF WCO–ECCEO10
May 5 - 8, 2010
Florence, Italy
More information

19th IOF Advanced Training Course on Osteoporosis
February 2 - 4, 2010
Lyon, France
More information

2010 IOF-Servier Young Investigator Research Grant

Applications are now being accepted. This grant supports young scientists who are carrying out outstanding original research of international relevance in the field of osteoporosis. More information

FRAX® – WHO Fracture Risk Assessment Tool
Helping health professionals worldwide to improve identification of patients at high risk of fracture for treatment . More information

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Ozymandias

I met a traveller from an antique land
Who said: Two vast and trunkless legs of stone
Stand in the desert. Near them on the sand,
Half sunk, a shatter'd visage lies, whose frown
And wrinkled lip and sneer of cold command
Tell that its sculptor well those passions read
Which yet survive, stamp'd on these lifeless things,
The hand that mock'd them and the heart that fed.
And on the pedestal these words appear:
"My name is Ozymandias, king of kings:
Look on my works, ye Mighty, and despair!"
Nothing beside remains: round the decay
Of that colossal wreck, boundless and bare,
The lone and level sands stretch far away.

Percy Bysshe Shelley

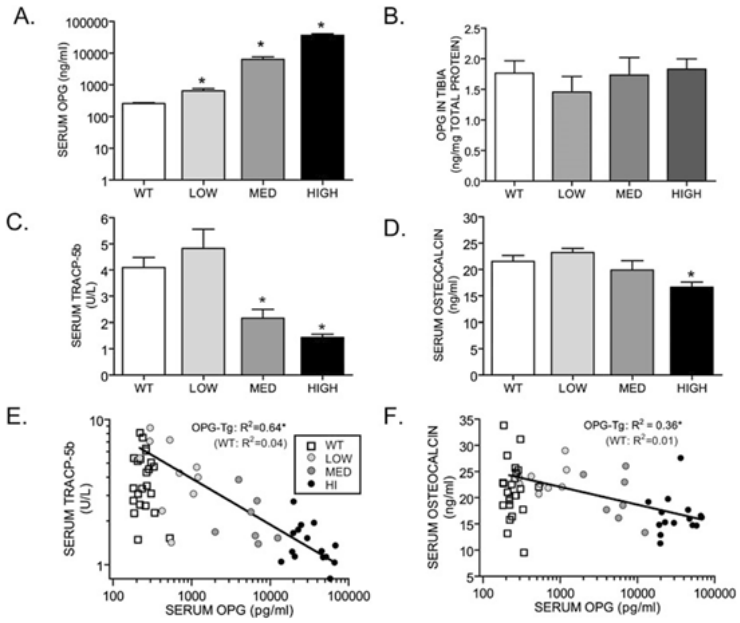
Overview

An anabolic future

Eddleston et al report that Scl-Abl prevents inflammation-induced bone loss in a model of colitis in animals. Scl-Abl-treated animals had a higher femoral BMD and reversed the decline of both intrinsic and extrinsic mechanical properties of the femur when initiated after colitis associated bone loss had occurred so strength was no different to noncolitic controls. J Bone Miner Res 2009;24:1662-71

OPG is not an option

Ominsky et al report overexpression of OPG reduced osteoclasts and turnover, and increased peak load in vertebrae; but in femurs of OPG-Tg rats, osteopetrotic changes, reduced periosteal perimeter (-6%) and reduced bending strength were observed. J Bone Miner Res 2009;24:1234-46

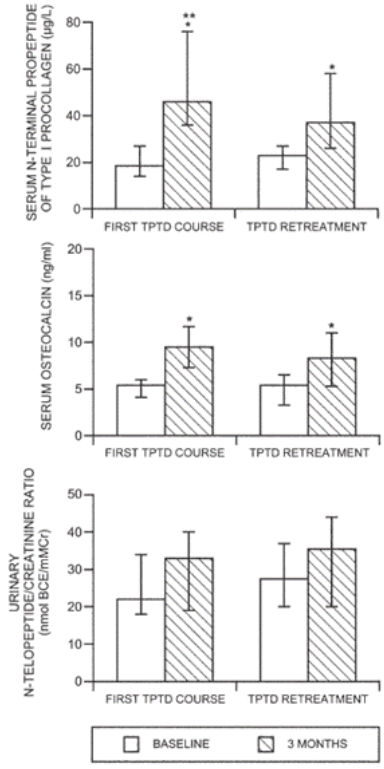


Biochemical markers of bone turnover. Serum was collected from 1-yr-old WT (n=23) and OPG-Tg rats (n=32) at necropsy. Transgenic groups were binned by serum OPG level (low, medium, and high). A tibia was harvested for analysis of OPG protein concentration. (A) Increasing levels of serum OPG in OPG-Tg rats. (B) No difference in OPG concentrations in whole bone protein extracts from OPG-Tg rats vs. WT controls. (C and D) OPG-Tg rats had reduced serum levels of the osteoclast marker TRACP5b and the formation marker osteocalcin. Data represent means±SE. *Significantly different from WT littermates, p<0.05. (E and F) Serum OPG concentrations in OPG-Tg rats, but not in WT controls, showed significant inverse correlations with serum TRACP5b and with serum osteocalcin. Regression lines represent OPG-Tg rats only. *Significant correlation, p<0.01. Reproduced from J Bone Miner Res 2009;24:1234-46 with permission of the American Society of Bone and Mineral Research.

Blunting or no blunting the response to PTH

Finkelstein et al compared 30 months of alendronate (ALN), teriparatide (TPTD) or both. TPTD was stopped, then administered to all subjects. BMD increased 12.5% and 16.9%, respectively, during the first 12 months of TPTD and 5.2% and 6.2%, respectively, during retreatment. Increases in osteocalcin, P1NP, and N-telopeptide were greater during the first tTPTD administration. The response to TPTD is attenuated when re-administered after a 12-month hiatus. J Clin Endocrinol Metab 2009;94:2495-501

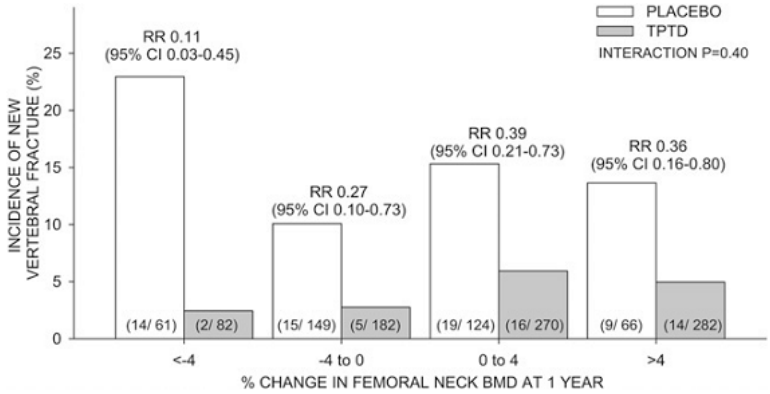
Cosman et al report 126 women taking ALN continued ALN and received daily TPTD, cyclic TPTD (3-mo cycles), or ALN alone for 15 mo. Of the 72 patients who completed either original TPTD regimen, 49 completed a 12-mo follow-up on continued ALN alone. 32 patients recruited into the retreatment protocol and 27 completed another course of TPTD daily for 15 mo. P1NP and osteocalcin increased during both TPTD courses with median 3-mo increments of 120% and 72% above baseline during the original course and 60% and 40% above baseline during retreatment, respectively. Mean spine BMD increments were 6.2% after the first daily course and 4.7% after retreatment and 4.1% after the first course of cyclic TPTD and 4.9% after retreatment. Retreatment stimulates bone formation and increases spine BMD to a similar extent as seen during the original TPTD course. J Bone Miner Res 2009;24:1110-5



Median levels of biochemical bone turnover indices (PINP, OC, and NTX) at baseline and 3 mo during the first TPTD course and during the TPTD retreatment (daily and cyclic groups pooled). *p<0.001 vs. baseline; **p<0.001 for increment

Median levels of biochemical bone turnover indices (PINP, OC, and NTX) at baseline and 3 mo during the first TPTD course and during the TPTD retreatment (daily and cyclic groups pooled). *p<0.001 vs. baseline; **p<0.001 for increment during first TPTD course vs. TPTD retreatment (by signed rank test). Reproduced from J Bone Miner Res 2009;24:1110-5 with permission of the American Society of Bone and Mineral Research.

Watts et al report that decreases of >4% femoral neck (FN) BMD were less common in women receiving TPTD (10%) vs. placebo (16%, p<0.05), yet women on TPTD who lost FN BMD had reductions in vertebral fracture (VF) risk (RR=0.11; 95% CI: 0.03-0.45). VF risk reduction with TPTD was similar across categories of FN BMD change from baseline at 12 mo (loss >4%, loss 0-4%, gain 0-4%, or gain >4%; interaction p=0.40). Irrespective of FN BMD loss or gain, TPTD-treated women had increases in LS BMD and P1NP. J Bone Miner Res 2009;24:1125-31



The incidence of new vertebral fractures in women treated with PL or TPTD by category of percent change in FN BMD at 1 yr. Women with paired baseline and postbaseline spinal radiographs who had FN BMD measurements at baseline and 1 yr are included in this analysis. The risk of new vertebral fractures was significantly reduced with TPTD compared with PL, irrespective of the percent change in femoral neck BMD. Reproduced from J Bone Miner Res 2009;24:1125-31 with permission of the American Society of Bone and Mineral Research.

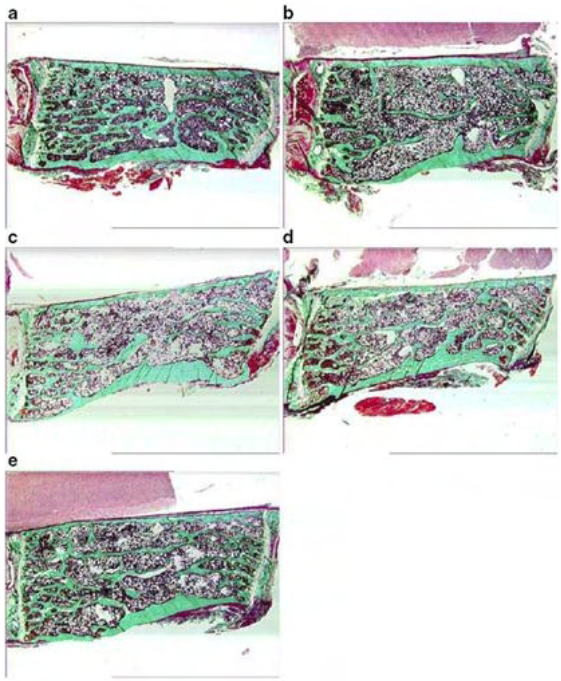
Denosumab and fracture risk reduction

Cummings et al report 7868 women between 60 and 90 years with T-score of <-2.5 at the spine or total hip were randomly assigned to 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. Denosumab reduced new VF; 2.3% in treated vs. 7.2% in placebo (RR, 0.32; 95% CI, 0.26-0.41; P<0.001) – decrease of 68%, reduced the risk of hip fracture; 0.7% vs. 1.2% in placebo (HR, 0.60; 95% CI, 0.37-0.97; P=0.04) – a decrease of 40%; and reduced the risk of nonVF, 6.5% vs. 8.0% in placebo (HR, 0.80; 95% CI, 0.67-0.95; P=0.01) – a decrease of 20%. N Engl J Med 2009;361:756-65

Bone strength and strontium ranelate

Meunier et al report 1649 osteoporotic women randomized to strontium ranelate (SrR) or placebo for 4 years followed by a 1-year treatment-switch period for half of the patients. Over 4 years, risk of VF was reduced by 33%. Among patients with two or more prevalent VFs, risk reduction was 36%. Lumbar BMD increased over 5 years in patients who continued with SrR, and decreased in patients who switched to placebo. Osteoporos Int 2009;20:1663-73

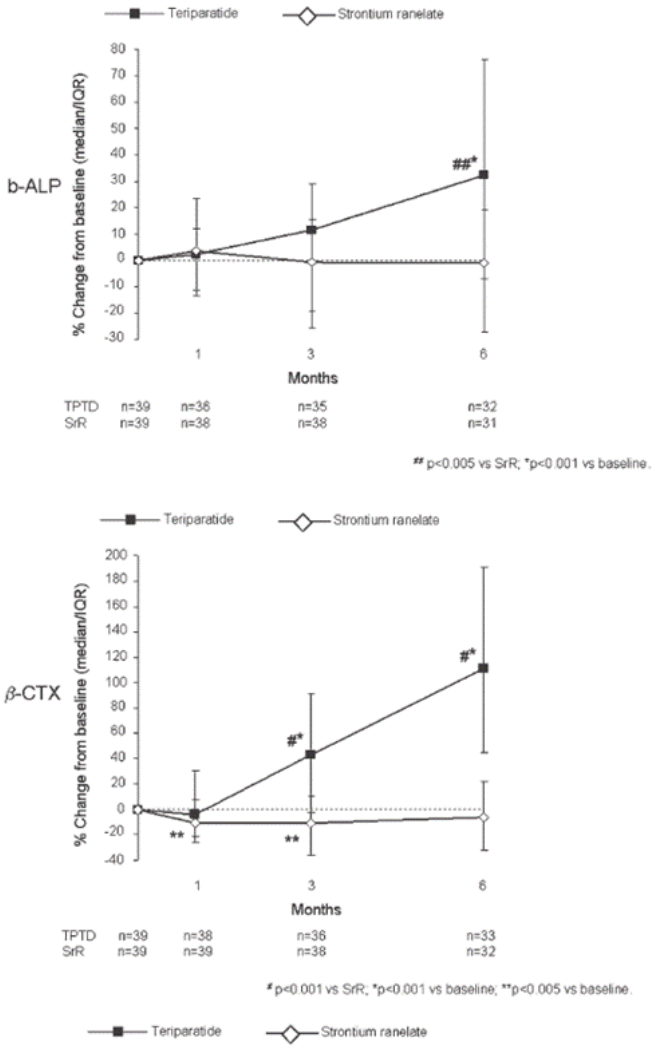
Bain et al report OVX rats treated for 52 weeks with 125, 250, or 625 mg SrR/kg were protected from deterioration in mechanical properties with energy necessary for fracture maintained at 625 mg/kg/day. This was related to a dose-dependent effect on bone volume, higher trabeculae number, and lower trabecular separation in SrR vs. OVX. Bone formation was maintained. Osteoporos Int 2009;20:1417-28



L3 lumbar vertebra representative pictures of each group (Goldner's trichrome staining, ×10 magnification). (a) SHAM animal; (b) OVX animal; (c, d, and e) strontium ranelatetreated animals with 125, 250, and 625 mg/kg/day, respectively. Reproduced from Osteoporos Int 2009;20:1417-28 with permission from Springer.

L3 lumbar vertebra representative pictures of each group (Goldner's trichrome staining, ×10 magnification). (a) SHAM animal; (b) OVX animal; (c, d, and e) strontium ranelatetreated animals with 125, 250, and 625 mg/kg/day, respectively. Reproduced from Osteoporos Int 2009;20:1417-28 with permission from Springer.

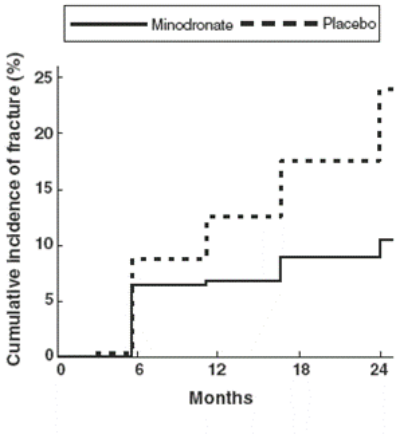
Recker et al compared daily TPTD and SrR in postmenopausal women with osteoporosis. Based on a single bone biopsies from 29 patients in the TPTD group and 22 in the SrR group after 6 mo, mineral apposition rate on trabeculae did not differ between treatments but did at the endocortical surface (17.22±3.06% and 9.70±2.07%, respectively, p=0.052). Cortical porosity was higher in the TPTD than SrR group. TPTD increased markers of bone formation and resorption, significant for P1NP after 1 mo (+57%, p<0.001). SrR induced small significant reductions in P1NP at 3 mo (-14%, p=0.005) and 6 mo (-19%, p<0.001) and in βCTX at 1 mo and 3 mo (-11%, for both, p<0.05). J Bone Miner Res 2009;24:1358-68



Changes in median values for biochemical markers of bone formation (PINP and b-ALP) and resorption (β-CTX) from baseline at 1, 3, and 6 mo of treatment with teriparatide or strontium ranelate. Vertical bars represent interquartile ranges (IQR). Reproduced from J Bone Miner Res 2009;24:1358-68 with permission of the American Society of Bone and Mineral Research.

Minodronate and fracture risk reduction

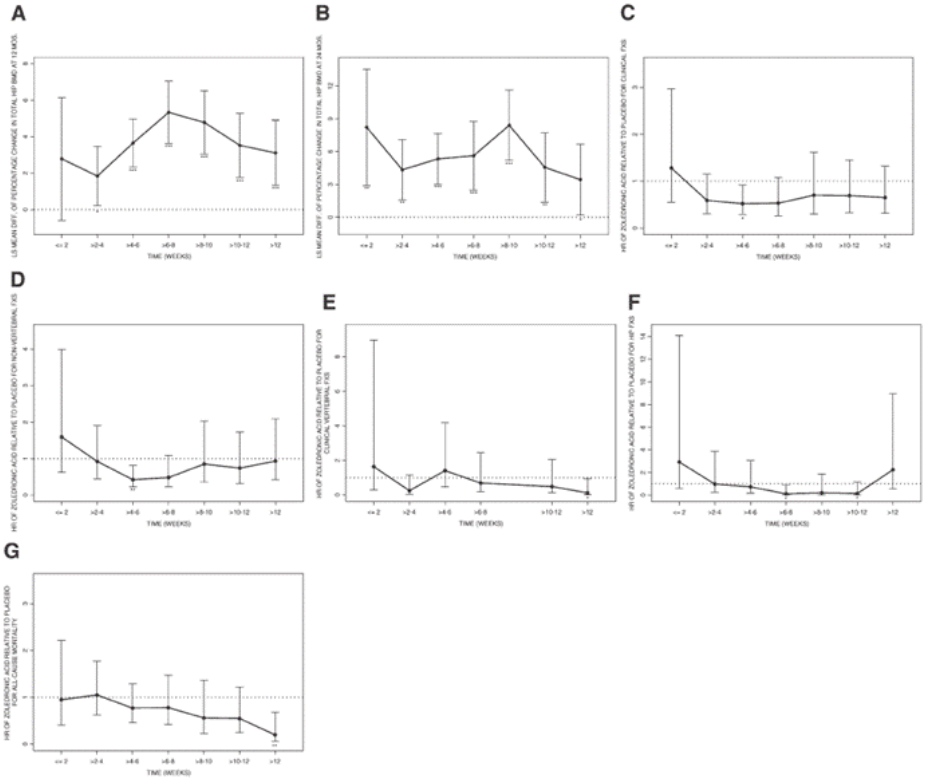
Matsumoto et al report that in 704 postmenopausal osteoporotic patients randomized to daily oral 1 mg minodronate (n=359) or placebo (n=345) for 24 mo, treatment reduced the risk of VFs by 59% (95% CI, 36.6-73.3%). Osteoporos Int 2009;20:1429-37



Kaplan-Meier estimates of the effect of daily oral 1 mg minodronate for 24 months on the risk of vertebral fractures in osteoporotic subjects. Cumulative incidence of vertebral fractures from the start of the study. Minodronate treatment reduced relative risk of vertebral fractures by 59%. Reproduced from Osteoporos Int 2009;20:1429-37 with permission from Springer.

Zolendronic acid, longevity and marked suppression of remodelling

Eriksen et al report that in 2127 patients (1065 treatment, 1062 placebo; mean age, 75 yr; 76% women and 24% men) within 90 days of surgery and annually, with a median follow-up time of 1.9 yr. post hoc analyses by 2-wk intervals showed a reduction of overall clinical fractures and mortality in patients receiving the first dose 2 wk or later after surgery. J Bone Miner Res 2009;24:1308-13



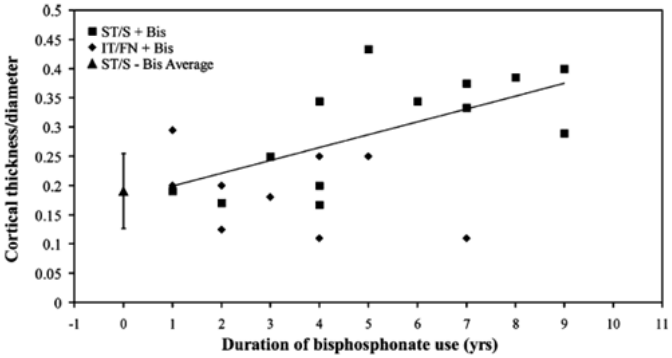
(A) Least-squares (LS) mean between-treatment differences (zoledronic acid vs. placebo) in the percentage change in total hip BMD at 12 mo by timing of first study drug infusion after hip fracture repair. (B) LS mean between-treatment differences (zoledronic acid vs. placebo) in the percentage change in total hip BMD at 24 mo by timing of first study drug infusion after hip fracture repair. (C) Hazard ratios (HRs) for reductions in clinical fractures by timing of first study drug infusion.† (D) HR for reductions in nonvertebral fractures by timing of first study drug infusion.† (E) HR for reductions in hip fractures by timing of first study drug infusion.† (F) HR for reductions in clinical vertebral fractures by timing of first study drug infusion.† (G) HR for reductions in death by timing of first study drug infusion.† **p<0.05; **p<0.01; ***p<0.001. †Significance determined based on log-rank test. Reproduced from J Bone Miner Res 2009;24:1308-13 with permission of the American Society of Bone and Mineral Research.

Allen et al report that in beagle dogs, monthly intravenous zoledronic acid (ZOL, 0.067 mg/kg); or oral ALN for 3 months, reduced remodelling; by 6 months ZOL produced nearly complete suppression (-99%). ZOL also suppressed remodelling in the rib cortex at 3 (-83%) and 6 (-85%) months. Remodelling suppression was greater than in ALN-treated animals; ALN and vehicle were not different. Compared across skeletal sites, the absolute level of remodelling suppression with ZOL treatment was greater at those sites with higher remodelling while the percent reduction was similar among the sites. J Bone Miner Res 2009 [Epub ahead of print]

Houston, we have a problem

Lenart et al report that 41 subtrochanteric and femoral shaft fracture cases were identified and matched to one intertrochanteric and femoral neck fracture each. Bisphosphonate use was observed in 15 of the 41 subtrochanteric/shaft cases, compared to nine of the 82 intertrochanteric/femoral neck controls (OR, 4.44). In 10 of the 15 subtrochanteric/shaft cases on a bisphosphonate,

cortical tenting x-ray pattern was associated with bisphosphonate use (OR, 15.33). Osteoporos Int 2009;20:1353-62



Correlation of duration of bisphosphonate use with normalized cortical thickness. Cortical thickness normalized to diameter for all subtrochanteric/shaft cases, and those intertrochanteric/femoral neck on bisphosphonate treatment was correlated to duration of bisphosphonate use. While blinded to all patient information, including bisphosphonate history, normalized cortical thickness was measured distal to the fracture site in each case. Duration represents length of time on bisphosphonate up to the date of fracture. The mean normalized cortical thickness of all subtrochanteric/shaft cases not. on a bisphosphonate was 0.19±0.048, represented as a triangle data point with error bars depicting ±SD. Spearman's rank coefficient, ρ, for correlation of subtrochanteric/shaft cases cortical thickness/diameter with duration of bisphosphonate use was 0.7, yielding P<0.001. ST/S+Bis subtrochanteric/shaft cases on a bisphosphonate, IT/FN+Bis intertrochanteric/femoral neck controls on a bisphosphonate, ST/S−Bis Average mean value for subtrochanteric/shaft not on a bisphosphonate. Reproduced from Osteoporos Int 2009;20:1353-62 with permission from Springer.

Repeating BMD is unnecessary

Bell et al report that 6459 postmenopausal women showed mean effect of 3 years ALN was to increase hip BMD by 0.030 g/cm^2. There was small between-person variation compared with within-person variation. ALN increased hip bone density ≥0.019 g/cm^2 in 97.5% of patients. Monitoring BMD in postmenopausal women in the first 3 years after starting treatment is unnecessary. BMJ 2009;338:b2266

Stroke and raloxifene

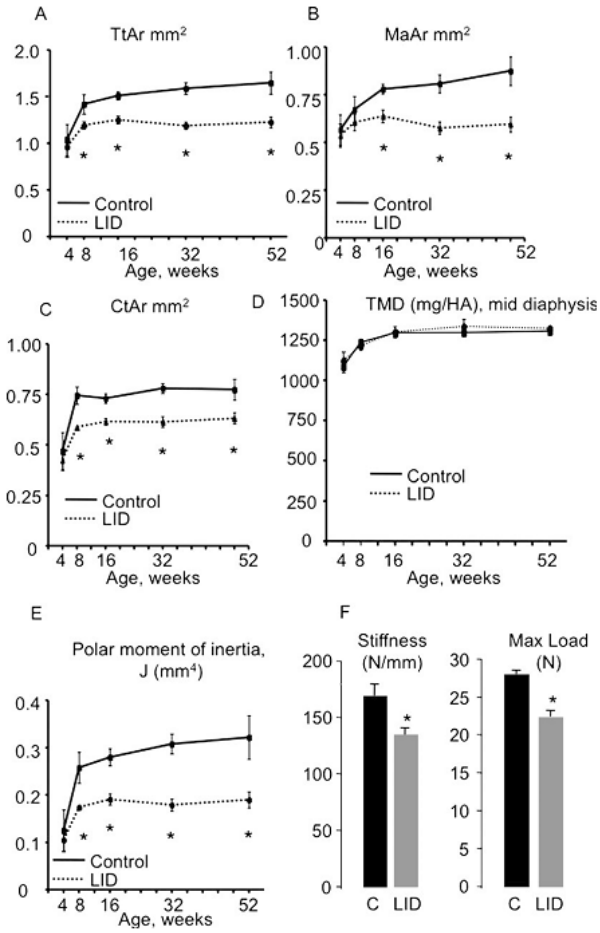
Barrett-Connor et al report a Framingham Stroke Risk Score (FSRS) calculated for subjects in RUTH (10,101 women) and MORE (7705 women). There was no difference in nonfatal strokes between raloxifene and placebo. In RUTH, women with FSRS <13 showed no increase in raloxifene-associated fatal stroke risk. Those with FSRS ≥13 had a 75% increased risk of raloxifene-associated fatal stroke (HR 1.75, 1.01-3.02). In MORE, 80% had a FSRS <13 and no increase in fatal stroke risk. Am J Med 2009;122:754-61

Noncompliance at lower cost but at what price

Blouin et al report women with medical possession ratio (MPR) <80% incurred higher physician care costs and hospital care costs than compliant subjects. In 15,027 women initiating ALN or risedronate predicted physician care cost (Canadian dollars) was $51 among women with MPR<80% and $34 among those with MPR≥80%. Mean predicted hospital care cost was $568 among women with MPR<80% and $379 among those with MPR≥80%. Mean predicted drug cost was $439 among women with MPR<80% and $1068 among those with MPR≥80%. Noncompliant women incurred higher physician care and hospital care costs. Due to lower drug costs, total direct health care costs were lower among noncompliant women. Osteoporos Int 2009;20:1571-81

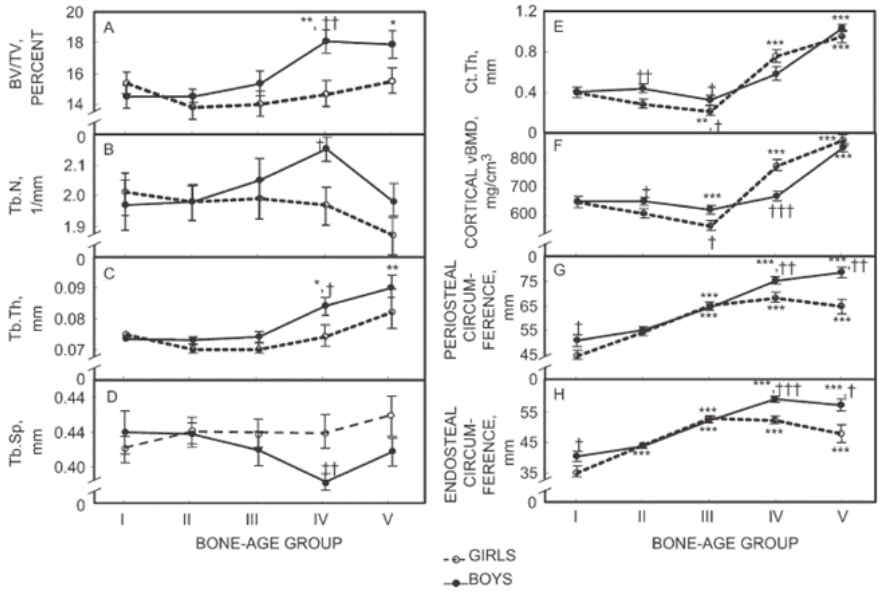
Growth, IGF-1, structure, fractures in childhood

Yakar et al report adult liver-specific IGF-1-deficient (LID) mice have 75% reductions in serum IGF-1 and reductions in periosteal circumference, femoral cross-sectional area, cortical thickness, and total volumetric BMD. Reduced bone strength associated with low levels of IGF-1 in serum results in impaired subperiosteal expansion with impaired endosteal apposition. J Bone Miner Res 2009;24:1481-92



LID mice have slender and more fragile bones. Cortical bone parameters were assessed during growth at the femoral midshaft using µCT. LID mice show reduced Tt.Ar. (A), Ma.Ar (B), and Ct.Ar (C) starting at 8 wk of age. TMD (D), measured by µCT, did not differ significantly between control and LID mice at all ages. LID mice cannot restore mechanical properties; LID mice show decreased polar moment of inertia (E) throughout growth and reduced stiffness and max load at four-point bending assay at 20 wk of age (F). Results are presented as mean±SD of n>8 mice per age group per genotype. Reproduced from J Bone Miner Res 2009;24:1481-92 with permission of the American Society of Bone and Mineral Research.

Kirmani et al studied 6- to 21-yr-old girls (n=66) and boys (n=61). Trabecular parameters (bone volume fraction, trabecular number, and thickness) did not change in girls but increased in boys from late puberty onward. Cortical thickness and density decreased from pre- to midpuberty in girls but were unchanged in boys, before rising to higher levels at the end of puberty. Total bone strength, assessed using microfinite element models, increased across bone age with boys showing greater bone strength than girls after midpuberty. The proportion of load borne by cortical bone, and the ratio of cortical to trabecular bone volume, decreased transiently during mid- to late puberty in both sexes, with apparent cortical porosity peaking. J Bone Miner Res 2009;24:1033-42

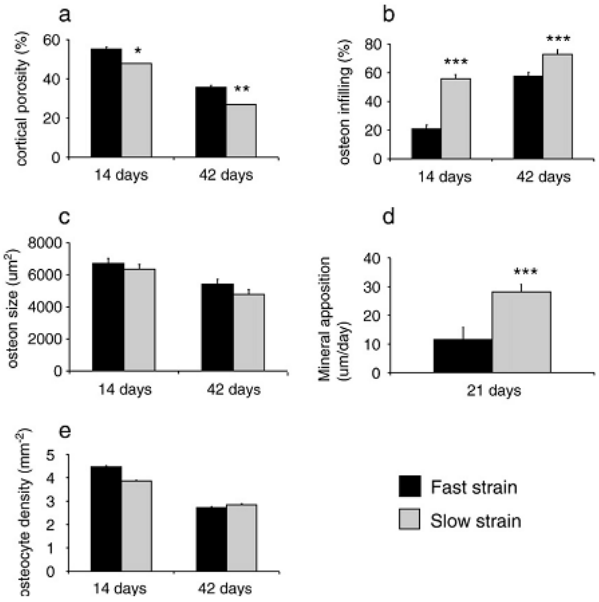


Trabecular and cortical bone parameters in bone-age groups I through V. (A) BV/TV, bone volume/total volume; (B) Tb.N, trabecular number; (C) Tb.Th, trabecular thickness; (D) Tb.Sp, trabecular spacing; (E) Ct.Th, cortical thickness; (F) cortical vBMD; (G) periosteal circumference; (H) endosteal circumference. *p<0.05, **p<0.01, and ***p<0.001 vs. group I; †p<0.05, ††p<0.01, and †††p<0.001 for comparison with the respective group of girls. Reproduced from J Bone Miner Res 2009;24:1033-42 with permission of the American Society of Bone and Mineral Research.

Cheng et al report that in 396 girls with a 7.5-year follow-up, fracture incidence peaked during puberty and 38% were in the upper limb. Girls who sustained upper limb fracture at ages 8-14 years had lower distal radial vBMD at baseline, 1-, 2- and 7-

year follow-up with larger bone cross-sectional area in the fracture cohort. Low vBMD during childhood is not a transient deficit. Bone 2009;45:480-6

Rawlinson et al report fast growth in the tibiotarsi of chicks produces bones with reduced stiffness and lower resistance to fracture. Bones from fast-growing embryonic chicks display rapid radial expansion and incomplete osteonal infilling and lack mechanical responsiveness. Bone 2009;45:357-66



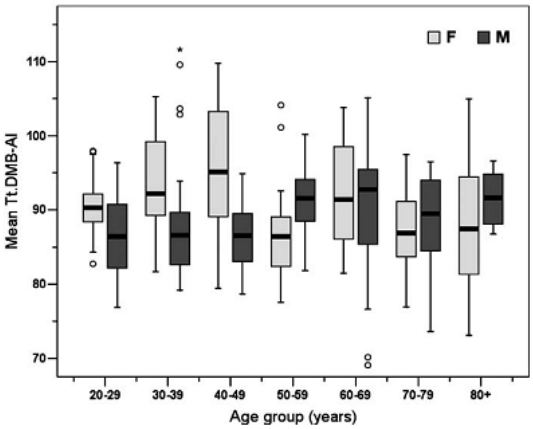
Cortical bone in post-hatch fast-growing chicks is more porous and exhibits reduced mineral appositional rate and osteonal infilling. Bone architecture was analysed in transverse sections of the mid-diaphyseal region of the tibiotarsi from fast (FS) and slow (SS) growth strains of chick at 14 or 42 days of age as described. Cortical bone of FS chick tibiotarsi exhibited greater cortical porosity (a), reduced osteon infilling (b) without any modification in osteon size (c) or osteocyte density (e) than SS chicks at both 14 and 42 days of age. Analysis of mineral appositional rate (d) in transverse sections of the mid-diaphyseal region from FS and SS strains of chick at 21 days of age demonstrated a reduced rate of mineral apposition on cortical bone surfaces between 18 and 21 days in the FS chicks. Data are shown as mean±SEM and * denotes P<0.05; **P<0.01; ***P<0.001. Reproduced from Bone, 45:357-66, Copyright (2009), with permission from Elsevier.

Structural failure in trabeculae before cortical bone in rat vertebrae

Kummari et al report that rat caudal vertebrae subjected to cyclic compressive loading terminated in the secondary and tertiary phases of the creep-fatigue curve resulted in trabecular microfracture with few microcracks in the cortical shell; damage occurs primarily in regions of cancellous bone before macroscopic cracks in the cortical shell. Calcif Tissue Int 2009;85:127-33

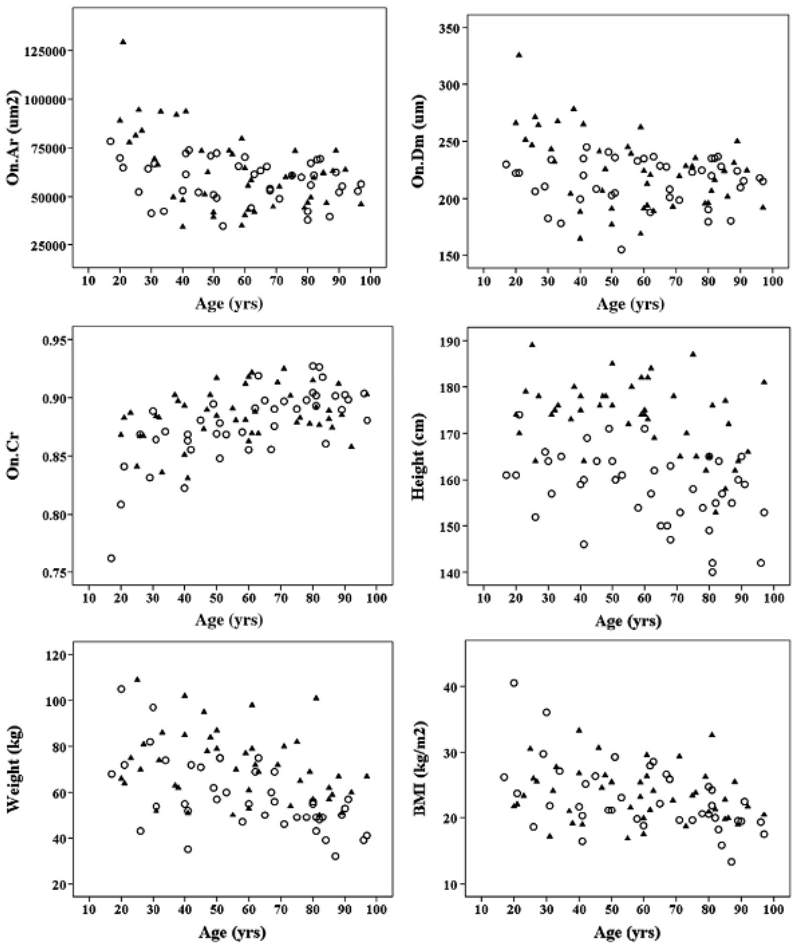
Bone microstructure – cortical bone tissue mineralization and osteons

Bergot et al report cortical bone from 193 femurs (99 female, 94 male) showed the degree of tissue mineralization (Tt.DMB-Al) decreased with age in females not in males. Tt.DMB-Al was higher in females than males until 50 years then lower in elderly females than elderly males. The first DMB-Al quartiles in osteons and interstitial tissue were not different between males and females, but the third quartile differed with greater heterogeneity in females than males. Bone 2009;45:435-42



Whisker plots for Tt.DMB-Al in females (light) and males (dark) in each age group. Reproduced from Bone, 45:435-42, Copyright (2009), with permission from Elsevier.

Britz et al report osteons (n=12,690) in the midfemoral mid-diaphyseal specimens (n=88; 45 male, 43 female; 17-97 yrs) were mapped. Weight was negatively related to On.Ar and On.Dm. Age was related to osteon and it was also related to circularity (all p<0.001). This relation was negative for On.Ar and On.Dm and positive for On.Cr (increasing circularity with age). Females had smaller osteons. Age accounted for the largest proportion of the variance in geometry. Bone 2009;45:77-83



Scatter plots of the geometric and anthropometric measures against age. Solid triangles represents males while open circles represent females. Note that age on the x-axis is untransformed while log-transformed age was used in the quantitative analysis. Reproduced from Bone, 45:77-83, Copyright (2009), with permission from Elsevier.

Shoot the messenger

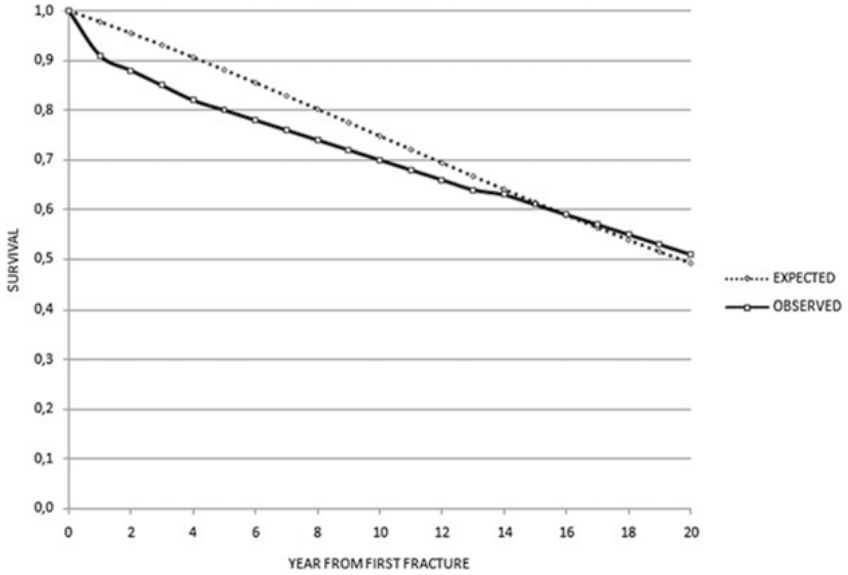
Lin et al report unloading decreases Wnt/beta-catenin signaling and upregulation of Sost. Sclerostin inhibited Wnt/beta-catenin in vivo and suppressed the activity of osteoblast and viability of osteoblasts and osteocytes. Sost(-/-) mice were resistant to unloading-induced bone loss and unaccompanied by reduced bone formation or decreased Wnt/beta-catenin signaling. Sclerostin is a target for preventing disuse osteoporosis. J Bone Miner Res 2009;24:1651-61

Two is better than one, but just

Johansson et al report data from 10 prospective population based cohorts used to compute the 10-year probabilities of hip fracture. BMD selected women at higher risk of hip fracture than CRFs (6.1% vs. 5.3%) and identified more hip fracture cases (219/1000) than CRFs alone (140/1000). The combined use identified fewer women above a threshold risk than BMD alone (168/1000 vs. 219/1000, respectively), but with a higher hip fracture risk (PPV, 8.6% vs. 6.1%), and so a lower number needed to treat (33 vs. 47). The PPV and NNT were better for the combination. Osteoporos Int 2009;20:1675-82

The second hip

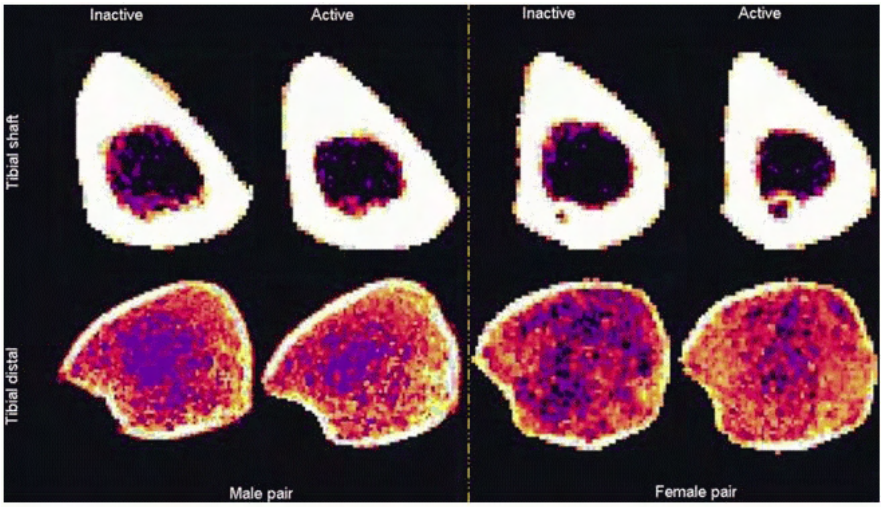
Ryg et al report that in 169,145 patients with a first hip fracture (HFx) followed a median of 3.8 yr, 27,834 had a second HFx; a cumulative incidence of 9% after 1 yr and 20% after 5 yr. The RR of second HFx was 2.2 (2.0-2.5) at 1 yr and normalized at 15 yr. Mortality at 1 and 5 yr after a second HFx compared with expected (men-1 yr: 27 vs. 9%; 5 yr: 64% vs. 40%; women-1 yr: 21 vs. 10%; 5 yr: 58 vs. 41%). J Bone Miner Res 2009;24:1299-307



Risk of second HFx compared with the risk of HFx in an age- and sex-matched normal population. Calculated as actuarial survival. Because of the large cohorts, CIs were too small to be presented on the curves. Reproduced from J Bone Miner Res 2009;24:1299-307 with permission of the American Society of Bone and Mineral Research.

Discordancy in exercise – twins convince

Ma et al studied long-term leisure time physical activity (LTPA) in twin pairs discordant for activity for at least 30 yr in 16 middle-aged (50-74 yr) same-sex twin pairs (7 MZ and 9 DZ pairs). Active members of MZ twin pairs had larger cortical bone cross-sectional area (intrapair difference: 8%, p=0.006), thicker cortex (12%, p=0.003), and greater moment of inertia (I_{max}, 20%, p=0.024) at the tibia shaft than their inactive co-twins. At the distal tibia, trabecular BMD (12%, p=0.050) and compressive strength index (18%, p=0.038) were higher in the active MZ pair members than their inactive co-twins. The trends were similar, but less consistently so, in DZ pairs. J Bone Miner Res 2009;24:1427-33

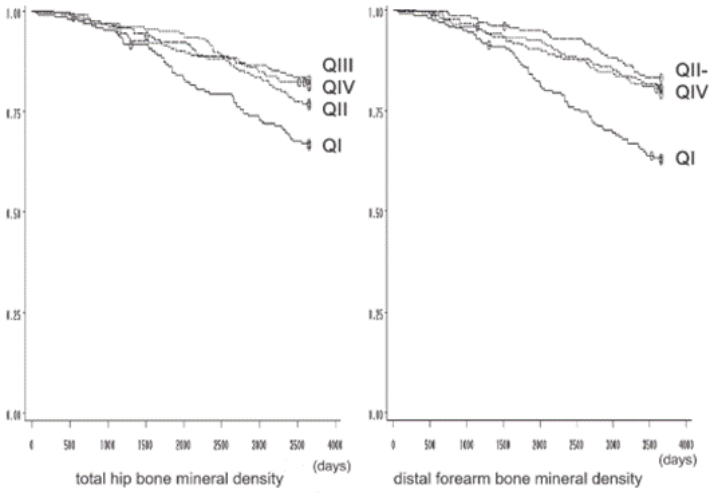


Typical pQCT images of one male (mean LTPA physical activity index throughout the follow-up 11.8 vs. 1.7 METh/d) and one female (13.1 vs. 2.7 METh/d) MZ twin pair. In the bottom panel, different colors indicate different volumetric density values (from low to high density: blue-brown-red-yellow-white). In the male pair, the values of the active and inactive member for BMC_{tot} were 456 vs. 438 mg/cm, for Th_c they were 5.3 vs. 4.5 mm in the shaft, values for BMC_{tot} were 314 vs. 295 mg/cm, and values for BMD_{trab} were 238 vs. 207 mg/cm³ in the distal tibia, respectively. In the female pair, the values of the active and inactive member for BMC_{tot} were 322 vs. 310 mg/cm, values for Th_c were 4.1 vs. 3.6 mm in the shaft, values for BMC_{tot} were 240 vs. 207 mg/cm, and values for BMD_{trab} were 232 vs. 187 mg/cm³ in the distal tibia, respectively. Reproduced from J Bone Miner Res 2009;24:1427-33 with permission of the American Society of Bone and Mineral Research.

Accelerating bone loss in elderly men

Bone loss accelerates as age advances because the same or a higher intensity of remodelling removes the same or an increasing volume of bone from an ever decreasing volume. Cawthon et al report that among 4720 community-dwelling men followed over 4.6 yr, FN BMD loss was 1.7% and accelerated with age. FN BMD in men 85 yr of age (was 2.5 times greater than for men 65 yr of age increasing the risk of hip fracture by 25%)/ Men with lower BMD at baseline lost the most BMD over follow-up. J Bone Miner Res 2009;24:1728-35

Szulc et al report that in 781 men ≥50 yr of age followed for 10 yr, those who died had lower BMD and higher BTM. In multivariate models, mortality was higher in men with low BMD (lowest quartile) at the total hip, whole body, and ultradistal radius (HR=1.49-1.70, p<0.05). After exclusion of the first 3 yr, higher levels (fourth quartile) of free and total deoxypyridinoline and urinary and serum type I collagen C-telopeptide predicted mortality (HR=1.58-2.44, p<0.05-0.001). J Bone Miner Res 2009;24:1116-24



Survival of men according to baseline BMD. Survival of men from the MINOS cohort during the 10 yr of follow-up according to the quartiles (QI, lowest; QII; QIII; QIV, highest) of BMD presented with Kaplan-Meier curves: (left) total hip BMD and (right) distal forearm BMD. Reproduced from J Bone Miner Res 2009;24:1116-24 with permission of the American Society of Bone and Mineral Research.

Denosumab in men

Smith et al report a double-blind, multicenter study in men receiving denosumab 60 mg subcutaneously 6 months or placebo (734 patients in each group). At 24 months, denosumab reduced new VFs at 36 months (1.5% vs. 3.9% placebo) (RR, 0.38; 0.19-0.78; P=0.006). Spine BMD increased by 5.6% with denosumab and decreased 1.0% with placebo (P<0.001). Denosumab increased BMD at the total hip, femoral neck, and distal third of the radius. N Engl J Med 2009;361:745-55

"She should have died hereafter;
There would have been a time for such a word.
To-morrow, and to-morrow, and to-morrow,
Creeps in this petty pace from day to day,
To the last syllable of recorded time;
And all our yesterdays have lighted fools
The way to dusty death. Out, out, brief candle!
Life's but a walking shadow, a poor player
That struts and frets his hour upon the stage
And then is heard no more. It is a tale
Told by an idiot, full of sound and fury
Signifying nothing."

Macbeth (Act 5, Scene 5, lines 17-28)
William Shakespeare

Note from the Editor

The purpose of *Progress in Osteoporosis* is to provide the reader with a summary of the most important literature published in the preceding three to four months in the field of osteoporosis. Most reviews and original research are cited. In addition, summaries and figures are provided for readers who may not have easy access to all the specialist literature. The summaries are based on the contents of abstracts, which have been abbreviated to concisely convey the main theme. The contents of the abstracts and figures should be used only as a means of directing the reader to the original literature and should not be quoted verbatim or cited as a reference. The opinions expressed in the Overview are my own and do not necessarily reflect those of the International Osteoporosis Foundation.

Ego Seeman

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Epidemiology

10.4.1 Osteoporosis in China

Wang Y, Tao Y, Hyman ME, Li J, Chen Y
Osteoporos Int 2009;20:1651-62

Related studies published in English and Chinese between January 1980 and May 2008 were reviewed and analyzed. In the mainland, overall prevalence of osteoporosis based on nationwide surveys ranged from 6.6-19.3% (average=13.0%). The prevalence varied across studies, and by regions, gender, and bone sites, but the urban to rural difference was small. In Hong Kong, the prevalence among women ≥50 years ranged from 34.1-37% in the spine; was 7% in the same aged men. In Taiwan, among those aged ≥50 years, average prevalence of osteoporosis was 11.4% in women and 1.6% in men.

10.4.2 The incidence and risk of hip fracture in Poland

Czerwinski E, Kanis JA, Trybulec B, Johansson H, Borowy P, Osieleniec J
Osteoporos Int 2009;20:1363-7

In 2005, there were 17,625 hip fractures diagnosed in Poland which was 30.2% less than the number of hospital discharge notes containing such a diagnosis in that year. In the over-50-year-old population, hip fracture incidence was found to be 89/100,000 for men and 165/100,000 for women. In the 50-65-year band, hip fracture incidence was higher in men than in women. The remaining lifetime probability of hip fracture at the age of 50 years was 2.0% for men and 4.5% for women which are among the lowest in Europe. Hip fracture incidence and thus the probability of hip fracture risk in Poland is amongst the lowest in Europe.

10.4.3 Trends in hip fracture epidemiology in Australia: Possible impact of bisphosphonates and hormone replacement therapy

Fisher AA, O'Brien ED, Davis MW
Bone 2009;45:246-53

Annual sex- and age-specific incidence rates (per 100,000 population) were determined and standardized using the Australian 2006 population. The projected number of HFs was estimated by two models applying age- and sex-specific HF rates averaged for 2002-2006 (model 1) or continuously changing as observed in this period (model 2, Poisson regression) to the projected population. In 2006 compared to 2001, the population ≥60 years in the ACT increased by 19.7%. Over the last 5 years the average annual incidence HF rate compared to the previous 3-year period decreased in females ≥60 years of age by 28.3%. Between 2001 and 2006 the number of prescriptions for HRT dispensed in the ACT declined by 54.6%, while the number of prescriptions for bisphosphonate increased by 245%, accompanied by a decline in standardized incidence of HF rates of 36.4%, mainly in women (42.1%). This represents an annual cost for bisphosphonates per one prevented HF, of 45,250 AUD or 576 AUD/ person/year. Compared to 2006 the total number of HFs in Australia according to model 1 will increase in 2011 by 20.1% and in 2021 by 58.8%, but according to model 2 will decrease by 15.5% in 2011 and 27.5% in 2021. The data suggest that the predicted rising trend in HFs in elderly women reversed, but not so for men. This was coincident with a significant fall in HRT use and increased prescribing of bisphosphonates, which is cost-effective. If trends in HF observed in 2002-2006 continue, the absolute number of HFs in Australia in 2011-2021 will stabilise or decline (which is more likely).

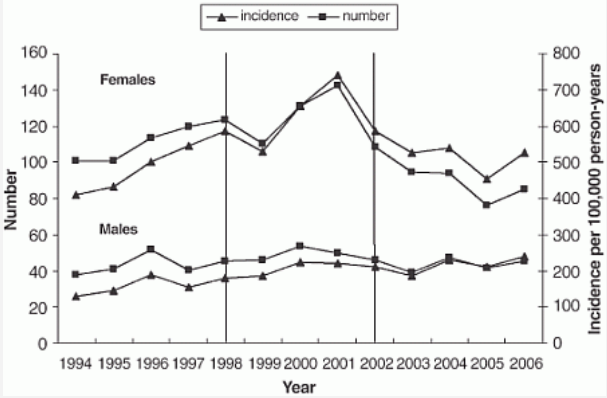


Fig. 10.4.3a Number and sex-specific incidence rates (per 100,000 person-years) of hip fracture in people aged 60 years and over in ACT between 1994 and 2006. Three study periods are indicated with vertical lines. Reproduced from Bone, 45:246-53, Copyright (2009), with permission from Elsevier.

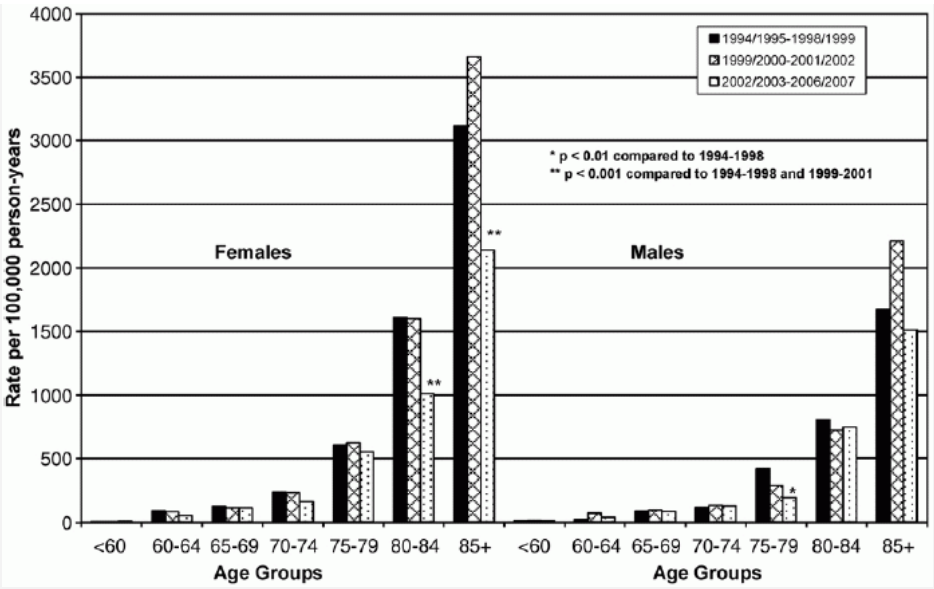


Fig. 10.4.3b Secular trends in age- and gender-specific incidence rates of hip fractures in ACT between 1994/1995 and 2006/2007. Reproduced from Bone, 45:246-53, Copyright (2009), with permission from Elsevier.

10.4.4 Spatial temporal modeling of hospitalizations for fall-related hip fractures in older people
Turner RM, Hayen A, Dunsmuir WT, Finch CF
Osteoporos Int 2009;20:1479-85

The study determined the spatial temporal characteristics of fall-related hip fractures in the elderly using routinely collected injury hospitalization data. All New South Wales (NSW), Australia residents aged 65+ years who were hospitalized for a fall-related hip fracture between 1 July 1998 and 30 June 2004 were included. Bayesian Poisson regression was used to model rates in local government areas (LGAs). Hip fracture rates were decreasing in one LGA, and there were no increases in any LGAs. The proportion of the population in residential aged care facilities was associated with the rate of hospitalized hip fractures with a relative risk (RR) of 1.003 (95% credible interval 1.002, 1.004). Socioeconomic status was also related to hospitalized hip fractures with those in the 3rd and 4th quintiles being at decreased risk of hip fracture compared to those in the least disadvantaged (5th) quintile [RR=0.837 (0.717, 0.972) and RR=0.855 (0.743, 0.989), respectively]. There was significant variation in hospitalized hip fracture rates in NSW, Australia. The use of Bayesian methods was crucial to allow for spatial correlation, covariate effects, and LGA boundary changes.

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Morbidity/Mortality

10.4.5 Excess mortality following hip fracture: A systematic epidemiological review

Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C
Osteoporos Int 2009;20:1633-50

This systematic literature review reports that patients experiencing hip fracture are at excess risk for death compared with controls for several years. Excess mortality during the first year after fracture ranging from 8.4-36%. An increased risk for mortality was double that for the age-matched controls, became less pronounced with advancing age, was higher among men than women regardless of age, was highest in the days and weeks following the index fracture, and remained elevated for months and perhaps even years.

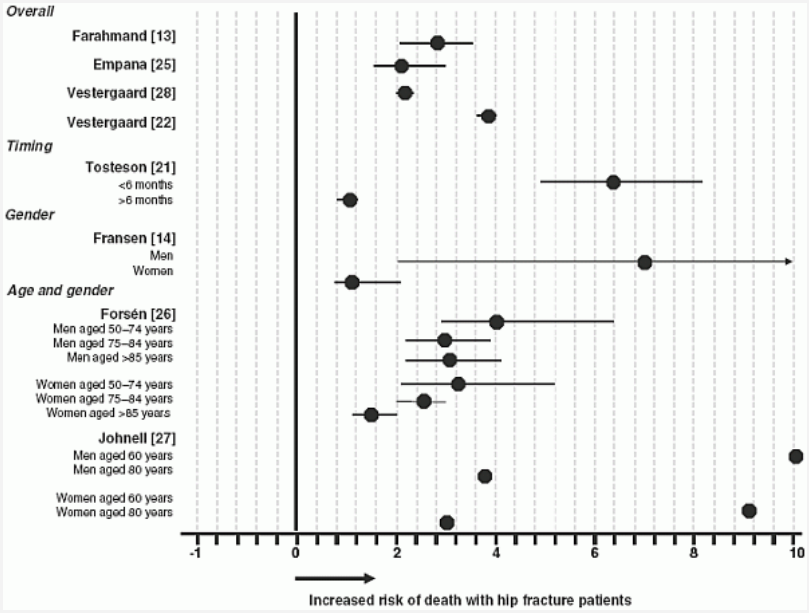

Fig. 10.4.5 Forest plot of risk (relative risk, odds ratio, or hazard ratio, with 95% CIs where available) of death following hip fracture compared with general population values. Reproduced from Osteoporos Int 2009;20:1633-50 with permission from Springer.

10.4.6 Cross-geographic region differences in quality of life in women with and without vertebral fracture

van Schoor NM, Yu H, Bobula J, Lips P
Osteoporos Int 2009;20:1759-66

The study was performed using baseline data of the bazedoxifene study. The study was carried out in 25 countries in six continents (n=7117). QoL was assessed using the index and Visual Analogue Scale (VAS) scores of the EQ-5D, Qualeffo-41, and Women's Health Questionnaire (WHQ). VFX were assessed using semi-quantitative and quantitative morphometric methods. In general, all four instruments followed more or less the same pattern. In most analyses, the reported QoL was lowest in Asia and Europe and highest in North America and Oceania. To examine the influence of ethnicity, North and South America were stratified on race. In both continents, a lower QoL was observed in Hispanic people. QoL differed between continents, countries, and ethnicities. The observed differences in QoL appeared larger between most continents and countries than the difference in QoL between women with or without mild to moderate VFX.

10.4.7 Impact of spinal kyphosis on gastroesophageal reflux disease symptoms in patients with osteoporosis

Miyakoshi N, Kasukawa Y, Sasaki H, Kamo K, Shimada Y
Osteoporos Int 2009;20:1193-8

Osteoporosis and spinal kyphosis have been speculated to participate in the increased frequency of gastroesophageal reflux disease (GERD). In 112 patients with osteoporosis (mean age, 78 years) who responded to the Frequency Scale for Symptoms of GERD (FSSG) questionnaire, regardless of complaints. Relationships between total FSSG score and number of vertebral fractures, angles of kyphosis, use of bisphosphonates and nonsteroidal anti-inflammatory drugs (NSAIDs), and total number of oral medicines per day were evaluated. Logistic regression identified factors associated with GERD. Bisphosphonates and NSAIDs did not affect total FSSG score. Total FSSG score showed positive correlations with total number of medicines (r=0.283, p=0.0025), angle of lumbar kyphosis (r=0.576, p=0.0001), and numbers of thoracic vertebral fractures (r=0.214, p=0.0232) and lumbar vertebral fractures (r =0.471, p<0.0001). Angle of lumbar kyphosis and number of lumbar vertebral fractures were identified by multivariate analysis as indices affecting the presence of GERD. Increases in angle of lumbar kyphosis and number of lumbar vertebral fractures may represent very important risk factors for GERD in osteoporotic patients.

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Financial Cost

10.4.8 The health and economic consequences of osteopenia- and osteoporosis-attributable hip fractures in Germany: Estimation for 2002 and projection until 2050

Konnopka A, Jerusel N, Konig HH
Osteoporos Int 2009;20:1117-29

The health and economic burden of osteopenia- and osteoporosis-attributable hip fractures (OHF) in Germany was estimated for 2002 and projected until 2050. 108,341 OHF resulting in 2,998 million EUR cost, which will more than double by the year 2050. 108,341 OHF resulting in 3485 deaths, 22,724 YPLL, 114,058 QALYs, 2,736 million EUR direct cost and 262 million EUR indirect costs. Projection to 2020 showed corresponding increases of 44%, 62%, 56%, 49%, 47% and 33%, whereas the projection to 2050 resulted in changes of 128%, 215%, 196%, 152%, 138% and 90%, respectively.

10.4.9 Comparison of direct health care costs related to the pharmacological treatment of osteoporosis and to the management of osteoporotic fractures among compliant and noncompliant users of alendronate and risedronate: A population-based study

Blouin J, Dragomir A, Fredette M, Ste-Marie LG, Fernandes JC, Perreault S
Osteoporos Int 2009;20:1571-81

During a 2-year follow-up period, compared to those with medication possession ratio (MPR) ≥80%, women with MPR<80% incurred higher physician care costs and hospital care costs. This study aimed to compare direct health care costs related to the treatment of osteoporosis and 15,027 women initiated alendronate or risedronate was identified. MPR and direct health care costs (physician care, hospital care, drugs) were assessed during a 2-year period. Regression models were used to estimate mean predicted cost for compliant (MPR≥80%) and noncompliant (MPR<80%) women. Mean predicted physician care cost (in CAD) was $51 among women with MPR<80% and $34 among those with MPR≥80%: mean difference $17, 95% CI $2-22. Mean predicted hospital care cost was $568 among women with MPR<80% and $379 among those with MPR≥80%: mean difference $189, 95% CI $56-320. Mean predicted drug cost was $439 among women with MPR<80% and $1068 among those with MPR≥80%: mean difference $-639, 95% CI $-649 to -629. Noncompliant women incurred significantly higher physician care and hospital care costs. Due to lower drug costs, total direct health care costs were lower among noncompliant women.

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Genetics

10.4.10 Polymorphisms of the WNT10B gene, BMD, and fractures in postmenopausal women

Perez-Castrillon JL, Olmos JM, Nan DN, Castillo J, Arozamena J, Montero A, Perez-Nunez MI, Riancho JA
Calcif Tissue Int 2009;85:113-8

In 1438 Caucasian postmenopausal women, including 146 with vertebral fractures and 432 with hip fractures, no association between single SNPs and spine or hip BMD was found. In the multilocus analysis, some haplotypes showed a slight association with spine BMD (P=0.03), but it was not significant after multiple-test correction. WNT10B is expressed in the bone microenvironment and may be an important regulator of osteoblastogenesis, but no evidence for a robust association of common WNT10B gene allelic variants with either BMD or fractures in postmenopausal women was found

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10.4.11 Bone mineral density variation in men is influenced by sex-specific and non sex-specific quantitative trait loci

Peacock M, Koller DL, Lai D, Hui S, Foroud T, Econs MJ
Bone 2009;45:443-8

In 515 pairs of brothers, aged 18-61 (405 white pairs, 110 black pairs) linkage analysis in the brother sample was compared with results in 774 sister pairs. A genomewide scan identified QTL (LOD>3.6) for aBMD on chromosomes 4q21 (hip), 7q34 (spine), 14q32 (hip), 19p13 (hip), 21q21 (hip), and 22q13 (hip). QTL on chromosomes 7q34, 14q32, and 21q21 were male-specific, whereas the others were not sex-specific. This study demonstrates that six QTL were significantly linked with aBMD in men. One was linked to the spine and five were linked to the hip. When compared to published data in women from the same geographical region, the QTL on chromosomes 7, 14 and 21 were male-specific.

10.4.12 The -9247 T/C polymorphism in the SOST upstream regulatory region that potentially affects C/EBPα and FOXA1 binding is associated with osteoporosis

Huang QY, Li GH, Kung AW
Bone 2009;45:289-94

A gene-wide tag SNP-based association study in 1243 Chinese subjects with low BMD (Z-scores ≤–1.28, equivalent to the lowest 10% of the population) and high BMD (Z-score ≥+1.0) using 22 tag SNPs were selected and genotyped. Allelic and haplotype association tests were conducted by Haploview and binary logistic regression analyses. The -9247 polymorphism rs1230399 in the upstream regulatory region of the sclerostin gene showed genotypic/allelic associations with spine, femoral neck, trochanter and total hip BMD (P=0.03-0.004). The T-allele of rs1230399 increased the risk of osteoporosis (OR=1.52, P=0.005). Computational analysis showed that rs1230399 is located at the core consensus recognition site of two cooperating transcription factors C/EBPα and FOXA1 that modulate estrogen receptor function. T-->C polymorphism abolishes the binding of both C/EBPα and FOXA1 to the sclerostin gene. Our data suggest a mechanistic link between rs1230399 and BMD through estrogen ERα/FOXA1 signaling pathways driven by long distance enhancers.

10.4.13 Association analyses of RANKL/RANK/OPG gene polymorphisms with femoral neck compression strength index variation in Caucasians

Dong SS, Liu XG, Chen Y, Guo Y, Wang L, Zhao J, Xiong DH, Xu XH, Recker RR, Deng HW
Calcif Tissue Int 2009;85:104-12

Femoral neck compression strength index (fCSI), a novel phenotypic parameter that integrates bone density, bone size, and body size, has potential to improve hip fracture risk assessment. In 1873 subjects from 405 Caucasian nuclear families of the 37 total SNPs studied in these three genes, three SNPs, namely rs12585014, rs7988338, and rs2148073, of RANKL were associated with fCSI (P=0.0007, 0.0007, and 0.0005, respectively) after conservative Bonferroni correction. Moreover, the three SNPs were in linkage disequilibrium. Haplotype-based association tests corroborated the single-SNP results since haplotype 1 of block 1 of the RANKL gene achieved an even more significant association with fCSI (P=0.0003) than any of the individual SNPs. RANKL gene may play an important role in variation in fCSI, independent of fBMD and non-fBMD components.

10.4.14 Association of a RUNX2 promoter polymorphism with BMD in postmenopausal Korean women

Lee HJ, Koh JM, Hwang JY, Choi KY, Lee SH, Park EK, Kim TH, Han BG, Kim GS, Kim SY, Lee JY
Calcif Tissue Int 2009;84:439-45

To determine whether RUNX2 is associated with BMD in an ethnically distinct population, SNPs within the two RUNX2 promoters (P1 and P2) were assessed in 729 postmenopausal Korean women. Subjects bearing the minor homozygote genotype (CC) at the RUNX2 -1025 T>C SNP (rs7771980) located in P2 showed an association with reduced lumbar spine BMD (p=0.02) and BMDs at proximal femur sites (trochanter, p=0.05; total femur, p=0.04) compared with subjects carrying the major homozygote genotype (TT) or the heterozygote genotype (TC), respectively. RUNX2 P2 polymorphism (-1025 T>C) may be a useful genetic marker for bone metabolism and may play an important role in BMD in postmenopausal Korean women.

10.4.15 Polymorphisms in the Annexin gene family and the risk of osteonecrosis of the femoral head in the Korean population

Kim TH, Hong JM, Shin ES, Kim HJ, Cho YS, Lee JY, Lee SH, Park EK, Kim SY
Bone 2009;45:125-31

Annexins (ANXs) have been implicated in blood coagulation, inflammation, apoptosis, as well as Ca^{2+} homeostasis in bone cells, all of which may be associated with ONFH. To evaluate any association of Annexin A (ANXA) gene polymorphisms with ONFH, 52 SNPs from three genes of the ANXA family were selected from public databases and genotyped in 443 ONFH patients and 273

control subjects. The rs9324679, rs9324677, rs10037814, and rs11960458 SNPs of the ANXA6 gene were associated with the risk of ONFH in all alternative analysis models (odds ratio: 0.63-1.72). SNPs were also associated with the risk of ONFH in at least one subgroup (p-range: 0.0017-0.049). Haplotype association analysis showed that several haplotypes were associated with a risk of ONFH (OR range: 0.44-1.76). These findings indicate that the polymorphisms of ANXA6 are associated with ONFH.

10.4.16 Genetic regulation of bone traits is influenced by sex and reciprocal cross in F_2 progeny from GK and F344 rats

Lagerholm S, Li LS, Jiao H, Park HB, Ohlsson C, Akesson K, Luthman H
J Bone Miner Res 2009;24:1066-74

A genomewide linkage analysis to identify quantitative trait loci (QTLs) for bone phenotypes was performed in an F_2 intercross of inbred spontaneously type 2 diabetic GK and normoglycemic F344 rats (108 males and 98 females). pQCT was used to determine tibial bone phenotypes in the F_2 rats, comprising reciprocal crosses with divergent mitochondrial (mt) DNA.

Four genomewide significant QTLs linked to cortical vBMD, tibia length, body length, or metaphyseal area were identified in males on chromosomes (chr) 1, 8, and 15. In females, three QTLs linked to cortical BMC or metaphyseal total vBMD were identified on chr 1 and 2. Several suggestive loci for trabecular and cortical traits were detected in both males and females. Four female-specific QTLs on chr 2, 3, 5, and 10 and four reciprocal cross-specific QTLs on chr 1, 10, and 18 were identified, suggesting that both sex and mt genotype influence the expression of bone phenotypes.

10.4.17 Leukocyte telomere length is not associated with BMD, osteoporosis, or fracture in older adults: Results from the Health, Aging and Body Composition Study

Sanders JL, Cauley JA, Boudreau RM, Zmuda JM, Strotmeyer ES, Opresko PL, Hsueh WC, Cawthon RM, Li R, Harris TB, Kritchevsky SB, Newman AB
J Bone Miner Res 2009;24:1531-6

10.4.18 A study of relationships between single nucleotide polymorphisms from the growth hormone-insulin-like growth factor axis and bone mass: The Hertfordshire cohort study

Dennison EM, Syddall HE, Jameson KA, Sayer AA, Gaunt TR, Rodriguez S, Day IN, Cooper C, Lips MA
J Rheumatol 2009;36:1520-6

10.4.19 Association of the aromatase gene alleles with BMD: Epidemiological and functional evidence

Riancho JA, Sanudo C, Valero C, Pipaon C, Olmos JM, Mijares V, Fernandez-Luna JL, Zarrabeitia MT
J Bone Miner Res 2009;24:1709-18

10.4.20 Further genetic evidence suggesting a role for the RhoGTPase-RhoGEF pathway in osteoporosis

Mullin BH, Prince RL, Mamotte C, Spector TD, Hart DJ, Dudbridge F, Wilson SG
Bone 2009;45:387-91

10.4.21 Association of a high mobility group gene (HMGA2) variant with BMD

Kuipers A, Zhang Y, Cauley JA, Nestlerode CS, Chu Y, Bunker CH, Patrick AL, Wheeler VW, Hoffman AR, Orwoll ES, Zmuda JM
Bone 2009;45:295-300

10.4.22 Effects of a synonymous variant in exon 9 of the CD44 gene on pre-mRNA splicing in a family with osteoporosis

Vidal C, Cachia A, Xuereb-Anastasi A
Bone 2009;45:736-42

10.4.23 Vitamin D binding protein genotype and osteoporosis

Fang Y, van Meurs JB, Arp P, van Leeuwen JP, Hofman A, Pols HA, Uitterlinden AG
Calcif Tissue Int 2009;85:85-93

10.4.24 New variants in the Enpp1 and Ptpn6 genes cause low BMD, crystal-related arthropathy, and vascular calcification

Babij P, Roudier M, Graves T, Han CY, Chhoa M, Li CM, Juan T, Morony S, Grisanti M, Li X, Yu L, Dwyer D, Lloyd DJ, Bass MB, Richards WG, Ebeling C, Amato J, Carlson G
J Bone Miner Res 2009;24:1552-64

10.4.25 Association of the tag SNPs in the human SKT gene (KIAA1217) with lumbar disc herniation

Karasugi T, Semba K, Hirose Y, Kelempisioti A, Nakajima M, Miyake A, Furuichi T, Kawaguchi Y, Mikami Y, Chiba K, Kamata M, Ozaki K, Takahashi A, Makela P, Karppinen J, Kimura T, Kubo T, Toyama Y, Yamamura K, Mannikko M, Mizuta H, Ikegawa S
J Bone Miner Res 2009;24:1537-43

10.4.26 Genome-wide haplotype association mapping in mice identifies a genetic variant in CER1 associated with BMD and fracture in southern Chinese women

Tang PL, Cheung CL, Sham PC, McClurg P, Lee B, Chan SY, Smith DK, Tanner JA, Su AI, Cheah KS, Kung AW, Song YQ
J Bone Miner Res 2009;24:1013-21

10.4.27 Localization of the cis-enhancer element for mouse type X collagen expression in hypertrophic chondrocytes in vivo

Zheng Q, Keller B, Zhou G, Napierala D, Chen Y, Zabel B, Parker AE, Lee B
J Bone Miner Res 2009;24:1022-32

10.4.28 Inbred strain-specific response to biglycan deficiency in the cortical bone of C57BL6/129 and C3H/He mice
Wallace JM, Golcuk K, Morris MD, Kohn DH
J Bone Miner Res 2009;24:1002-12

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Measurement of Bone Mass

10.4.29 Age, gender, and race/ethnic differences in total body and subregional bone density

Looker AC, Melton LJ, 3rd, Harris T, Borrud L, Shepherd J, McGowan J
Osteoporos Int 2009;20:1141-9

Total body DXA data offer the opportunity to compare bone density of demographic groups across the entire skeleton. Mean BMD varied in expected ways for some demographic characteristics (men>women and nonHispanic blacks>nonHispanic whites) but not others (nonHispanic whites>Mexican Americans). Differences in age patterns in BMD also emerged for some characteristics (sex) but not others (race/ethnicity). Differences in cross-sectional age patterns in BMD and lean mass by degree of weight-bearing in older adults were observed for the pelvis, leg, and arm.

10.4.30 Spinal deformity index (SDI) is a good predictor of incident vertebral fractures

Kerkeni S, Kolta S, Fechtenbaum J, Roux C
Osteoporos Int 2009;20:1547-52

The study subjects were women from the placebo groups of two studies of strontium ranelate in postmenopausal osteoporosis (N=723 and 637 patients, respectively). There was a linear relationship between baseline SDI and the 3-year incidence of vertebral fracture (adjusted R^2=0.76). The 3-year incidence of vertebral fractures was different among the tertiles of baseline SDI: 17.3±3.6%, 25.4±2.6%, and 47.6±3.1% from the lowest to the highest, respectively. There was no relationship between SDI and nonvertebral fractures incidence. SDI is a good predictor of incident vertebral fractures. Patients with highest SDI should receive highest priority to treatment.

10.4.31 Contribution of the vertebral posterior elements in anterior-posterior DXA spine scans in young subjects

Lee DC, Campbell PP, Gilsanz V, Wren TA
J Bone Miner Res 2009;24:1398-403

In 294 females and 280 males, age 6-25 yr, QCT measures for cancellous bone and for the vertebral body including and excluding the posterior elements and DXA was used to measure the entire L3 vertebra and for a 10-mm slice corresponding to the QCT scan region. The posterior elements accounted for 51.4±4.2% of the total BMC (males, 49.9±4.0% and females 52.8±3.9%, p<0.001). This percentage increased with age in younger subjects of both sexes (p<0.001) but was relatively consistent after age 17 for males and 16 for females. DXA areal BMD and QCT volumetric BMD correlated for the whole vertebra including the posterior elements (R=0.83), with BMC measures showing a stronger relationship (R=0.93). Relationships were weaker when excluding the posterior elements. We conclude that DXA BMC provides a measure of bone that is most consistent with QCT and that the contribution of the posterior elements is consistent in young subjects after sexual maturity.

10.4.32 Accuracy of volumetric BMD measurement in high-resolution peripheral quantitative computed tomography

Sekhon K, Kazakia GJ, Burghardt AJ, Hermannsson B, Majumdar S
Bone 2009;45:473-9

A series of idealized hydroxyapatite (HA) phantoms with varying densities and geometries to quantify the accuracy of HR-pQCT analysis revealed errors in measured vBMD(trab). Overestimation of vBMD(trab) increased proportional to cortical shell thickness and decreased proportional to insert density. The most pronounced vBMD(trab) overestimation occurred in the phantoms with the lowest insert densities and highest shell thickness, where error was as high as 20 mg HA/cm^3 (33%) in the radius phantom and 25 mg HA/cm^3 (41%) in the tibia phantom. Error in vBMD(trab) propagates to the calculation of microarchitectural measures; 41% error in vBMD(trab) will produce 41% error in volume fraction (BV/TV) and trabecular thickness (Tb.Th), and 5% error in trabecular separation (Tb.Sp). Geometric and densitometric variations influence the accuracy of HR-pQCT vBMD(trab) measurements.

10.4.33 A reference database for the Stratec XCT-2000 peripheral quantitative computed tomography (pQCT) scanner in healthy children and young adults aged 6-19 years

Ashby RL, Ward KA, Roberts SA, Edwards L, Mughal MZ, Adams JE
Osteoporos Int 2009;20:1337-46

pQCT was used to measure the 4% and 50% sites of the nondominant radius in a cohort of healthy white Caucasian children and young adults aged between 5 and 25 years. The lambda, mu, sigma (LMS) technique was used to produce gender-specific reference centile curves and LMS tables for calculating individual standard deviations scores. The study population consisted of 629 participants (380 males). Reference centile curves were produced; total and trabecular BMD for age (distal radius) and for age and height, bone area (distal and midshaft radius), cortical area, cortical thickness, BMC, axial moment of inertia, stress-strain index and muscle area (midshaft radius).

10.4.34 Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting

Fuerst T, Wu C, Genant HK, von Ingersleben G, Chen Y, Johnston C, Econs MJ, Binkley N, Vokes TJ, Crans G, Mitlak BH
Osteoporos Int 2009;20:1199-205

10.4.35 Spine radiographs to improve the identification of women at high risk for fractures

Netelenbos JC, Lems WF, Geusens PP, Verhaar HJ, Boermans AJ, Boomsma MM, Mulder PG, Papapoulos SE

Osteoporos Int 2009;20:1347-52

10.4.36 Comparison of QCT-derived and DXA-derived areal BMD and T-scores
Khoo BC, Brown K, Cann C, Zhu K, Henzell S, Low V, Gustafsson S, Price RI, Prince RL
Osteoporos Int 2009;20:1539-45

10.4.37 The geographic availability and associated utilization of dual-energy X-ray absorptiometry (DXA) testing among older persons in the United States
Curtis JR, Laster A, Becker DJ, Carbone L, Gary LC, Kilgore ML, Matthews RS, Morrisey MA, Saag KG, Tanner SB, Delzell E
Osteoporos Int 2009;20:1553-61

10.4.38 Quantitative computed tomography (QCT) of the forearm using general purpose spiral whole-body CT scanners: Accuracy, precision and comparison with dual-energy X-ray absorptiometry (DXA)
Engelke K, Libanati C, Liu Y, Wang H, Austin M, Fuerst T, Stampa B, Timm W, Genant HK
Bone 2009;45:110-8

10.4.39 Measurement of human trabecular bone by novel ultrasonic bone densitometry based on fast and slow waves
Yamamoto T, Otani T, Hagino H, Katagiri H, Okano T, Mano I, Teshima R
Osteoporos Int 2009;20:1215-24

10.4.40 The impact of accurate positioning on measurements made by peripheral QCT in the distal radius
Marjanovic EJ, Ward KA, Adams JE
Osteoporos Int 2009;20:1207-14

10.4.41 Lateral bone density variations in the scoliotic spine
Adam CJ, Askin GN
Bone 2009;45:799-807

Progress in
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editor E. Seeman

Volume 10, Issue 4, 2009

Bone Material

10.4.42 Cortical bone mineralization differences between hip-fractured females and controls: A microradiographic study

Wu Y, Bergot C, Jolivet E, Zhou LQ, Laredo JD, Bousson V
Bone 2009;45:207-12

The degree of mineralization of bone tissue (DMB) was compared in femoral neck cortex from 23 women with hip fractures (age, 65-96 years) and 14 female controls (age, 75-103 years) using quantitative microradiography. Variables were DMB in osteons (oDMB$_{Al}$mean) and interstitial tissue (exDMB$_{Al}$mean). DMB was lower in the osteons than in the interstitial tissue in both groups (hip fracture group, P=0.000; control group, P=0.001). DMB values in osteons and interstitial tissue were greater in the hip fracture patients than in the controls (P=0.007 and P=0.005, respectively).

10.4.43 Use of FTIR spectroscopic imaging to identify parameters associated with fragility fracture

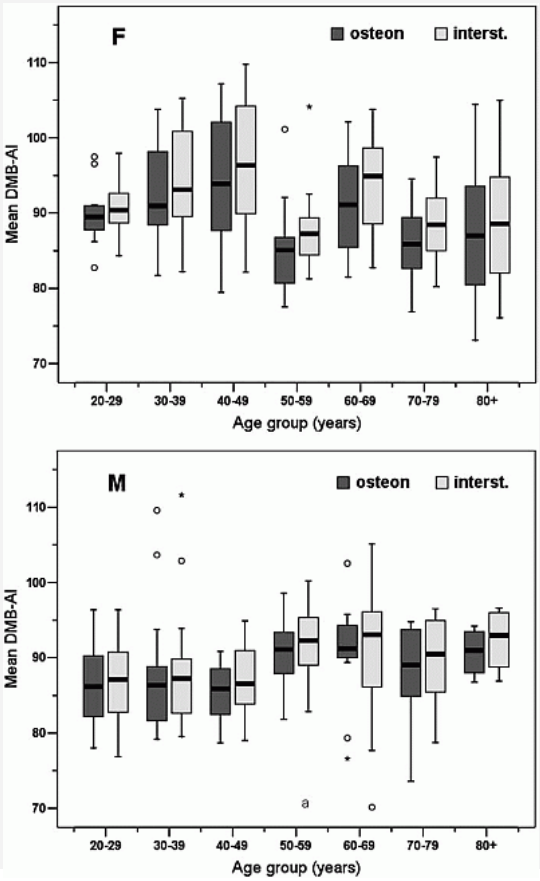
Gourion-Arsiquaud S, Faibish D, Myers E, Spevak L, Compston J, Hodsman A, Shane E, Recker RR, Boskey ER, Boskey AL
J Bone Miner Res 2009;24:1565-71

Fourier transform infrared spectroscopic imaging (FTIRI) and analysis revealed that cortical and cancellous bone from 54 women (32 with fractures, 22 without) age from 30-83 yr had parameters associated with fracture including cortical and cancellous collagen maturity (increased with increased fracture risk), cortical mineral/matrix ratio (higher with increased fracture risk), and cancellous crystallinity (increased with increased fracture risk). Hip BMD was associated with fracture risk in the cortical but not the cancellous model.

10.4.44 The degree and distribution of cortical bone mineralization in the human femoral shaft change with age and sex in a microradiographic study

Bergot C, Wu Y, Jolivet E, Zhou LQ, Laredo JD, Bousson V
Bone 2009;45:435-42

The aim of this in vitro cross-sectional study of human femoral midshafts was to define age- and sex-related differences in the degree and distribution of cortical mineralization. Cortical bone specimens from 193 femurs were studied using quantitative microradiography. The femurs were from 99 females and 94 males. Degree of tissue mineralization (Tt.DMB-Al) decreased with age in females (r=–0.257; P=0.010) but not in males. Tt.DMB-Al was higher in females than males until 50 years of age (P=0.001) but was lower in elderly females than elderly males (P=0.016). DMB-Al distribution varied with sex and age. The first DMB-Al quartiles in osteons and interstitial tissue were not different between males and females, but the third quartile and interquartile range differed (P=0.032 and P=0.000, respectively). The mineralization difference between the two tissues indicated greater bone heterogeneity in females than males (P=0.000). In females, mineralization started at a higher level than in males but was lower in the sixth decade, falling below the level in males. Mineralization was far more stable throughout life in males. In elderly females, the lower degree and greater heterogeneity of mineralization may have consequences on bone strength.



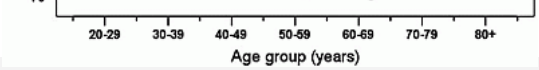


Fig. 10.4.44 Whisker plots for DMB-Al in osteons (dark) and interstitial tissue (light) by age group. F: females; M: males. Reproduced from Bone, 45:435-42, Copyright (2009), with permission from Elsevier.

10.4.45 Determining the elastic modulus of mouse cortical bone using electronic speckle pattern interferometry (ESPI) and micro computed tomography: A new approach for characterizing small-bone material properties
Chattah NL, Sharir A, Weiner S, Shahar R
Bone 2009;45:84-90

Electronic speckle pattern interferometry, an optical method, enables the measurement of displacements on the bone surface, as it is compressed under water. Tubular cortical bone segments (2 mm) were cut from the diaphyses of femora of four week old C57BL/6 (B6) female mice and compressed axially using a mechanical tension-compression device. Displacements in the loading direction were mapped on the bone surface after loading the specimen. A linear regression of the displacement vs. axial-position enabled the calculation of the effective strain. The effective elastic modulus was calculated from the stress to strain ratio. Diaphyses of mouse femora were shown to have mean elastic moduli of 10.4±0.9 GPa for femora frozen for eight months, 8.6±1.4 GPa for femora frozen for two weeks and 8.9±1.1 GPa for the fresh femora.

10.4.46 Spatial and temporal variations of mechanical properties and mineral content of the external callus during bone healing
Manjubala I, Liu Y, Epari DR, Roschger P, Schell H, Fratzl P, Duda GN
Bone 2009;45:185-92

The aim of this study is to correlate the spatial and temporal variations in the mineral content and the nanoindentation modulus of the callus formed via intramembranous ossification over the course of bone healing. Midshaft tibial samples from a sheep osteotomy model at time points of 2, 3, 6 and 9 weeks were employed. The resulting indentation modulus maps show the heterogeneity in the modulus in the selected regions of the callus. The indentation modulus of the embedded callus is about 6 GPa at the early stage. At later stages of mineralization, the average indentation modulus reaches 14 GPa. Most interestingly the average indentation modulus, even at 9 weeks, remains as low as 13 GPa, which is roughly 60% of that for cortical sheep bone.

10.4.47 Effects of 20% demineralization on surface physical properties of compact bone scaffold and bone remodeling response at interface after orthotopic implantation
Mo XT, Yang ZM, Qin TW
Bone 2009;45:301-8

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editor E. Seeman

Volume 10, Issue 4, 2009

Bone Structure

10.4.48 Bone microarchitecture and determinants of strength in the radius and tibia: Age-related changes in a population-based study of normal adults measured with high-resolution pQCT

Dalzell N, Kaptoge S, Morris N, Berthier A, Koller B, Braak L, van Rietbergen B, Reeve J
Osteoporos Int 2009;20:1683-94

In 58 males and 74 females aged 20-79 years, age-related changes and sex differences were similar for pQCT at the radius and tibia. At each site, bone density, cortical thickness and trabecular microarchitecture (number, separation and thickness) were lower (trabecular separation higher) in women than men. Changes with age were most apparent for bone density and cortical thickness, which declined with age, trabecular microarchitecture parameters were not associated with age ($p>0.05$) in either sex. Cortical bone density and thickness declined faster in women than men after age 50 and trabecular bone density was lower in women. FE analysis predicted failure load decreased with age and percentage of load carried by trabecular bone increased ($p<0.05$). The faster decline in cortical bone thickness and density in women than men after age 50 and lower trabecular bone density in women have implications for the excess risks of wrist and hip fractures in women.

10.4.49 The relation of femoral osteon geometry to age, sex, height and weight

Britz HM, Thomas CD, Clement JG, Cooper DM
Bone 2009;45:77-83

Van Oers et al. described a mechanism by which osteon size may be regulated inversely by strain. To determine if there is a link between weight and osteon geometry in human bone, osteons (n=12,690) were mapped within femoral mid-diaphyseal specimens (n=88; 45 males, 43 females; 17-97 yrs). Weight was negatively related to On.Ar and On.Dm ($p=0.006$ and $p=0.004$, respectively). Age was related to osteon and, it was also related to circularity (all $p<0.001$). This relation was negative for On.Ar and On.Dm and positive for On.Cr (increasing circularity with age). On.Ar and On.Dm were different between the sexes with females having smaller osteons. No relation between sex and On.Cr was detected ($p=0.449$). Height was not related to geometric parameters. Age accounted for the largest proportion (On.Ar: 28%; On.Dm: 18%; On.Cr: 30%), weight the second largest (On.Ar: 9%; On.Dm: 10%), and sex the smallest proportion (On.Ar: 6%; On.Dm: 7%), of the variance in geometry.

10.4.50 Geometry of a weight-bearing and non-weight-bearing bone in the legs of young, old, and very old men

McNeil CJ, Raymer GH, Doherty TJ, Marsh GD, Rice CL
Calcif Tissue Int 2009;85:22-30

Magnetic resonance images of the right leg were acquired in 13 young (26 yr), 13 old (66 yr), and 13 very old men (83 yr). Cortical CSA was approximately 14-22% smaller in the elderly in the tibia but similar across age in the fibula. Medullary CSA was larger with age (approximately 5-65%) in both bones but approximately 15-440% greater in the tibia than fibula. Total CSA was similar across age in both bones. Muscle mass was similar between young and old but approximately 25% less in the very old and as a consequence, the magnitude of differences in bone geometry at proximal and distal sites varied in the two elderly groups.

10.4.51 Race and sex differences in BMD and geometry at the femur

Peacock M, Buckwalter KA, Persohn S, Hangartner TN, Econs MJ, Hui S
Bone 2009;45:218-25

Healthy American white (n=612) and black (n=164) premenopausal women, aged 23-57 years, and healthy American white (n=492) and black (n=169) men, aged 20-63 years, had vBMD and geometry measured at the femur by CT, and aBMD at femoral neck measured by DXA. American blacks had higher vBMD at the femoral neck and femoral shaft cortex than American whites, whereas femoral axis length and femoral neck area were not different. Men had lower vBMD at the femoral neck and femoral cortex than women but had greater femoral axis length and femoral neck area than women. The higher aBMD in American blacks than whites persisted after correction for measured area whereas the higher aBMD in men than women disappeared. At the femoral neck, American whites have lower bone density than American blacks but similar geometry. Women have higher bone density than men in both races but have smaller geometry variables.

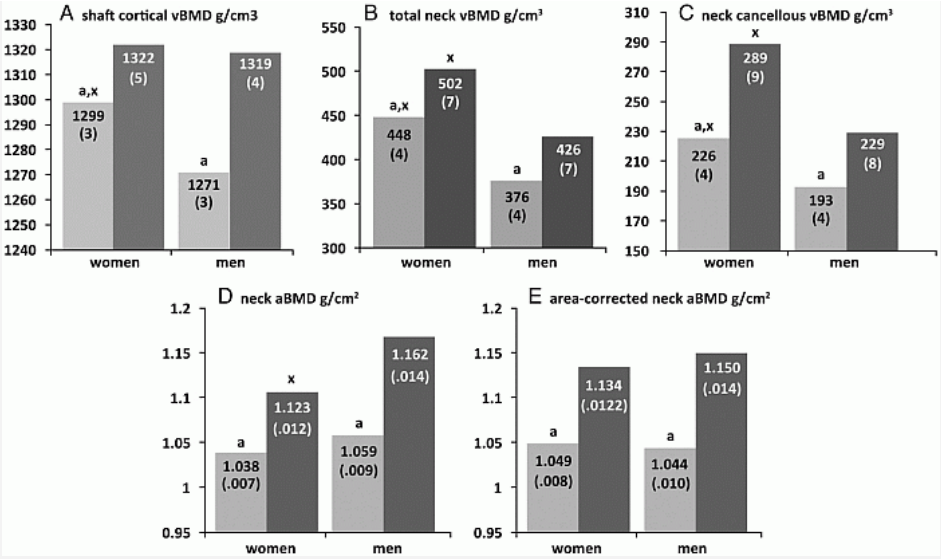

Fig. 10.4.51a Age-corrected: A. femoral shaft cortical vBMD; B. femoral total neck vBMD; C. femoral neck cancellous vBMD; D. femoral neck aBMD; E femoral neck aBMD also corrected for area measured, in white □ and black ■ women and men. Data are expressed as mean (standard error, se); a, p<0.001 difference between races; x, p<0.001 difference between sexes. Reproduced from Bone, 45:218-25, Copyright (2009), with permission from Elsevier.

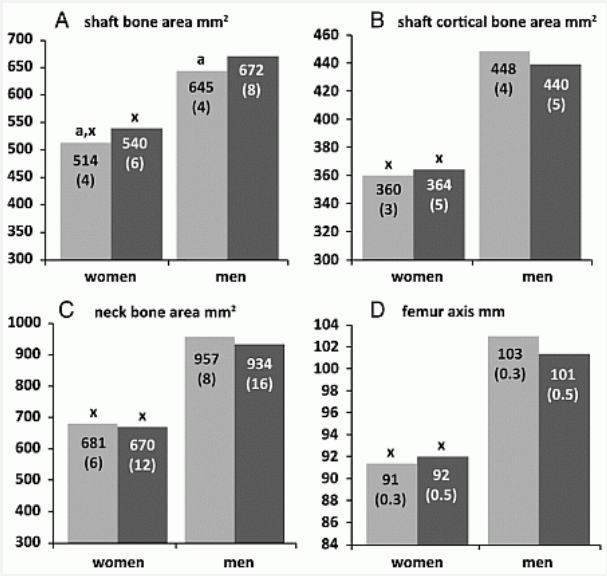

Fig. 10.4.51b Age-corrected: A. femoral shaft area; B. femoral shaft cortical area; C. femoral neck area; and D. femoral axis length in white □ and black ■ women and men. Data are expressed as mean (standard error, se); a, p<0.001 difference between races; x, p<0.001difference between sexes. Reproduced from Bone, 45:218-25, Copyright (2009), with permission from Elsevier.

10.4.52 Role of trabecular microarchitecture in whole-vertebral body biomechanical behavior

Fields AJ, Eswaran SK, Jekir MG, Keaveny TM
J Bone Miner Res 2009;24:1523-30

22 human T9 vertebral bodies (11 female; 11 male; age 53-97 yr, 81.5±9.6 yr) were scanned with μCT and analyzed. 16 were tested to measure compressive strength. To estimate vertebral compressive stiffness with and without the cortical shell for all 22 vertebrae, two high-resolution finite element models per specimen, one intact model and one with the shell removed, were created from the μCT scans and virtually compressed. BMC and the structural model index (SMI) were associated with strength (R^2=0.57 each). Adding microarchitecture variables to BMC in a stepwise multiple regression model improved this association (R^2=0.85). However, the microarchitecture variables in that regression model (degree of anisotropy, bone volume fraction) differed from those when BMC was not included in the model (SMI, mean trabecular thickness), and the association was slightly weaker for the latter (R^2=0.76). The finite element results indicated that the presence of the cortical shell did not alter the relationships between microarchitecture and vertebral stiffness.

10.4.53 Trabecular bone structure analysis in the osteoporotic spine using a clinical in vivo setup for 64-slice MDCT imaging: Comparison to microCT imaging and microFE modeling

Issever AS, Link TM, Kentenich M, Rogalla P, Schwieger K, Huber MB, Burghardt AJ, Majumdar S, Diederichs G
J Bone Miner Res 2009;24:1628-37

In 45 lumbar vertebral bodies MDCT (mean in-plane pixel size, 274 μm^2; slice thickness, 500 μm) correlated with structure by μCT (resolution 16 μm) and to μFE of apparent modulus and stiffness. MDCT-derived BMD and structure correlated with density and structure by μCT (BMD, R^2=0.86, p<0.0001; BV/TV, R^2=0.64, p<0.0001; Tb.Th, R^2=0.36, p<0.01). When comparing μCT measures with μFE models, the correlations (p<0.001) found for apparent modulus and stiffness, respectively: BMD (R^2=0.58 and 0.66), BV/TV (R^2=0.44 and 0.58), and SMI (R^2=0.44 and 0.49). The highest correlation (p<0.001) with μFE app. modulus (R^2=0.75) and stiffness (R^2=0.76) was achieved by the combination of QCT-derived BMD with the bone texture measure Minkowski Dimension. In summary, although still limited by its spatial resolution, trabecular bone structure assessment using MDCT is overall feasible. However, when comparing with μFE-derived bone properties, BMD is superior compared with

single parameters for microarchitecture, and correlations further improve when combining with texture measures.

10.4.54 Spatial variation in osteonal bone properties relative to tissue and animal age

Gourion-Arsiguaud S, Burket JC, Havill LM, DiCarlo E, Doty SB, Mendelsohn R, van der Meulen MCH, Boskey A
J Bone Miner Res 2009;24:1271-81

Based on Fourier transform infrared (FTIR) analysis from baboons between 0 and 32 yr of age, variations in bone properties as a function of tissue age are reported. The patterns observed were independent of animal age and positively correlated with bone tissue elastic behavior measured by nano-indentation. As long as tissue age is expressed as a percentage of the entire osteon radius, osteonal analyses can be used to characterize disease changes independent of the size of the osteon. These mineral and matrix analyses can be used to explain bone fragility. The mineral content (mineral-to-matrix ratio) correlated with the animal age in interstitial and newly formed bone tissue, showing that age-related changes in BMC can be explain by an alteration in the mineralization process.

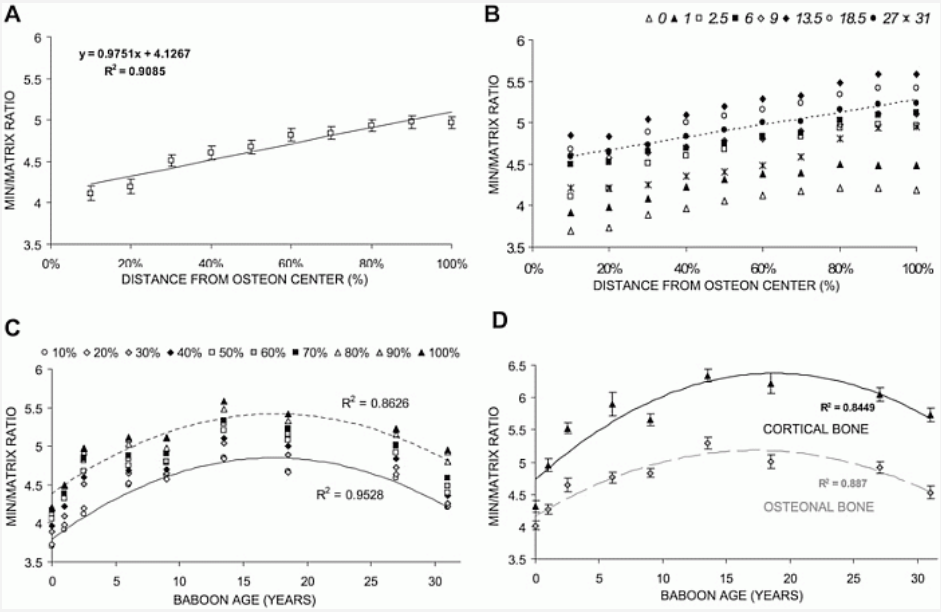

Fig. 10.4.54a FTIR analysis of the mineral-to-matrix ratio. (A) Typical data obtained for this ratio as a function of the distance along osteons from one baboon age group (2.5 yr). (B) Average mineral-to-matrix ratio calculated along the osteons for the nine baboon age groups. (C) Mineral-to-matrix ratio plotted as a function of the baboon age for each osteonal sections (0.83< r^2 <0.89). (D) Comparison of the mineral-to-matrix ratio plotted as a function of the baboon age recorded in the total cortical bone (triangles) and in individual osteons (diamonds) from the same baboon section. Values are mean±SD (n=36). Reproduced from J Bone Miner Res 2009;24:1271-81 with permission of the American Society of Bone and Mineral Research.

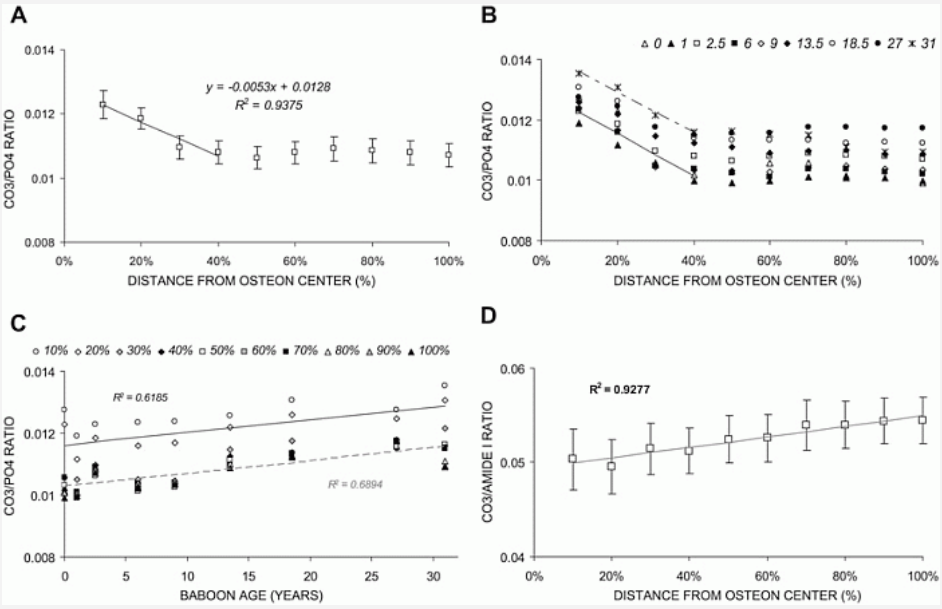

Fig. 10.4.54b FTIR analysis of carbonate substitution. (A) Typical data obtained for the carbonate-to-phosphate (CO_3/PO_4) ratio as a function of the distance along osteons from one baboon age group (2.5 yr). (B) CO_3/PO_4 ratio along the osteons for the nine baboon age groups. (C) CO_3/PO_4 ratio plotted in function of the baboon age for each section along the line from the osteon center (0.6< r^2). (D) Carbonate-to-matrix (CO_3/amide I) ratio plotted as a function of the distance along osteons from 2.5-yr-old baboon group. Values are mean±SD (n=36). Reproduced from J Bone Miner Res 2009;24:1271-81 with permission of the American Society of Bone and Mineral Research.

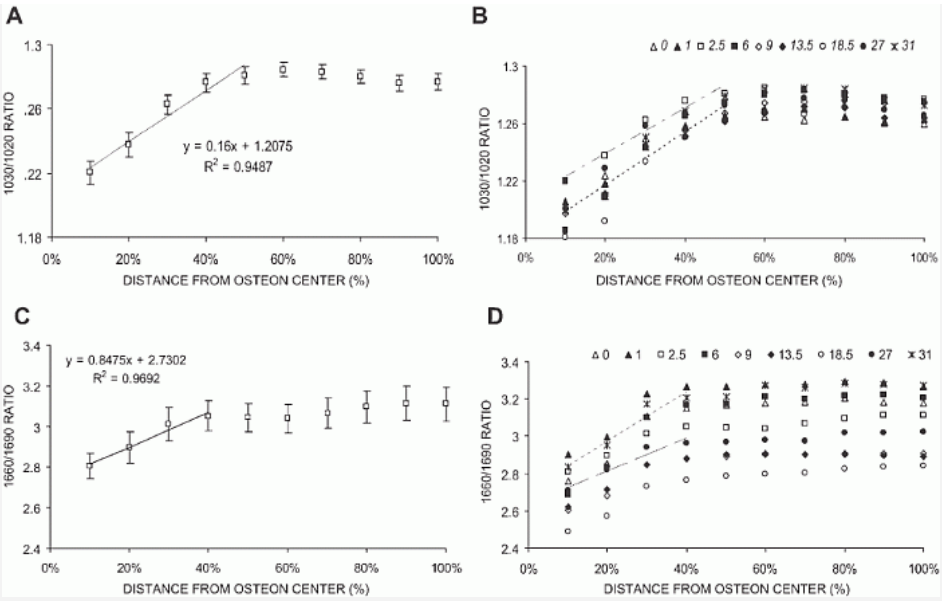

Fig. 10.4.54c Crystallinity (1030/1020 cm^{-1}) and crosslink (1660/1690 cm^{-1}) ratio in baboon osteonal bone. (A) Typical data for the crystallinity ratio plotted as a function of the distance along osteons from the 2.5-yr-old baboon group and (B) crystallinity along the osteons for the nine baboon age groups. (C) Typical data for the crosslink ratio plotted as a function of the distance along osteons from one baboon age group (2.5 yr) and (D) crosslink ratio along the osteons for the nine baboon age groups. Value are mean±SD (n=36). Reproduced from J Bone Miner Res 2009;24:1271-81 with permission of the American Society of Bone and Mineral Research.

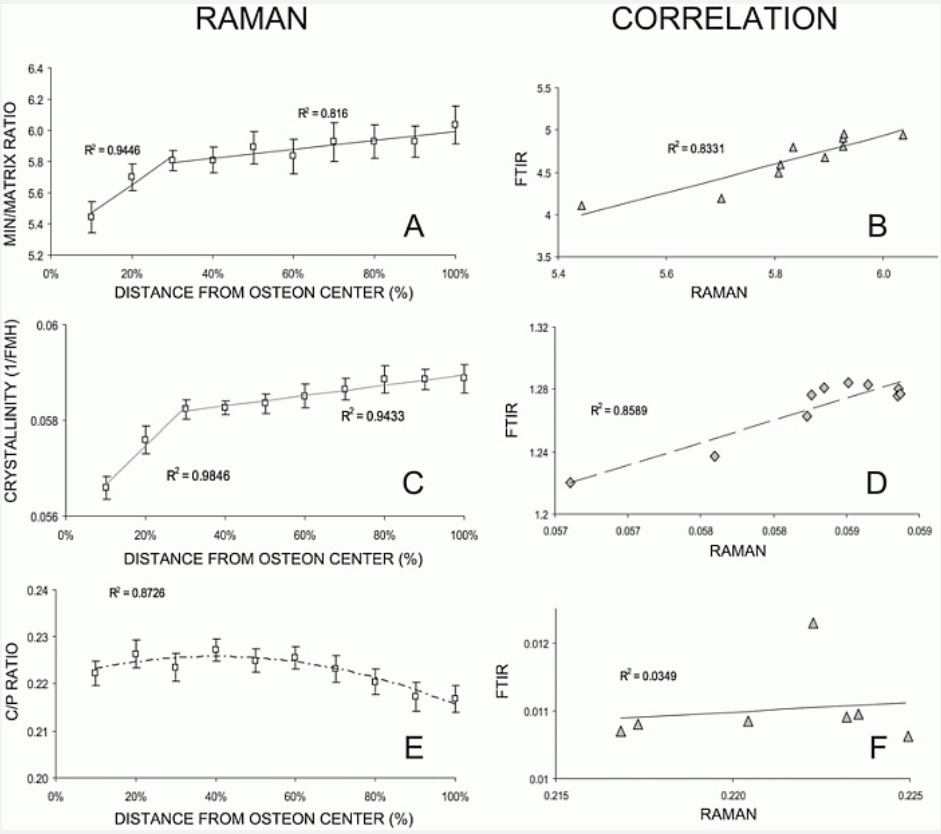

Fig.10.4.54d Raman data and correlation between Raman and FTIR parameters. All parameters were plotted as a function of the distance along individual osteons from the 2.5-yr baboon age group. Where shown, error bars are ±SD (n=36). (A) Typical Raman data for mineral-to-matrix ratio and (B) the linear correlation found between the Raman ratio and the FTIR mineral-to-matrix ratio. (C) Typical Raman data for the crystallinity (=1/bandwidth [960 cm^{-1}]) and (D) the linear correlation between the crystallinity parameter calculated by Raman and by FTIR. (E) Raman carbonate-to-phosphate ratio along osteons and (F) the linear regression calculated between Raman and FTIR parameters. Reproduced from J Bone Miner Res 2009;24:1271-81 with permission of the American Society of Bone and Mineral Research.

10.4.55 Transient overexpression of sonic hedgehog alters the architecture and mechanical properties of trabecular bone

Kiuru M, Solomon J, Ghali B, van der Meulen M, Crystal RG, Hidaka C

J Bone Miner Res 2009;24:1598-607

10.4.56 Formation of tethers linking the epiphysis and metaphysis is regulated by vitamin D receptor-mediated signaling

Chen J, Lee CS, Coleman RM, Yoon JY, Lohmann CH, Zustin J, Guldberg RE, Schwartz Z, Boyan BD

Calcif Tissue Int 2009;85:134-45

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Biomechanics

10.4.57 Bone creep can cause progressive vertebral deformity

Pollintine P, Luo J, Offa-Jones B, Dolan P, Adams MA
Bone 2009;45:466-72

Sustained compressive loading can cause progressive creep deformity in elderly human vertebrae. 27 thoracolumbar "motion segments" (two vertebrae and the intervening disc and ligaments) were dissected from 20 human cadavers aged 42-91 yrs. A constant compressive force of 1.0 kN was applied to each specimen for either 0.5 h or 2 h, while the anterior, middle and posterior heights of each of the 54 vertebral bodies were measured at 1 Hz using a MacReflex 2D optical tracking system. In the 0.5 h tests, creep deformation in the anterior, middle and posterior vertebral cortex averaged 4331, 1629 and 614 microstrains respectively, where 10,000 μ-strains represents 1% loss in height. Anterior creep strains exceeded posterior ($P<0.01$) so that anterior wedging increased by an average 0.08° (STD 0.14°). Similar results were obtained after 2 h, indicating that creep rate slowed with time. Less than 40% of the creep strain was recovered after 2 h. Increases in anterior wedging during the 0.5 h creep test were inversely proportional to BMD, but only in a selected subset of 20 specimens with average BMD<0.15 g/cm^3 ($P=0.042$). Creep deformation caused more than 5% height loss in four vertebrae.

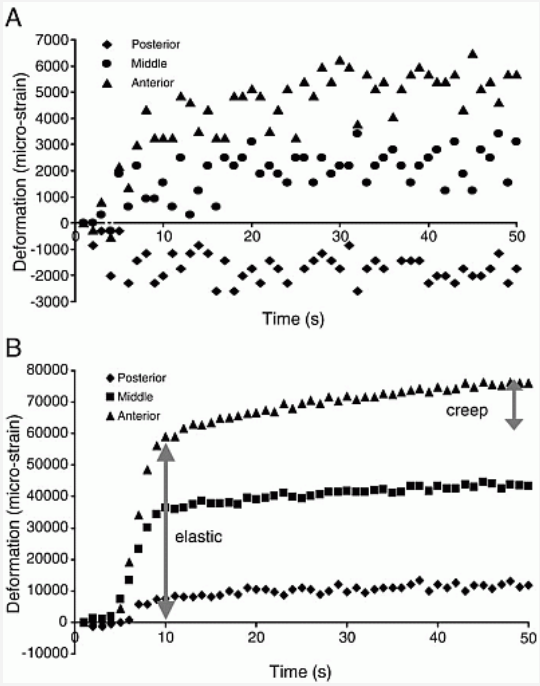

Fig. 10.4.57a MacReflex data (unsmoothed) showing deformations of the posterior, middle and anterior vertebral body during the first 50 s of creep tests. (A) This specimen showed typical deformations of several thousand microstrains. Note the considerable random errors. Compressive strains are shown as positive, so the posterior vertebral body appears to increase slightly in height when loading is applied, possibly as a result of pin-movement artifact. (B) Much larger deformations occurred in four Group B vertebrae, including this one (female, aged 52 yrs, T11/12). "Elastic" deformations were defined as those occurring during load application (3-8 s) and during the following 2 s, and "creep deformation" was defined as all deformation after 10 s. These deformations are labelled for the anterior vertebral body. Reproduced from Bone, 45:466-72, Copyright (2009), with permission from Elsevier.

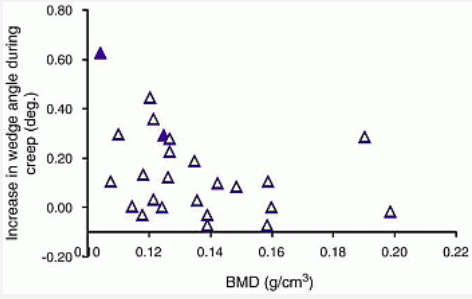

Fig. 10.4.57b Increased anterior wedging of the vertebral body during 0.5 h creep loading appeared to depend on volumetric BMD. Data is presented for all specimens in which neural arch load-bearing was less than 20%, and so would not have interfered greatly in the creep process. In vertebral bodies with BMDb0.15 g/cm^3, anterior wedging increased as BMD decreased, but this was significant only if two specimens were included (solid symbols) which may have been damaged prior to testing ($r^2=0.21$, $P=0.042$, $n=20$). Reproduced from Bone, 45:466-72, Copyright (2009), with permission from Elsevier.

10.4.58 Prediction of proximal femur strength using a CT-based nonlinear finite element method: Differences in predicted fracture load and site with changing load and boundary conditions

Bessho M, Ohnishi I, Matsumoto T, Ohashi S, Matsuyama J, Tobita K, Kaneko M, Nakamura K
Bone 2009;45:226-31

Contralateral femora were analyzed in 42 women with hip fracture (mean age, 82.4 years), comprising 20 neck fractures and 22 trochanteric fractures. One stance loading configuration (SC) and four different fall loading configurations (FC) were assigned. Mean predicted fracture load in the SC was 3150 N. Mean fracture loads were 2270 N in FC1, 1060 N in FC2, 980 N in FC3, and 710 N in FC4. The correlation between predicted fracture loads in SC and those in each FC was 0.467-0.631. Predicted fracture sites in the SC appeared at the subcapital region (neck fracture). However, trochanteric fractures occurred in all fall configurations, except FC1. In FC1, a correlation was seen between real fracture type and predicted type.

10.4.59 Calcium response in single osteocytes to locally applied mechanical stimulus: Differences in cell process and cell body

Adachi T, Aonuma Y, Tanaka M, Hojo M, Takano-Yamamoto T, Kamioka H
J Biomech 2009;42:1989-95

A mechanical stimulus was applied to a single osteocyte. Application of the local deformation induced calcium transients in the vicinity of the stimulated point and caused diffusive wave propagation of the calcium transient to the entire intracellular region. The rate of cell response was higher when applied to the cell processes than applied to the cell body. A large deformation was necessary at the cell body to induce calcium transients, whereas a relatively small deformation was sufficient at the cell processes, suggesting that the mechanosensitivity of the cell processes was higher than that of the cell body.

10.4.60 Osteocyte morphology in human tibiae of different bone pathologies with different BMD – is there a role for mechanosensing?

van Hove RP, Nolte PA, Vatsa A, Semeins CM, Salmon PL, Smit TH, Klein-Nulend J
Bone 2009;45:321-9

Confocal laser scanning microscopy and nano-CT were used to quantitatively determine 3D morphology and alignment of osteocytes and osteocyte lacunae in human proximal tibial bone with relatively low (osteopenic), medium (osteoarthritic), and high (osteopetrotic) BMD. Osteopenic osteocytes were relatively large and round (lengths 8.9:15.6:13.4 μm), osteopetrotic osteocytes were small and discoid shaped (lengths 5.5:11.1:10.8 μm), and osteoarthritic osteocytes were large and elongated (lengths 8.4:17.3:12.2 μm). Osteopenic osteocyte lacunae showed 3.5-fold larger volume and 2.2-fold larger surface area than osteoarthritic lacunae, whereas osteopetrotic lacunae were 1.9-fold larger and showed 1.5-fold larger surface area than osteoarthritic lacunae. Osteopetrotic osteocyte lacunae had lower alignment than osteopenic and osteoarthritic lacunae as indicated by their lower degree of anisotropy. The differences in 3D morphology of osteocytes and their lacunae in long bones of different pathologies.

10.4.61 Correlation of pQCT bone strength index with mechanical testing in distraction osteogenesis

Kokoroghiannis C, Charopoulos I, Lyritis G, Raptou P, Karachalios T, Papaioannou N
Bone 2009;45:512-6

Distraction osteogenesis is a method of treatment of non-unions and limb length discrepancies. The hypothesis was that a noninvasive strength marker, the strength-strain index (SSI) measured by peripheral quantitative computerized tomography (pQCT), correlated with a biomechanical bone strength index, the maximum load at bone failure (F_{max}), assessed in a 3-point bending. The right tibias of 15 male New Zealand White rabbits were subjected to lengthening using an external fixator. SSI showed a positive correlation with the maximum load (F_{max}), R=0.846 ($p<0.001$), and it was a good predictor of F_{max} since it was able to describe the 71.6% of variability of F_{max} ($R^2=0.716$). Furthermore, cortical bone area correlated with F_{max} ($p<0.005$), but it was a less efficient predictor of F_{max} ($R^2=0.471$). There was, also, a significant correlation between SSI and bone stiffness as assessed in the 3-point bending test ($p<0.005$). SSI can be used as a sensitive index of adequate consolidation of the regenerate bone.

10.4.62 Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models

Tanck E, van Aken JB, van der Linden YM, Schreuder HW, Binkowski M, Huizenga H, Verdonschot N
Bone 2009;45:777-83

10 human cadaver femurs were scanned using QCT. In one femur of each pair a hole (size 22, 40, or 45 mm diameter) was drilled at the anterior or medial side to simulate a metastatic lesion. All femurs were tested to failure under single-limb stance-type loading. The failure force was calculated using nonlinear FE-models, and 6 clinical experts were asked to rank the femurs from weak to strong based on X-rays, gender, age, and the loading protocol. Kendall Tau correlation coefficients were calculated to compare the predictions of the FE-model with the predictions of the cliniciansThe FE-failure predictions correlated with the experimental failure force ($r^2=0.92$, $p<0.001$). For the clinical experts, the Kendall Tau coefficient between the experimental ranking and predicted ranking ranged between tau=0.39 and tau=0.72, whereas this coefficient was considerably higher (tau=0.78) for the FE-model. Use of a nonlinear FE-model can improve the prediction of bone strength compared to the prediction by clinical experts.

10.4.63 Trabecular microfracture precedes cortical shell failure in the rat caudal vertebra under cyclic overloading

Kummari SR, Davis AJ, Vega LA, Ahn N, Cassinelli EH, Hernandez CJ
Calcif Tissue Int 2009;85:127-33

Rat caudal vertebrae (C7-C9, n=22) were potted in bone cement and subjected to cyclic compressive loading from 0 to 260 N. Loading was terminated in the secondary and tertiary phases of the creep-fatigue curve using custom data-monitoring software. In cancellous bone, trabecular microfracture was the primary form of microdamage observed with few microcracks. Trabecular microfracture prevalence increased with the amount of cyclic loading and occurred in nine out of 10 specimens loaded into the tertiary phase. Only small amounts of microdamage were observed in the cortical shell of the vertebrae, demonstrating that, under axial cyclic loading, damage occurs primarily in regions of cancellous bone before overt fracture of the bone (macroscopic cracks in the cortical shell).

10.4.64 Time-lapsed assessment of microcrack initiation and propagation in murine cortical bone

at submicrometer resolution
Voide R, Schneider P, Stauber M, Wyss P, Stampanoni M, Sennhauser U, van Lenthe GH, Muller R
Bone 2009;45:164-73

Femora from C3H and B6 were loaded axially under compression, from 0% strain to failure, with 1% strain steps. Between each step, a high-resolution 3D image (700 nm nominal resolution) was acquired at the mid-diaphysis using synchrotron radiation (SR) CT for quantitative analysis of canal network, the osteocyte lacunar system and the emerging microcracks. For C3H mice, the canal, lacunar, and microcrack volume densities accounted for 1.91%, 2.11%, and 0.27% of the cortical total volume at 2% apparent strain, respectively. At 2% apparent strain, the average microcrack thickness for both strains was 2.0 µm. Microcracks initiated at canal and at bone surfaces, whereas osteocyte lacunae provided guidance to the microcracks. Microcracks could appear as linear cracks in one plane, but as diffuse cracks in a perpendicular plane. Images permitted visualization of uncracked ligament bridging.

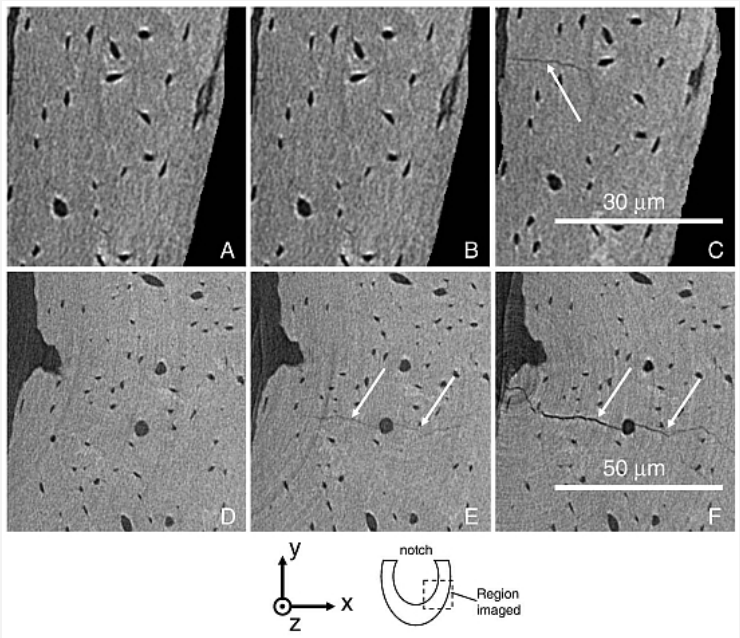

Fig. 10.4.64a Microcrack initiation and propagation in the femoral mid-diaphyseal reduced cross-section. (A) No visible microcracks at 0% apparent strain for the B6 specimen. (B) No visible microcracks at 1% apparent strain for the B6 specimen. (C) Microcrack initiation (arrow) at 2% apparent strain for the B6 specimen. (D) No visible microcracks at 0% apparent strain for the C3H specimen. (E) Microcrack initiation (white arrow) at 1% apparent strain for the C3H specimen. (F) Microcrack propagation (white arrows) at 2% apparent strain for the C3H specimen. (A-F) Data were assessed using SR CT at 700 nm nominal resolution. Reproduced from Bone, 45:164-73, Copyright (2009), with permission from Elsevier.

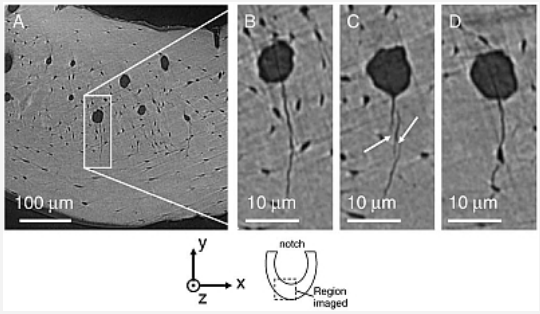

Fig. 10.4.64b Microcrack initiation in the femoral mid-diaphyseal reduced cross-section at 1% apparent strain. (A) Canal network (big void spaces) and osteocyte lacunae (small void spaces). (B) Microcrack initiation at the surface of a canal. (C) Uncracked ligament bridging along the microcrack path (arrows). (D) Microcrack propagation through two osteocyte lacunae. (A-D) The C3H specimen was assessed using SR CT at 700 nm nominal resolution. Reproduced from Bone, 45:164-73, Copyright (2009), with permission from Elsevier.

10.4.65 Subject-specific hip geometry and hip joint centre location affects calculated contact forces at the hip during gait
Lenaerts G, Bartels W, Gelaude F, Mulier M, Spaepen A, Van der Perre G, Jonkers I
J Biomech 2009;42:1246-51

10.4.66 Osteocyte calcium signaling response to bone matrix deformation
Adachi T, Aonuma Y, Ito SI, Tanaka M, Hojo M, Takano-Yamamoto T, Kamioka H
J Biomech 2009;[Epub ahead of print]

10.4.67 Contributions of trabecular rods of various orientations in determining the elastic properties of human vertebral trabecular bone
Liu XS, Zhang XH, Guo XE
Bone 2009;45:158-63

10.4.68 Relating crack-tip deformation to mineralization and fracture resistance in human femur

cortical bone
Chan KS, Chan CK, Nicolella DP
Bone 2009;45:427-34

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Summaries and Critical Analyses of the Current Literature
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Volume 10, Issue 4, 2009

Growth

10.4.69 Prenatal growth restriction and postnatal growth restriction followed by accelerated growth independently program reduced bone growth and strength

Romano T, Wark JD, Owens JA, Wlodek ME
Bone 2009;45:132-41

Bilateral uterine vessel ligation (Restricted) or sham surgery (Control) was performed on gestational day 18 in WKY rats. Control, Reduced (reduced Control litter size to match Restricted) and Restricted pups were cross-fostered onto Control (normal lactation) or Restricted (impaired lactation) mothers one day after birth. Restricted pups were born lighter than Controls with males, not females, remaining smaller than Control-on-Control at 6 months (P<0.05). Pups born of normal weight from a reduced litter suckling on a Restricted mother (Reduced-on-Restricted) grew slowly during lactation then quicker after weaning compared to Controls (P<0.05). Cortical bone mineral content, dimensions and strength were lower in Restricted-on-Restricted and Reduced-on-Restricted offspring compared to Controls with lower density in Reduced-on-Restricted females (P<0.05). The stress strain index of bone bending strength remained lower in the Restricted male offspring when body weight adjustments were made. Cross-fostering Restricted females, but not males, onto mothers with normal lactation (Restricted-on-Control) restored growth and bone parameters to Controls (P<0.05). Being born small, or postnatal growth restriction for normal birth weight offspring followed by accelerated growth, programs bone content and strength deficits. Deficits were corrected by improving postnatal nutrition for females born small, highlighting sex specific programming outcomes and impact of postnatal nutrition.

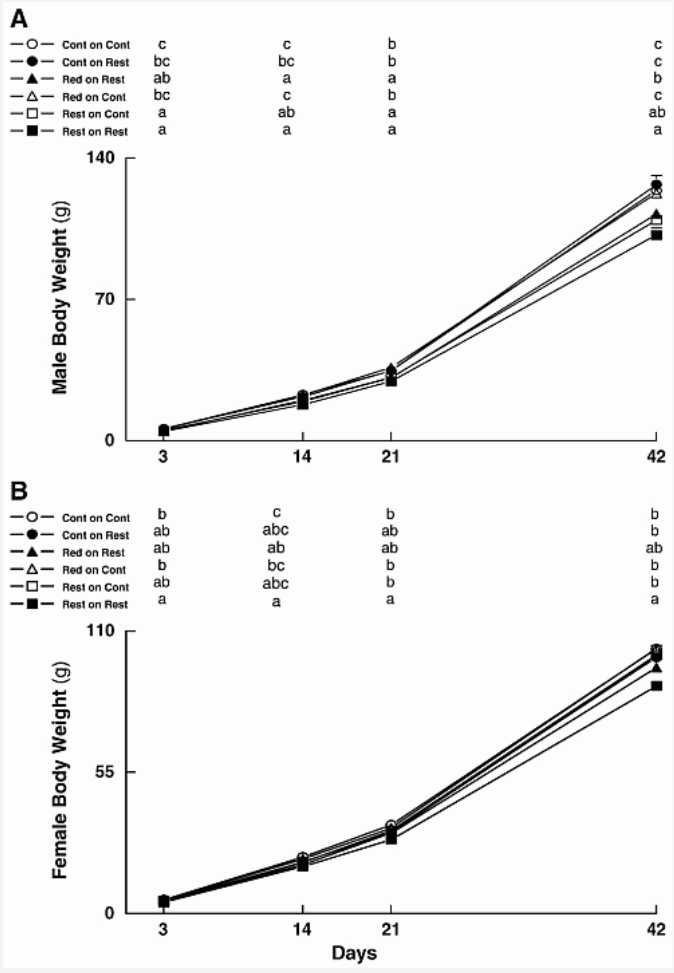

Fig. 10.4.69 Male (A) and female (B) body weight from day 3 to day 42. Male (A) Reduced-on-Restricted, Restricted-on-Control, and Restricted-on-Restricted rats were smaller at all time points compared to Controls (P<0.05). Female (B) Reduced-on-Restricted rats were smaller than Controls on day 14 (P<0.05). Female (B) Restricted-on-Restricted rats were smaller than Control at all ages (P<0.05). By day 21 female (B) Restricted-on-Control rats were larger than Restricted-on-Restricted rats (P<0.05). Data are means±SEM. Significant differences (P<0.05) across groups at a given age are indicated by different letters; for example, "a" is different from "b" but not different from "ab". Reproduced from Bone, 45:132-41, Copyright (2009), with permission from Elsevier.

10.4.70 Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm

Fewtrell MS, Williams JE, Singhal A, Murgatroyd PR, Fuller N, Lucas A
Bone 2009;45:142-9

A 20-year follow-up of 202 subjects (43% male; 24% of survivors) born preterm and randomized to preterm formula vs. banked breast milk or preterm vs. term formula as sole diet or supplement to maternal milk. Infant dietary randomization did not influence peak bone mass or turnover. The proportion of human milk in the diet was associated with whole body bone area and BMC.

Subjects receiving >90% human milk had higher whole body bone are (by 3.5%, p=0.01) and BMC (by 4.8%, p=0.03) than those receiving <10%. Compared to population data, subjects had lower height (-0.41 (SD 1.05)), higher BMI (0.31 (1.33)) and lower lumbar spine BMD (-0.29 (1.16)); height and bone mass deficits were greatest in those born SGA with birth weight <1250 g (height -0.81 (0.95), lumbar spine BMD -0.61 (1.3)). Infant dietary randomization group did not affect peak bone mass or turnover suggesting the reduced height and lumbar spine bone mass may not be related to suboptimal early nutrition. The higher whole body bone mass associated with human milk intake, despite its low nutrient content, may reflect non-nutritive factors in breast milk.

10.4.71 Relationships of appendicular LMI and total body LMI to bone mass and physical activity levels in a birth cohort of New Zealand five-year olds

Goulding A, Taylor RW, Grant AM, Jones S, Taylor BJ, Williams SM
Bone 2009;45:455-9

158 children (59% male) were studied close to their fifth birthday. Girls and boys had similar heights, weights and daily accelerometry counts, but boys had lower fat mass, and higher lean mass and total body BMC than the girls (P<0.00l). In both sexes, children with greater quantities of total and regional lean mass and higher lean mass index (LMI) values had higher bone mass. Appendicular LMI was more strongly associated with BMC than LMI. Accelerometry counts showed no associations with height but were positively associated with lean mass (r=0.23, P<0.03), appendicular LMI (r=0.25 P<0.01), total body BMC (r=0.24, P<0.02) and total body less head BMC (r=0.27 P<0.009) in the boys, but not in the girls. Greater time spent in more intense physical activity was also associated with higher appendicular lean mass and total body less head BMC only in the boys

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10.4.72 Childhood fractures do not predict future fractures: Results from the European Prospective Osteoporosis Study

Pye SR, Tobias J, Silman AJ, Reeve J, O'Neill TW
J Bone Miner Res 2009;24:1314-18

6451 men (mean age, 63.8 yr) and 6936 women (mean age, 63.1 yr) were followed 3 yr. Of these, 574 (8.9%) men and 313 (4.5%) women reported a first fracture (any site) between the ages of 8 and 18 yr. A recalled history of any childhood fracture or forearm fracture was not associated with an increased risk of future limb fracture or prevalent vertebral deformity in either men or women. Among the 4807 subjects who had DXA measurements, there was no difference in bone mass among those subjects who had reported a childhood fracture and those who did not. Self-reported previous childhood fracture is not associated with an increased risk of future fracture in men or women.

10.4.73 Influence of drop-landing exercises on bone geometry and biomechanical properties in prepubertal girls: A randomized controlled study

Greene DA, Wiebe PN, Naughton GA
Calcif Tissue Int 2009;85:94-103

In a 28-week school-based exercise trial of single-leg drop-landing exercise with 42 girls (Tanner stage 1, 6-10 years old) were randomly assigned to control (C), low-drop (LD), or high-drop (HD) exercise groups. The LD and HD groups performed single-leg drop-landings (3 sessions/week and 50 landings/session) from 14 and 28 cm, respectively, using the nondominant leg. Single-leg peak ground-reaction impact forces in a subsample ranged between 2.5- and 4.4-times body weight. A series of ANOVA and ANCOVA tests showed no within- or between-group differences from baseline to post-training. Group comparisons assessing magnitude of change in side-to-side differences in geometry (area cm^2) and cross-sectional moment of inertia (cm^4) at proximal, mid, and distal sites revealed negligible effect sizes. Our findings suggest that strictly controlled unimodal, unidirectional single-leg drop-landing exercises involving low to moderate peak ground-reaction impact forces do not influence geometrical or biomechanical measures in the developing prepubertal female skeleton.

10.4.74 Bone and muscle development during puberty in girls: A seven-year longitudinal study

Xu L, Nicholson P, Wang Q, Alen M, Cheng S
J Bone Miner Res 2009;24:1693-8

This study tested the hypothesis that the growth of muscle size precedes that of bone size (width and length) and mass during puberty in 258 healthy girls at baseline (mean age, 11.2 yr) and 1-, 2-, 3-, 4- and 7-yr follow-up. 70 premenopausal adults, comprising a subset of the girl's mothers (mean age, 41.5 yr), were included. In contrast to the hypothesis, the growth velocity of mCSA peaked one year later than that of tibial outer dimensions (tibial length (TL) and total cross-sectional area (tCSA)) and earlier than total BMC. Whereas TL ceased to increase 2 yr after menarche, tCSA, cortical CSA, total BMC, and muscle CSA continued to increase and were still lower than adult values at the age of 18 yr (all p<0.01). The results do not support the view that muscle force drives the growth of bone size during puberty.

10.4.75 Bone structure at the distal radius during adolescent growth

Kirmani S, Christen D, van Lenthe GH, Fischer PR, Bouxsein ML, McCready LK, Melton LJ, 3rd, Riggs BL, Amin S, Muller R, Khosla S
J Bone Miner Res 2009;24:1033-42

The incidence of distal forearm fractures peaks during the adolescent growth spurt, but the structural basis for this is unclear. Thus, the authors studied healthy 6- to 21-yr-old girls (n=66) and boys (n=61) using high-resolution pQCT (voxel size, 82 μm) at the distal radius. Subjects were classified into five groups by bone-age: group I (prepuberty, 6-8 yr), group II (early puberty, 9-11 yr), group III (midpuberty, 12-14 yr), group IV (late puberty, 15-17 yr), and group V (postpuberty, 18-21 yr). Compared with group I, trabecular parameters (bone volume fraction, trabecular number, and thickness) did not change in girls but increased in boys from late puberty onward. Cortical thickness and density decreased from pre- to midpuberty in girls but were unchanged in boys, before rising to higher levels at the end of puberty in both sexes. Total bone strength, assessed using microfinite element models, increased linearly across bone age groups in both sexes, with boys showing greater bone strength than girls after midpuberty. The proportion of load borne by cortical bone, and the ratio of cortical to trabecular bone volume, decreased transiently during mid- to late puberty in both sexes, with apparent cortical porosity peaking during this time. This mirrors the incidence of distal forearm fractures in prior studies. It was concluded that regional deficits in cortical bone may underlie the adolescent peak in forearm fractures. Whether these deficits are more severe in children who sustain forearm fractures or persist into later life warrants further study.

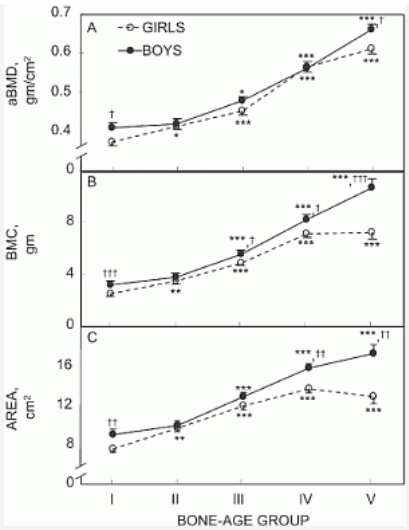

*Fig. 10.4.75a DXA parameters at the radius in bone-age groups I through V. (A) aBMD, (B) BMC, and (C) bone area. *p<0.05, **p<0.01, and ***p<0.001 vs. group I; †p<0.05, ††p<0.01, and †††p<0.001 for comparison with the respective group of girls. Reproduced from J Bone Miner Res 2009;24:1033-42 with permission of the American Society of Bone and Mineral Research.*

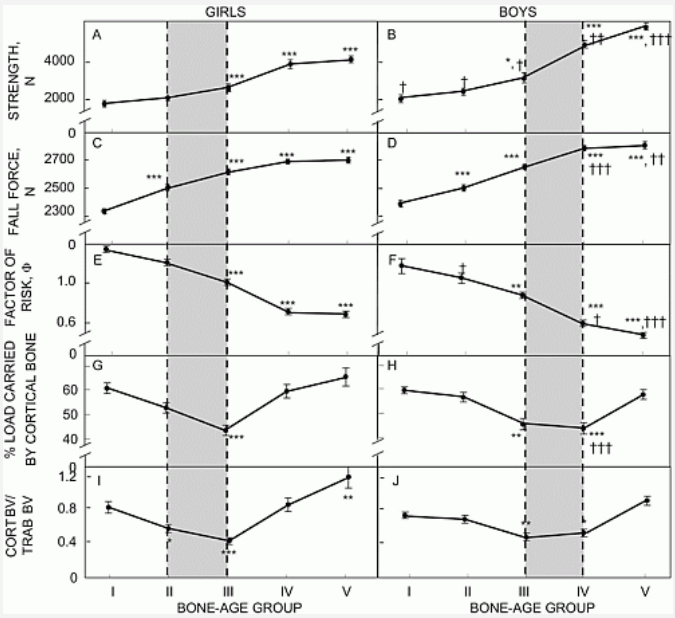

*Fig. 10.4.75b (A and B) Total bone strength; (C and D) estimated fall loads; (E and F) factor of risk (F, ratio of fall loads to bone strength); (G and H) percent of load carried by cortical bone; and (I and J) ratio of cortical to trabecular bone volume in girls (left column) and boys (right column). Shaded regions represent the approximate chronological age ranges when the incidence of adolescent forearm fractures peaks based on previous data from Rochester, MN, and elsewhere. *p<0.05, **p<0.01, and ***p<0.001 vs. group I; †p<0.05, ††p<0.01, and †††p<0.001 for comparison with the respective group of girls. Reproduced from J Bone Miner Res 2009;24:1033-42 with permission of the American Society of Bone and Mineral Research.*

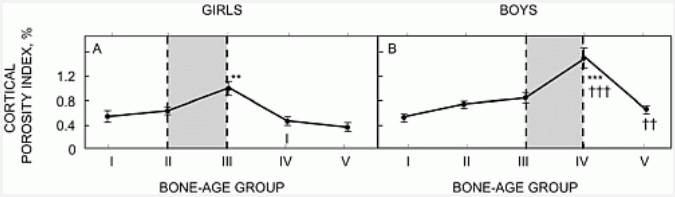

*Fig. 10.4.75c Cortical porosity index in girls (A) and boys (B). Shaded regions represent the approximate chronological age ranges when the incidence of adolescent forearm fractures peaks based on previous data from Rochester, MN, and elsewhere. ***p<0.001 vs. group I; ††p<0.01 and †††p<0.001 for comparison with the respective group of girls. Reproduced from J Bone Miner Res 2009;24:1033-42 with permission of the American Society of Bone and Mineral Research.*

10.4.76 Low volumetric BMD is linked to upper-limb fracture in pubertal girls and persists into adulthood: A seven-year cohort study

Cheng S, Xu L, Nicholson PH, Tylavsky F, Lyytikainen A, Wang Q, Suominen H, Kujala UM, Kroger H, Alen M

Bone 2009;45:480-6

Fracture history from birth to 20 years was obtained in 1034 Finnish girls aged 10-13 years. Bone density and geometry at distal radius, biomarkers and lifestyle/behavioural factors were assessed in a subset of 396 girls with a 7.5-year follow-up. Fracture incidence peaked during puberty (relative risk 3.1 at age of 8-14 years compared to outside this age window), and 38% of fractures were in the upper limb. Compared to the nonfracture cohort, girls who sustained upper limb fracture at ages 8-14 years had lower distal radial vBMD at baseline (258.9±37.5 vs. 287.5±34.1 mg/cm^3, p=0.001), 1-year (252.0±29.3 vs. 282.6±33.5 mg/cm^3, p=0.001), 2-year (258.9±32.2 vs. 289.9±40.1 mg/cm^3, p=0.003), and 7-year follow-up (early adulthood, 307.6±35.9 vs. 343.6±40.9 mg/cm^3, p=0.002). There was a consistent trend towards larger bone cross-sectional area in the fracture cohort

compared to non-fracture. Lower vBMD (p=0.001) was the only predictor of upper-limb fracture during the period of 8-14 years. Low vBMD during childhood is not a transient deficit.

10.4.77 Higher milk requirements for bone mineral accrual in adolescent girls bearing specific Caucasian genotypes in the VDR promoter

Esterle L, Jehan F, Sabatier JP, Garabedian M
J Bone Miner Res 2009;24:1389-97

In 117 healthy European peri- and postmenarcheal girls (14.9±1.6 yr) during a 4-yr follow-up, calcium intakes from milk, nonmilk dairy products, and nondairy products averaged 199, 243, and 443 mg/d. No association between milk intakes and bone mass accrual in girls bearing an A/A genotype at the -1012 VDR promoter locus (30% of the cohort) were seen. A/G or G/G genotype carrying girls had lower spine BMC (-13%, p=0.031), BMD (-10%, p=0.004), and BMD Z-score (-0.84 SD, p=0.0003) when their milk intakes were <260 ml/d compared with genotype-matched girls with higher milk intakes and with girls with an A/A genotype. The negative impact of low milk intake persisted up to 19.0±1.7 yr.

10.4.78 Dairy vs. calcium carbonate in promoting peak bone mass and bone maintenance during subsequent calcium deficiency

Weaver CM, Janle E, Martin B, Browne S, Guiden H, Lachcik P, Lee WH
J Bone Miner Res 2009;24:1411-9

During growth, femurs from rats fed nonfat dry milk solids (NFDM) had 8.4% higher peak breaking force, 6.4% greater Ca content, 4.8% greater weight, 4% greater width, 1.2% greater density, 13.1% greater midshaft cortical thickness, and 16.7% greater midshaft cortical area than from rats fed $CaCO_3$. NFDM group had higher rates of bone formation. If maintained on an adequate calcium diet, many of these advantages disappeared. However, rats fed adequate Ca as NFDM vs. $CaCO_3$ during growth and subsequently switched to deficient Ca as $CaCO_3$ had higher femoral BMD (1.3%), total bone Ca (7.2%), Ca concentration (4.6%), and cortical thickness (9.4%) and a trend (p=0.02) toward greater peak breaking force (17%). Thus, NFDMs improved bone measures during growth and protected bone against a subsequent period of calcium depletion compared with $CaCO_3$.

10.4.79 Relationships of acylated and des-acyl ghrelin levels to bone mineralization in obese children and adolescents

Pacifico L, Anania C, Poggiogalle E, Osborn JF, Prossomariti G, Martino F, Chiesa C
Bone 2009;45:274-9

A prospective cross-sectional study was performed on 100 obese children [age, 8.9 (8.3 to 9.4); BMI-standard deviation score (SDS), 2.2 (2.0 to 2.3)], and 100 age-matched lean healthy subjects. In healthy children, acylated ghrelin was a negative predictor of whole body (WB) BMD, and WB BMC/height, while lean mass was positively associated with these measures. In obese children, a positive association was observed between des-acyl ghrelin and WB BMD as well as WB BMC/height, along with lean mass, and to a lesser degree, with fat mass. Acylated as well as des-acyl ghrelin were not predictors of LS BMD and lumbar spine volumetric BMD in obese as well as control children.

10.4.80 Risedronate in the treatment of mild pediatric osteogenesis imperfecta: A randomized placebo-controlled study

Rauch F, Munns CF, Land C, Cheung M, Glorieux FH
J Bone Miner Res 2009;24:1282-9

26 children and adolescents (age, 6.1-17.7 yr; 11 girls) with OI type I were randomized to placebo (N=13) or risedronate (N=13) for 2 yr. Risedronate doses were 15 mg once per week in patients weighing <40 kg and 30 mg once per week in patients weighing >40 kg. After 2 yrs, risedronate decreased collagen type I N-telopeptide by 35% compared with a 6% reduction with placebo (p=0.003). Risedronate increased lumbar spine areal BMD Z-scores by 0.65, whereas patients receiving placebo experienced a decrease of 0.15 (p=0.002). No differences were found at the radial metaphysis and diaphysis, the hip, and the total body. Bone biopsies did not show a treatment difference in cortical width, trabecular bone volume, or parameters of bone turnover. Similarly, there was no detectable treatment effect on vertebral morphometry, second metacarpal cortical width, grip force, bone pain, or number of new fractures. These results suggest that the skeletal effects of oral risedronate are weaker than those that are commonly observed with intravenous pamidronate but still lead to an increase in lumbar spine areal BMD.

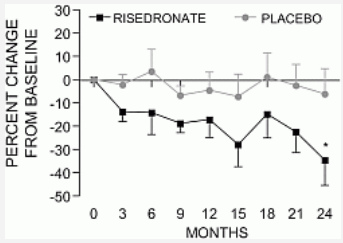

Fig. 10.4.80a Change in serum levels of collagen type I N-telopeptide. Reproduced from J Bone Miner Res 2009;24:1282-9 with permission of the American Society of Bone and Mineral Research.

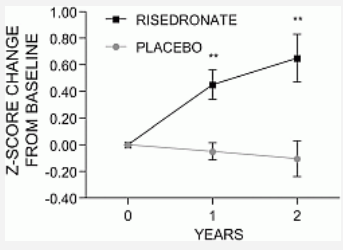

Fig. 10.4.80b Change in lumbar spine (L1-L4) areal BMD. Reproduced from J Bone Miner Res 2009;24:1282-9 with permission of the American Society of Bone and Mineral Research.

10.4.81 Bone health in children and adolescents after renal transplantation
Valta H, Makitie O, Ronnholm K, Jalanko H
J Bone Miner Res 2009;24:1699-708

106 pediatric RTx patients (median age, 12.6 yr; median follow-up, 5.1 yr after RTx) median lumbar spine BMD Z-score was lowest (median, -1.0) at 1 yr postoperatively but increased to a peak value of -0.2 at 5 yr. In boys, the lumbar spine BMD Z-score increased also during puberty but decreased in girls. In cross-sectional analysis, the lumbar spine, hip, and whole body BMD Z-scores were <–2 SD in 4%, 6%, and 6% of the patients, respectively. 16% had sustained peripheral fractures, and 8% had vertebral fractures. Female sex and age >15 yr (OR, 56.26; 95% CI, 5.17-611.82; p=0.0007) as well as high plasma PTH levels (OR, 4.03; 95% CI, 1.37-11.85; p=0.009) were predictors for low BMD. Three-year cumulative glucocorticoid dose, outside the immediate post-RTx years, was not associated with BMD parameters. The observed BMD results were satisfactory. However, the high (8%) prevalence of vertebral fractures warrants careful evaluation of bone health in these patients.

10.4.82 Sex steroids during bone growth: A comparative study between mouse models for hypogonadal and senile osteoporosis
Ophoff J, Venken K, Callewaert F, Boonen S, Bouillon R, Vanderschueren D
Osteoporos Int 2009;20:1749-57

This study characterizes the mechanisms of deficient peak bone mass acquisition in models for senile (SAMP6) and hypogonadal (orchidectomized SAMR1) osteoporosis. Bone mineral acquisition was investigated in SAMP6 and orchidectomized SAMR1 mice SAMP6 mice showed an early (4 weeks) medullary expansion of the cortex due to impaired endocortical bone formation (-43%). Despite compensatory periosteal bone formation (+47%), cortical thickness was reduced in 20-week-old SAMP6 vs. SAMR1. Orchidectomy reduced periosteal apposition between 4 and 8 weeks of age and resulted in high bone turnover and less trabecular bone gain in SAMP6 and SAMR1. DHT and E2 stimulated periosteal expansion and trabecular bone in orchidectomized SAMP6 and SAMR1. E2 stimulated endocortical apposition in SAMP6. Moreover, sex steroid action occurred between 4 and 8 weeks of age. Bone fragility resulted from deficient bone build-up during early puberty. DHT and E2 improved bone mass acquisition in orchidectomized animals, suggesting a role for AR and ER in male skeletal development.

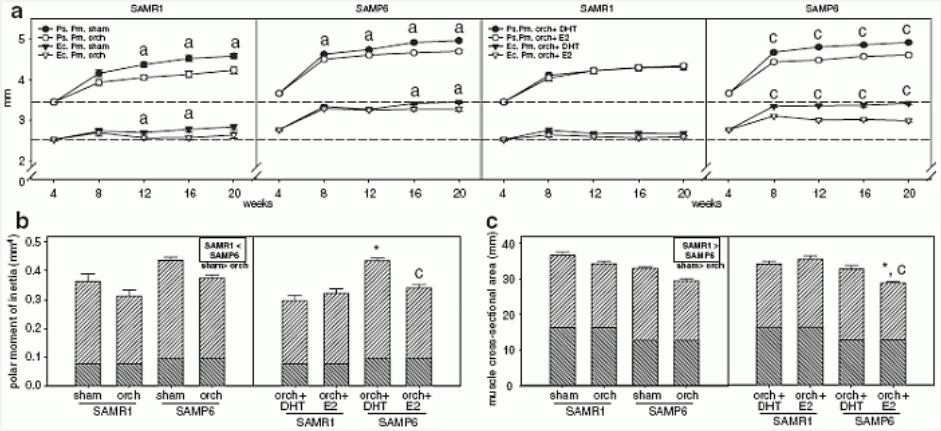

*Fig. 10.4.82 (a) Periosteal (Ps.Pm.) and endosteal perimeter (Ec.Pm.) during the experimental period, (b) polar moment of inertia, and (c) calf muscle cross-sectional area at the end of the experimental period as measured by in vivo pQCT in tibia of sham-operated (sham) and orchidectomized (orch) SAMR1 and SAMP6 mice. Orch mice were treated with either vehicle, 5α-dihydrotestosterone (DHT) or 17β-oestradiol (E2). Data are expressed as mean±SE, n=8-17 mice per group. (a) [a]P<0.05 Student's t-test sham versus orch, [c]P<0.05 orch+DHT versus orch+E2 within genotype. (b-c) Results of two-way ANOVA of values at 20 weeks are shown in the inset. Fisher's least significant difference multiple comparison test was performed after significant interaction (P<0.05): *SAMP6 versus respective SAMR1 group corch+DHT versus orch+E2 within genotype. Baseline values are marked in gray. Reproduced from Osteoporos Int 2009;20:1749-57 with permission from Springer.*

10.4.83 Iliac cortical thickness in the neonate – the gradient effect
Cunningham CA, Black SM
J Anat 2009;215:364-70

10.4.84 Differences in early osteogenesis and bone micro-architecture in anterior lumbar interbody fusion with rhBMP-2, equine bone protein extract, and autograft
Foldager C, Bendtsen M, Nygaard JV, Zou X, Bunger C
Bone 2009;45:267-73

10.4.85 Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: Results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Research Program
Halton J, Gaboury I, Grant R, Alos N, Cummings EA, Matzinger M, Shenouda N, Lentle B, Abish S, Atkinson S, Cairney E, Dix D, Israels S, Stephure D, Wilson B, Hay J, Moher D, Rauch F, Siminoski K, Ward LM
J Bone Miner Res 2009;24:1326-34

10.4.86 Mustn1 is expressed during chondrogenesis and is necessary for chondrocyte proliferation and differentiation in vitro
Gersch RP, Hadjiargyrou M

Bone 2009;45:330-8

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Remodelling Markers

10.4.87 Bone turnover markers are correlated with quantitative ultrasound of the calcaneus: 5-year longitudinal data

Lenora J, Gerdhem P, Obrant KJ, Ivaska KK

Osteoporos Int 2009;20:1225-32

Bone turnover markers are associated with areal BMD, but the knowledge on the association with QUS is limited. 810 women, all 75 years old, were investigated at baseline. 506 completed a 5-year follow-up. Bone turnover markers and calcaneal QUS [speed of sound (SoS), broadband ultrasound attenuation (BUA), stiffness] were investigated at baseline. QUS was investigated at follow-up. All bone turnover markers were correlated with baseline QUS [standardized regression (Beta(std)) values from -0.07, $p<0.05$ to -0.23, $p<0.001$], with the exception of bone-specific alkaline phosphatase (S-Bone ALP). When the correlations between baseline bone turnover markers and 5-year changes in QUS were analyzed, three serum osteocalcins were correlated with changes of SoS and stiffness index (Beta(std)=–0.11, $p<0.05$ to -0.17, $p<0.001$). Also S-CTX-I correlated with changes of SoS and stiffness index (Beta(std)=–0.10 and -0.09, respectively, $p<0.05$). S-TRACP5b, urinary deoxypyridinoline/crea, and U-MidOC/crea correlated with changes of SoS (Beta(std)=–0.10 and $p<0.05$ for all). S-Bone ALP did not correlate with change of QUS. None of the bone turnover markers correlated with changes of BUA.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Bone Formation

10.4.88 Positive regulation of adult bone formation by osteoblast-specific transcription factor osterix

Baek WY, Lee MA, Jung JW, Kim SY, Akiyama H, de Crombrugghe B, Kim JE
J Bone Miner Res 2009;24:1055-65

Osterix (Osx) is essential for osteoblast differentiation and bone formation; mice lacking Osx die within one hour birth with absence of intramembranous and endochondral bone formation. Osx was inactivated in all osteoblasts. No bone defects were observed in newborn mice but osteopenia in growing mice. BMD and bone forming rate were decreased in lumbar vertebra, and the cortical bone of the long bones was thinner and more porous with reduced bone length. The trabecular bones were increased, but they were immature or premature. The expression of early marker genes for osteoblast differentiation such as Runx2, osteopontin, and alkaline phosphatase was markedly increased, but the late marker gene, osteocalcin, was decreased. No functional defects were found in osteoclasts. These findings suggest a significant role of Osx in positively regulating osteoblast differentiation and bone formation in adult bone.

10.4.89 Epimedium-derived flavonoids promote osteoblastogenesis and suppress adipogenesis in bone marrow stromal cells while exerting an anabolic effect on osteoporotic bone

Songlin P, Ge Z, Yixin H, Xinluan W, Pingchung L, Kwoksui L, Ling Q
Bone 2009;45:534-44

Epimedium-derived flavonoids (EFs) prevent bone loss in ovariectomized (OVX) rats and late postmenopausal women. 11-month-old female Wistar rats were divided into Sham, OVX, Sham+soluble vehicle (Sham+SV), OVX+SV and OVX+EFs (10 mg/kg/day) groups. 3 months after surgery, rats from the first two groups were euthanized to verify the establishment of OVX-induced osteoporosis. Other groups were orally treated with daily SV or EFs for 4 months. The serum level of osteocalcin was higher and TRACP 5b was lower in EFs vs. SV-treated OVX rats. BMD, BV/TV, Tb.N and Conn.D in EFs-treated OVX rats were greater than those of SV-treated OVX rats. OS/BS, MAR, and BFR/BS were higher in EFs vs. SV-treated OVX rats. EFs increased osteogenesis and decreased adipogenesis of BMSCs, as evidenced by CFU-ALP and CFU-Adipo assays, respectively. The mRNA level of Runx2 and bone sialoprotein was higher while PPARγ2 was lower in BMSCs from EFs-treated vs. SV-treated OVX rats. ALP activity and Runx2 mRNA was higher while adipocyte number and PPARγ2 mRNA was lower in human BMSCs after exposure to conditioned serum from EFs vs. SV-treated OVX rats. EFs exerted anabolic effect on osteoporotic bone by concomitantly promoting osteogenic and suppressing adipogenic differentiation of BMSCs.

10.4.90 Increased circulating heat shock protein 60 induced by menopause, stimulates apoptosis of osteoblast-lineage cells via upregulation of toll-like receptors

Kim YS, Koh JM, Lee YS, Kim BJ, Lee SH, Lee KU, Kim GS
Bone 2009;45:68-76

HSP60 stimulates osteoclast formation. Plasma HSP60 levels were higher in postmenopausal (median 1152.4 ng/ml; range 724.7-2123.4 ng/ml) than in premenopausal (median 316.3 ng/ml; range 164.6-638.4 ng/ml) women. In primary human marrow stromal cells (hBMSC) and the HS-5 hBMSC cell line, HSP60 reduced cell viability and increased caspase-dependent apoptosis. HSP60 activated caspase-3 and -9, but not caspase-8 in HS-5 cells, and increased the release of mitochondrial cytochrome c into the cytosol. HSP60 activated p38 and NFκB, but not ERK or JNK; inhibitors of p38 (SB203580) and NFκB (PDTC) abolished HSP60-induced apoptosis. HSP60 upregulated TLR-2 and TLR-4 expression, and pretreatment with blocking antibodies for TLR-2 and TLR-4 almost completely eliminated the effects of HSP60 on apoptosis, caspase-3 and -9 activation, and activation of NFκB and p38 MAPK. Most notably, ovariectomy-induced bone loss was attenuated in TLR-2 KO mice. Upregulation of TLR-2 by HSP60 may play a critical role in promoting bone loss in the estrogen-deficient state.

10.4.91 Endogenous glucocorticoid signalling in osteoblasts is necessary to maintain normal bone structure in mice

Kalak R, Zhou H, Street J, Day RE, Modzelewski JR, Spies CM, Liu PY, Li G, Dunstan CR, Seibel MJ
Bone 2009;45:61-7

The role of endogenous glucocorticosteroids (GC) in bone development is ill-defined. Using the Col2.3-11βHSD2 transgenic (tg) mouse model, the authors examined the effect of osteoblast-targeted disruption of intracellular GC signalling. Tibiae and L3 vertebrae of 3- and 7-week-old, male and female wildtype (WT) mice and their tg littermates were analysed. Transgenic mice had lower bone volume, lower trabecular number and higher trabecular separation in tibial bone, as well as lower tibial cortical bone area and periosteal and endosteal perimeters which decreased strength and stiffness. In the tibia, the observed transgene effect was present in 3- and 7-week-old animals. In the vertebral bones differences between tg and WT mice were seen in 7- but not in 3-week-old animals, suggesting that the effects of the transgene at this site may be modulated by age and/or changes in circulating sex hormone levels. Endogenous glucocorticoids may be required for normal bone growth but the effects on structure and strength are site and sexual maturity specific.

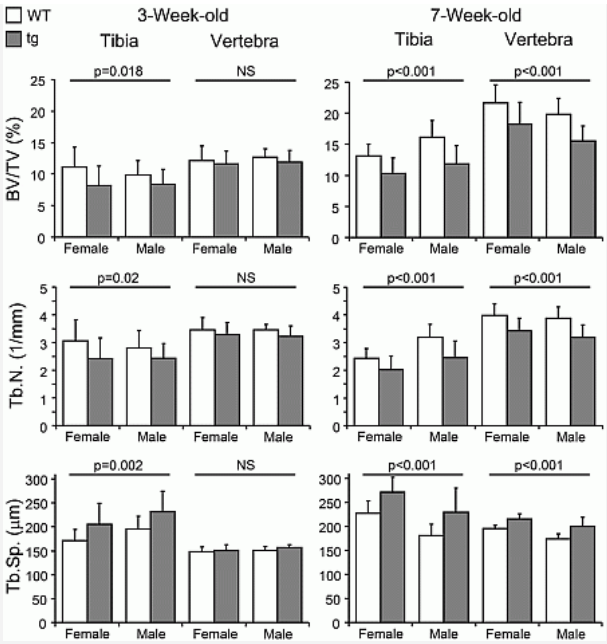

Fig. 10.4.91a Bone volume fraction, trabecular number and trabecular separation of tibial and vertebral trabecular bone. Data are shown as means±SD. p-values are for genotype effects by 2-way ANOVA with gender and genotype as factors. WT: wild type, tg: transgenic, BV/TV: bone volume fraction (bone volume/tissue volume), Tb.N.: trabecular number, Tb.Sp.: trabecular separation. Reproduced from Bone, 45:61-7, Copyright (2009), with permission from Elsevier.

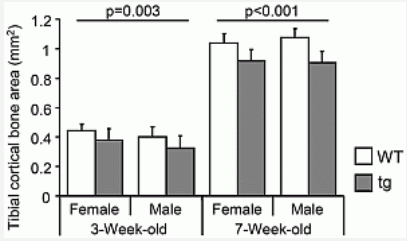

Fig. 10.4.91b Tibial cortical bone area. Data are shown as means±SD. p-values are for genotype effects by 2-way ANOVA with gender and genotype as factors. WT: wildtype, tg: transgenic. Reproduced from Bone, 45:61-7, Copyright (2009), with permission from Elsevier.

10.4.92 Elevated aromatase expression in osteoblasts leads to increased bone mass without systemic adverse effects

Sjogren K, Lagerquist M, Moverare-Skrtic S, Andersson N, Windahl SH, Swanson C, Mohan S, Poutanen M, Ohlsson C
J Bone Miner Res 2009;24:1263-70

Testosterone (T) may act through the androgen receptor (AR) or by aromatization to estradiol (E2), followed by activation of estrogen receptors (ERs) in bone. A transgenic mouse model (Coll-Iα1-Arom) over expresses the human aromatase gene had increased total body BMD, trabecular BMD, cortical BMD, and cortical thickness with elevated osteoprotegerin mRNA levels and reduced number of osteoclasts ($p<0.01$). Treatment of ovariectomized mice with T increased cortical and trabecular thickness in the Coll-Iα1-Arom mice ($p<0.001$) not wildtype. Elevated aromatase expression in osteoblasts results in stimulatory estrogenic effects in bone without increasing serum E2. Because osteoblast-specific aromatase expression results in an increased ER to AR activation ratio in bone, the authors propose that activation of ERs results in a more pronounced increase in bone mass than what is seen after activation of the AR.

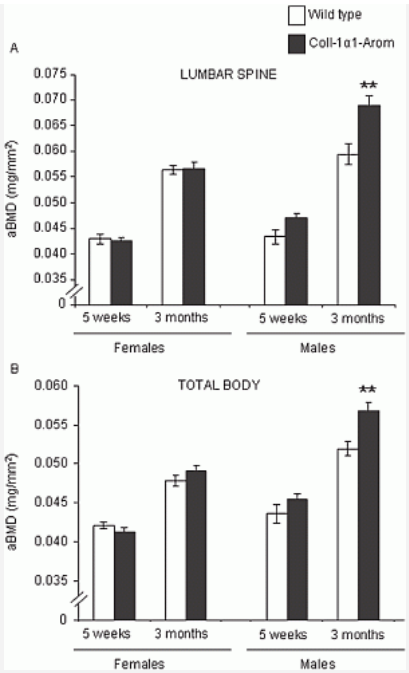

*Fig. 10.4.92a Increased aBMD in adult male Coll-1α1-Arom mice Lumbar spine (A) and total body (B) aBMD analyzed by DXA in 5-wk-old and 3-mo-old Coll-1α1-Arom mice and WT mice (n=8-12). Values are means±SE. **p<0.01 vs. WT. Reproduced from J Bone Miner Res 2009;24:1263-70 with permission of the American Society of Bone and Mineral Research.*

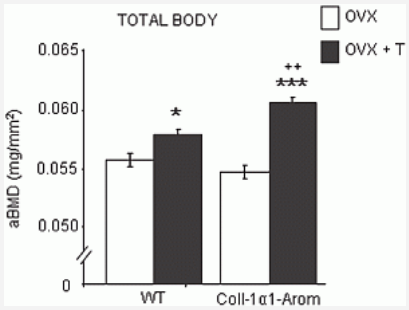

*Fig. 10.4.92b More pronounced effect of testosterone on total body aBMD in OVX Coll-1α1-Arom mice than in WT mice. Total body aBMD analyzed by DXA in 3-mo-old OVX Coll-1α1-Arom mice and WT mice that were either vehicle treated (OVX) or testosterone treated (OVX+T; n=10-11). Values are means±SE. *p<0.05 and ***p<0.001 vs. OVX. ++p<0.01, effect of testosterone in Coll-1α1-Arom mice vs. in WT mice. Reproduced from J Bone Miner Res 2009;24:1263-70 with permission of the American Society of Bone and Mineral Research.*

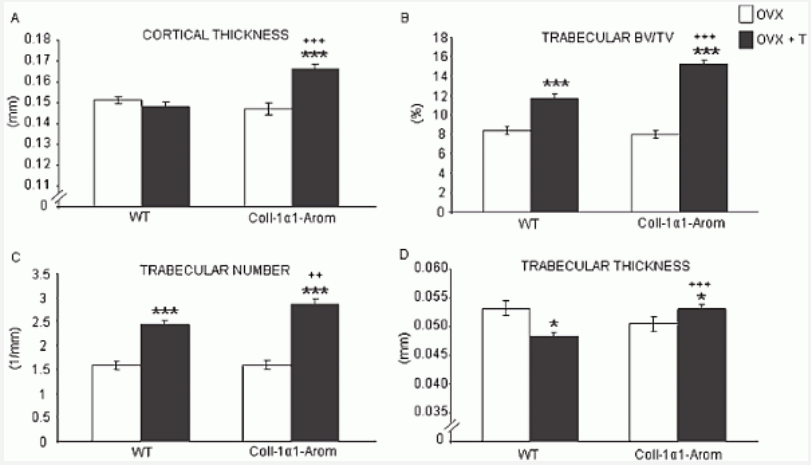

*Fig. 10.4.92c More pronounced effect of testosterone on cortical and trabecular bone parameters in OVX Coll-1α1-Arom mice than in WT mice. Cortical (A) and trabecular (B-D) bone parameters were analyzed by μCT analyses of proximal tibia in 3-mo-old Coll-1α1-Arom mice and WT mice that were either vehicle treated (OVX) or testosterone treated (OVX+T; n=10-11). Values are means±SE. BV, bone volume; TV, total volume. *p<0.05, **p<0.01, and ***p<0.001 vs. OVX. ++p<0.01 and +++p<0.001, effect of testosterone in Coll-1α1-Arom mice vs. in WT mice. Reproduced from J Bone Miner Res 2009;24:1263-70 with permission of the American Society of Bone and Mineral Research.*

10.4.93 Osteoblast function is compromised at sites of focal bone erosion in inflammatory arthritis

Walsh NC, Reinwald S, Manning CA, Condon KW, Iwata K, Burr DB, Gravallese EM

J Bone Miner Res 2009;24:1572-85

Bone formation rates at bone surfaces adjacent to inflammation were similar to those observed in nonarthritic bone; therefore, osteoblast activity is unlikely to compensate for the increased bone resorption. Within arthritic bone, actively mineralizing surface was reduced at surfaces adjacent to inflammation compared with surfaces adjacent to marrow. Consistent

with the reduction in mineralized bone formation, there was a paucity of cells expressing the mid- to late stage osteoblast lineage marker alkaline phosphatase, despite a clear presence of cells expressing the early osteoblast lineage marker Runx2. Several members of the Dickkopf and secreted Frizzled-related protein families of Wnt signaling antagonists were upregulated in arthritic synovial tissues, suggesting that inhibition of Wnt signaling could be one mechanism contributing to impaired osteoblast function within arthritic bone. Inflammation within arthritic bone impairs osteoblast capacity to form adequate mineralized bone contributing to the net loss of bone.

10.4.94 Sustained BMP signaling in osteoblasts stimulates bone formation by promoting angiogenesis and osteoblast differentiation

Zhang F, Qiu T, Wu X, Wan C, Shi W, Wang Y, Chen JG, Wan M, Clemens TL, Cao X
J Bone Miner Res 2009;24:1224-33

Bone morphogenetic protein (BMP) signaling is required for bone development and angiogenesis. Endosome-associated FYVE-domain protein (endofin) is a Smad anchor for BMP receptor activation. Endofin contains a protein-phosphatase pp1c binding domain, which negatively modulates BMP signals through dephosphorylation of the BMP type I receptor. A single point mutation of endofin (F872A) disrupts interaction between the catalytic subunit pp1c and sensitizes BMP signaling in vitro. To study the functional impact of this mutation in vivo, targeted expression of an endofin (F872A) transgene to osteoblasts increased levels of phosphorylated Smad1 in osteoblasts and increased bone formation. Trabecular bone volume was increased in the transgenic mice with increases in trabecular bone thickness and number and increase in the density of the bone vasculature. The vessel surface and volume were both increased in association with elevated VEGF in osteoblasts. Endothelial sprouting from the endofin (F872A) mutant embryonic metatarsals cultured ex vivo was increased and was abolished by an addition of a VEGF neutralizing antibody. Osteoblast expression of a mutant endofin protein lacking the pp1c binding activity results in sustained signaling of the BMP type I receptor, which increases bone formation and skeletal angiogenesis.

10.4.95 Effect of chitosan particles and dexamethasone on human bone marrow stromal cell osteogenesis and angiogenic factor secretion

Guzman-Morales J, El-Gabalawy H, Pham MH, Tran-Khanh N, McKee MD, Wu W, Centola M, Hoemann CD
Bone 2009;45:617-26

Chitosan is a polysaccharide scaffold used to enhance cartilage repair during treatments involving bone marrow stimulation, which increases angiogenesis and osteogenesis in vivo. Addition of chitosan particles to the media of human marrow stromal cell (BMSC) cultures stimulates osteogenesis by promoting osteoblastic differentiation and by favoring the release of angiogenic factors in vitro. Confluent BMSCs cultured for 3 weeks. Added chitosan particles accumulated intra- and extracellularly inhibited osteocalcin release and interfered with mineralized matrix deposition. Interestingly, dexamethasone promoted cell attachment and suppressed the release and activation of matrix metalloprotease-2 (MMP-2). While chitosan particles had no effect on the release of angiogenic factors, dexamethasone inhibited ($p<0.05$ to $p<0.0001$) the release of VEGF, GM-CSF, TNFα, interleukins 1β, 4, 6, and 10, and a host of other inflammatory factors constitutively secreted by BMSCs. Chitosan particles alone are not sufficient to promote osteoblast differentiation of BMSCs in vitro, and suggest that chitosan promotes osteogenesis in vivo through indirect mechanisms. Dexamethasone promotes osteoblastic differentiation in vitro partly by inhibiting gelatinase activity and by suppressing inflammatory cytokines which result in increased cell attachment and cell cycle exit.

10.4.96 Simvastatin locally applied from a biodegradable coating of osteosynthetic implants improves fracture healing comparable to BMP-2 application

Pauly S, Luttosch F, Morawski M, Haas NP, Schmidmaier G, Wildemann B
Bone 2009;45:505-11

Simvastatin increases the expression of bone morphogenetic protein (BMP-2). In this study, the effect of simvastatin locally applied from a bioactive polymer coating of implants on fracture healing was investigated. A closed fracture of the right tibia of 5-month-old Sprague Dawley rats was performed. Intramedullary stabilization was achieved with uncoated vs. polymer-only coated vs. polymer plus drug coated titanium Kirschner wires. Test substances (either simvastatin low or high dosed or BMP-2) were incorporated into a biodegradable layer of poly(d,l-lactide). Tibiae were harvested after 28 or 42 days. Radiographic results demonstrated progressed callus consolidation in the BMP-2- and simvastatin treated groups. The simvastatin-high dosed group revealed an increased torsional stiffness and elevated maximum load (d28) compared to control group as well as an increase in both parameters at d42. BMP-2 treated animals showed significantly elevated maximum load and stiffness at the early timepoint and elevated torsional stiffness after d42. The histomorphometric analysis revealed decreased cartilage area for BMP-2 treated animals at d28. Even though an increase of mineralized areas among periosteal callus was found at d42 for simvastatin-high as well as BMP-2 treated animals, no difference could be detected at both time points compared to the uncoated group. However, simvastatin-high treated animals revealed reduced cartilage areas within the periosteal callus at d42.

10.4.97 Effects of global or targeted deletion of the EP4 receptor on the response of osteoblasts to prostaglandin in vitro and on bone histomorphometry in aged mice

Gao Q, Zhan P, Alander CB, Kream BE, Hao C, Breyer MD, Pilbeam CC, Raisz LG
Bone 2009;45:98-103

A mouse with targeted EP4 receptor deletion was studied. KO mice had one targeted and one global deletion. In cultures of calvarial osteoblasts, PGE_2 increased alkaline phosphatase (ALP) activity in cells from WT mice, and this effect was decreased in cells from either G-HET or T-HET mice and further decreased in cells from KO mice. A selective agonist for EP4 receptor increased ALP activity and osteocalcin mRNA levels in cells from WT but not KO mice. A selective COX-2 inhibitor, NS-398, decreased osteoblast differentiation in WT but not KO cells. At 15 to 18 months of age there were no differences in serum creatinine, calcium, PTH, body weight or BMD among the different genotypes. Static and dynamic histomorphometry showed no consistent changes in bone volume or bone formation. Expression of the EP4 receptor in osteoblasts is critical for anabolic responses to PGE_2 in cell culture but may not be essential for maintenance of bone remodeling in vivo.

10.4.98 TNFα promotes osteogenic differentiation of human mesenchymal stem cells by triggering the NFκB signaling pathway

Hess K, Ushmorov A, Fiedler J, Brenner RE, Wirth T
Bone 2009;45:367-76

10.4.99 Pro-inflammatory cytokines TNF-related weak inducer of apoptosis (TWEAK) and TNFα induce

the mitogen-activated protein kinase (MAPK)-dependent expression of sclerostin in human osteoblasts
Vincent C, Findlay DM, Welldon KJ, Wijenayaka AR, Zheng TS, Haynes DR, Fazzalari NL, Evdokiou A, Atkins GJ
J Bone Miner Res 2009;24:1434-49

10.4.100 LPS-induced inhibition of osteogenesis is TNF**α** dependent in a murine tooth extraction model
Tomomatsu N, Aoki K, Alles N, Soysa NS, Hussain A, Nakachi H, Kita S, Shimokawa H, Ohya K, Amagasa T
J Bone Miner Res 2009;24:1770-81

10.4.101 Vps33a mediates RANKL storage in secretory lysosomes in osteoblastic cells
Kariya Y, Honma M, Aoki S, Chiba A, Suzuki H
J Bone Miner Res 2009;24:1741-52

10.4.102 1**α**,25$(OH)_2$ vitamin D3 induction of ATP secretion in osteoblasts
Biswas P, Zanello LP
J Bone Miner Res 2009;24:1450-60

10.4.103 NFATc1 mediates HDAC-dependent transcriptional repression of osteocalcin expression during osteoblast differentiation
Choo MK, Yeo H, Zayzafoon M
Bone 2009;45:579-89

10.4.104 **β**-arrestin2 regulates parathyroid hormone effects on a p38 MAPK and NF**κ**B gene expression network in osteoblasts
Bianchi EN, Ferrari SL
Bone 2009;45:716-25

10.4.105 Identification of differentially expressed genes between osteoblasts and osteocytes
Paic F, Igwe JC, Nori R, Kronenberg MS, Franceschetti T, Harrington P, Kuo L, Shin DG, Rowe DW, Harris SE, Kalajzic I
Bone 2009;45:682-92

10.4.106 BMP-2 is essential for postnatal osteogenesis but not for recruitment of osteogenic stem cells
Bais MV, Wigner N, Young M, Toholka R, Graves DT, Morgan EF, Gerstenfeld LC, Einhorn TA
Bone 2009;45:254-66

10.4.107 New insights into BMP-7 mediated osteoblastic differentiation of primary human mesenchymal stem cells
Lavery K, Hawley S, Swain P, Rooney R, Falb D, Alaoui-Ismaili MH
Bone 2009;45:27-41

10.4.108 Decreased osteogenesis, increased cell senescence and elevated Dickkopf-1 secretion in human fracture non union stromal cells
Bajada S, Marshall MJ, Wright KT, Richardson JB, Johnson WE
Bone 2009;45:726-35

10.4.109 Comparison of osteogenic potentials of BMP-4 transduced stem cells from autologous bone marrow and fat tissue in a rabbit model of calvarial defects
Lin L, Shen Q, Wei X, Hou Y, Xue T, Fu X, Duan X, Yu C
Calcif Tissue Int 2009;85:55-65

10.4.110 Influence of the proportion of particulate autogenous bone graft/platelet-rich plasma on bone healing in critical-size defects: An immunohistochemical analysis in rat calvaria
Nagata M, Messora M, Okamoto R, Campos N, Pola N, Esper L, Sbrana M, Fucini S, Garcia V, Bosco A
Bone 2009;45:339-45

10.4.111 Thrombospondin-2 influences the proportion of cartilage and bone during fracture healing
Taylor DK, Meganck JA, Terkhorn S, Rajani R, Naik A, O'Keefe RJ, Goldstein SA, Hankenson KD
J Bone Miner Res 2009;24:1043-54

10.4.112 Variations in the ratios of co-cultured mesenchymal stem cells and chondrocytes regulate the expression of cartilaginous and osseous phenotype in alginate constructs
Mo XT, Guo SC, Xie HQ, Deng L, Zhi W, Xiang Z, Li XQ, Yang ZM
Bone 2009;45:42-51

10.4.113 Interference by adrenaline with chondrogenic differentiation through suppression of gene transactivation mediated by Sox9 family members
Takarada T, Hojo H, Iemata M, Sahara K, Kodama A, Nakamura N, Hinoi E, Yoneda Y

Bone 2009;45:568-78

10.4.114 Modified titanium surfaces promote accelerated osteogenic differentiation of mesenchymal stromal cells in vitro
Wall I, Donos N, Carlqvist K, Jones F, Brett P
Bone 2009;45:17-26

10.4.115 The fabrication of nano-hydroxyapatite on PLGA and PLGA/collagen nanofibrous composite scaffolds and their effects in osteoblastic behavior for bone tissue engineering
Ngiam M, Liao S, Patil AJ, Cheng Z, Chan CK, Ramakrishna S
Bone 2009;45:4-16

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Bone Resorption

10.4.116 Voxel size and measures of individual resorption cavities in three-dimensional images of cancellous bone

Tkachenko EV, Slyfield CR, Tomlinson RE, Daggett JR, Wilson DL, Hernandez CJ

Bone 2009;45:487-92

3D images of a 1 mm cube of cancellous bone were collected at 0.7x0.7x5.0 µm/voxel using fluorescence based serial milling and uniformly coarsened to four other resolutions ranging from 1.4x1.4x5.0 to 11.2x11.2x10 µm/voxel. Cavities were identified in the 3D image as an indentation on the cancellous bone surface and were confirmed as eroded surfaces by viewing 2D cross-sections (mimicking histology techniques). The number of cavities observed in the 0.7x0.7x5.0 µm/voxel images (22.0±1.43, mean±SD) was not different from that in the 1.4x1.4x5.0 µm/voxel images (19.2±2.59) and an average of 79% of the cavities observed at both of these resolutions were coincident. However, at lower resolutions, cavity detection was confounded by low sensitivity (<20%) and high false positive rates (>40%). When voxel size exceeds 1.4x1.4x5.0 µm/voxel identification of resorption cavities is inaccurate.

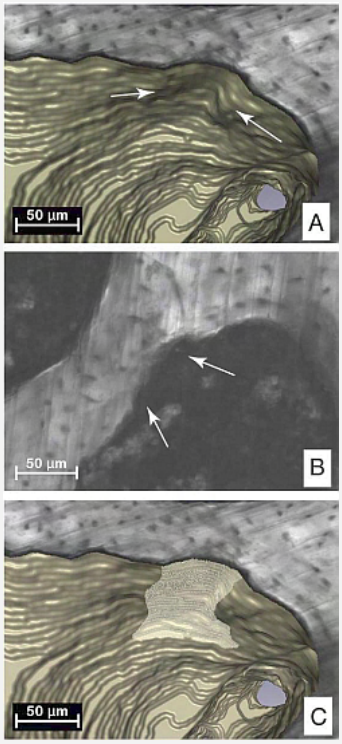

Fig. 10.4.116a (A) Initial identification of a resorption cavity on the cancellous bone surface is performed by observing an indentation on the cancellous bone surface in the threedimensional image (arrows). (B) The presence of a cavity is then confirmed by viewing a scalloped surface in a two-dimensional cross-section of the grayscale image (arrows). (C) The cavity is then labeled in the 3D image and recorded for future analysis. Reproduced from Bone, 45:487-92, Copyright (2009), with permission from Elsevier.

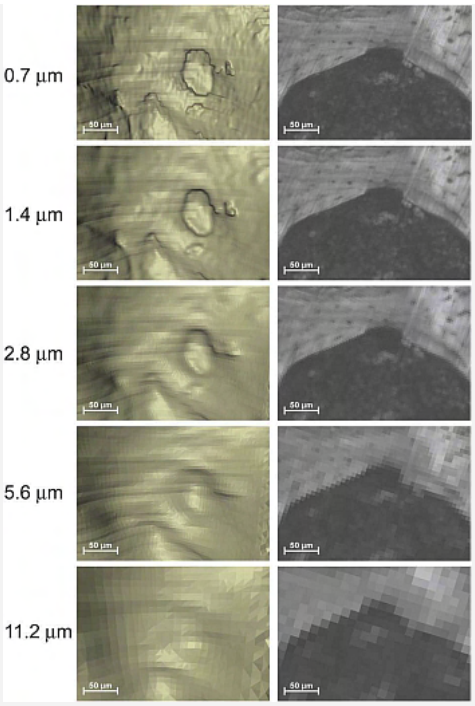

Fig. 10.4.116b A region of cancellous bone with a resorption cavity is shown at each of the image resolutions considered in the study. The three-dimensional image is shown on the left and a single cross-section from the image is shown on the right. As the voxel size increases the resorption cavity becomes increasingly difficult to observe and bone surface irregularities characteristic of resorption cavities become more difficult to distinguish from other bone surfaces. In images with the largest voxel size the eroded surfaces were not discernable from other bone surfaces and no cavities were found. Reproduced from Bone, 45:487-92, Copyright (2009), with permission from Elsevier.

10.4.117 Sclerostin mediates bone response to mechanical unloading through antagonizing Wnt/**β**-catenin signaling
Lin C, Jiang X, Dai Z, Guo X, Weng T, Wang J, Li Y, Feng G, Gao X, He L
J Bone Miner Res 2009;24:1651-61

Unloading of wildtype mice caused decrease of Wnt/β-catenin signaling activity accompanied by upregulation of Sost. Sclerostin inhibited Wnt/β-catenin in vivo, and sclerostin suppressed the activity of osteoblast and viability of osteoblasts and osteocytes. Interestingly, Sost(-/-) mice were resistant to unloading-induced bone loss. Reduction in bone formation in response to unloading was also abrogated in the mutant mice. Wnt/β-catenin signaling was not altered by unloading in Sost(-/-) mice. Sclerostin played an essential role in mediating bone response to mechanical unloading, likely through Wnt/β-catenin signaling. Sclerostin is a target for preventing disuse osteoporosis.

10.4.118 Loss of Cbl-b increases osteoclast bone-resorbing activity and induces osteopenia
Nakajima A, Sanjay A, Chiusaroli R, Adapala NS, Neff L, Itzsteink C, Horne WC, Baron R
J Bone Miner Res 2009;24:1162-72

10.4.119 Rac1 and Rac2 in osteoclastogenesis: A cell immortalization model
Wang Y, Belsham DD, Glogauer M
Calcif Tissue Int 2009;85:257-66

10.4.120 T-cell leukemia translocation-associated gene (TCTA) protein is required for human osteoclastogenesis
Kotake S, Nanke Y, Kawamoto M, Yago T, Udagawa N, Ichikawa N, Kobashigawa T, Saito S, Momohara S, Kamatani N, Yamanaka H
Bone 2009;45:627-39

10.4.121 Alteration of RANKL-induced osteoclastogenesis in primary cultured osteoclasts from SERCA2 (+/-) mice
Yang YM, Kim MS, Son A, Hong JH, Kim KH, Seo JT, Lee SI, Shin DM
J Bone Miner Res 2009;24:1763-9

10.4.122 Heat shock protein 60 causes osteoclastic bone resorption via toll-like receptor-2 in estrogen deficiency
Koh JM, Lee YS, Kim YS, Park SH, Lee SH, Kim HH, Lee MS, Lee KU, Kim GS
Bone 2009;45:650-60

10.4.123 Upregulation of MMP-13 via Runx2 in the stromal cell of Giant Cell Tumor of bone
Mak IW, Cowan RW, Popovic S, Colterjohn N, Singh G, Ghert M
Bone 2009;45:377-86

10.4.124 Macrophage migration inhibitory factor inhibits osteoclastogenesis
Jacquin C, Koczon-Jaremko B, Aguila HL, Leng L, Bucala R, Kuchel GA, Lee SK
Bone 2009;45:640-9

10.4.125 Reduction of particle-induced osteolysis by interleukin-6 involves anti-inflammatory effect and inhibition of early osteoclast precursor differentiation
Darowish M, Rahman R, Li P, Bukata SV, Gelinas J, Huang W, Flick LM, Schwarz EM, O'Keefe RJ
Bone 2009;45:661-8

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Osteocytes

10.4.126 Anatomic variations of the lacunar-canalicular system influence solute transport in bone

Zhou X, Novotny JE, Wang L
Bone 2009;45:704-10

Solute transport in the lacunar-canalicular system (LCS) is essential for bone metabolism and mechanotransduction. Transport rate (the reciprocal time constant for refilling the photobleached lacuna) increased linearly with canalicular number and decreased with canalicular length for both diffusion and convection. As a result, the transport enhancement of convection over diffusion was much less sensitive to the variations associated with chick, mouse, rabbit, bovine, dog, horse, and human LCS anatomy, when compared with the rates of diffusion or convection alone. Canalicular density did not affect transport enhancement, while solute size and the lacunar density had more complicated, nonlinear effects. This parametric study suggests that solute transport could be altered by varying LCS parameters, and that the anatomical details of the LCS need systemic examination to further understand the etiology of aged and osteoporotic bones.

10.4.127 Co-Cr-Mo alloy particles induce tumor necrosis factor alpha production in MLO-Y4 osteocytes: A role for osteocytes in particle-induced inflammation

Kanaji A, Caicedo MS, Virdi AS, Sumner DR, Hallab NJ, Sena K
Bone 2009;45:528-33

Wear debris-induced osteolysis affects joint arthroplasty. The effects of wear debris on osteocytes, which make up over 90% of all bone cells, remain unknown. Co-Cr-Mo alloy particle treatment ($p<0.05$) upregulated TNFα gene expression after 3 and 6 h and TNFα protein production after 24 h, but downregulated interleukin-6 gene expression after 6 h. Co-Cr-Mo alloy particle treatment also induced osteocyte apoptosis after 24 h. This apoptotic effect was partially (40%) dependent on TNFα.

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Systemic Factors

10.4.128 Serum IGF-1 determines skeletal strength by regulating subperiosteal expansion and trait interactions

Yakar S, Canalis E, Sun H, Mejia W, Kawashima Y, Nasser P, Courtland HW, Williams V, Bouxsein M, Rosen C, Jepsen KJ
J Bone Miner Res 2009;24:1481-92

Adult liver-specific IGF-1-deficient (LID) mice exhibit 75% reductions in serum IGF-1 levels and have reductions in periosteal circumference, femoral cross-sectional area, cortical thickness, and total volumetric BMD. Reduced bone strength associated with low levels of IGF-1 in serum (LID mice) results in impaired subperiosteal expansion with impaired endosteal apposition and lack of compensatory changes in mineralization throughout growth and aging. Serum IGF-1 affects cellular activity differently depending on the cortical surface. Reductions in serum IGF-1 indirectly affect bone strength through its effect on the marrow myeloid progenitor cell population. IGF-1 regulates bone size, shape, and composition during ontogeny and regulates an individual's ability to adapt its bone structure to mechanical loads during growth and development.

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Local Factors

10.4.129 Substance P stimulates bone marrow stromal cell osteogenic activity, osteoclast differentiation, and resorption activity in vitro
Wang L, Zhao R, Shi X, Wei T, Halloran BP, Clark DJ, Jacobs CR, Kingery WS
Bone 2009;45:309-20

10.4.130 PGE2 signaling through the EP4 receptor on fibroblasts upregulates RANKL and stimulates osteolysis
Tsutsumi R, Xie C, Wei X, Zhang M, Zhang X, Flick LM, Schwarz EM, O'Keefe RJ
J Bone Miner Res 2009;24:1753-62

10.4.131 Hypoxia and HIF-1α expression in the epiphyseal cartilage following ischemic injury to the immature femoral head
Kim HK, Bian H, Aya-ay J, Garces A, Morgan EF, Gilbert SR
Bone 2009;45:280-8

Progress in
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Risk Factors

10.4.132 BMD, clinical risk factors and their combination for hip fracture prevention

Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E
Osteoporos Int 2009;20:1675-82

Data from 10 prospective population based cohorts, in which BMD and CRFs were documented, were used to compute the 10-year probabilities of hip fracture calibrated to the fracture and death hazards of the UK. The base case examined the effects in women at the age of 65 years. The principal outcome measures were the number of women identified above an intervention threshold, the number of hip fracture cases that would be identified, the positive predicted value and the NNT to prevent a hip fracture during a hypothetical treatment with an effectiveness of 35% targeted to those above the threshold fracture risk. BMD alone selected women at higher risk of hip fracture than the use of CRFs alone (6.1% vs. 5.3%). BMD tests alone also identified a greater number of hip fracture cases (219/1000) than CRFs alone (140/1000). The combined use of CRFs and BMD identified fewer women above a threshold risk than the use of BMD alone (168/1000 vs. 219/1000, respectively), but with a higher hip fracture risk (PPV, 8.6% vs. 6.1%), and consequently a lower number needed to treat (NNT) (33 vs. 47). In sensitivity analyses, the PPV and NNT were better for the combination than either BMD or CRFs alone across all ages studied (50-70 years). The use of FRAX® with BMD increases the performance characteristics of fracture risk assessment.

10.4.133 Bone mass, size and previous fractures as predictors of prospective fractures in an osteoporotic referral population

Eklund F, Nordstrom A, Bjornstig U, Nordstrom P
Bone 2009;45:808-13

In 5701 women and 1376 men, aged 30 years and older BMD and vBMD were independent predictors for fracture in women and men (hazard ratio per standard deviation decrease (HR)=1.27-1.52, p<0.05). Bone size did not predict prospective fractures in either sex (HR=0.91-0.99, p>0.05), and bone size completely explained the higher BMD in men than in women. In women, retrospective low energy fractures (HR=1.78, p<0.001) and height (HR=1.02, p=0.006) were additional independent predictors of osteoporotic fractures after adjusting for age and BMD. In conclusion, we show that in a large osteoporotic referral population, age, BMD and previous fractures are independent predictors of prospective low energy fractures.

10.4.134 Hip fracture patients at risk of second hip fracture: A nationwide population-based cohort study of 169,145 cases during 1977-2001

Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P
J Bone Miner Res 2009;24:1299-307

In 169,145 patients with a first HFx followed a median of 3.8 yr, 27,834 had a second HFx. The cumulative incidence was 9% after 1 yr and 20% after 5 yr (expected 2% and 12%, respectively). The RR of second HFx was 2.2 (2.0-2.5) at 1 yr and normalized at 15 yr. Risk factors were female sex (HR=1.36, 95% CI: 1.32-1.40), age (HR=1.68, 95% CI: 1.60-1.76 in patients >85 yr), alcoholism (HR=1.61, 95% CI: 1.51-1.72), any prior fracture (HR=1.08, 95%CI: 1.04-1.11), and living alone (HR=1.06, 95% CI: 1.04-1.09). Mortality at 1 and 5 yr after a second HFx compared with expected (men-1 yr: 27% vs. 9%, p<0.05; 5 yr: 64% vs. 40%, p<0.05; women-1 yr: 21% vs. 10%, p<0.05; 5 yr: 58% vs. 41%, p<0.05).

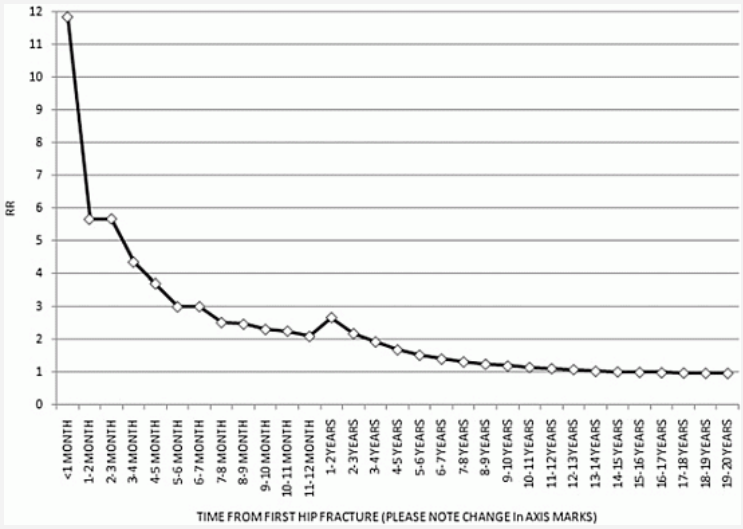

Fig. 10.4.134a RR of second HFx compared with the expected risk in an age- and sex-matched normal population in selected time intervals after the first HFx. Reproduced from J Bone Miner Res 2009;24:1299-307 with permission of the American Society of Bone and Mineral Research.

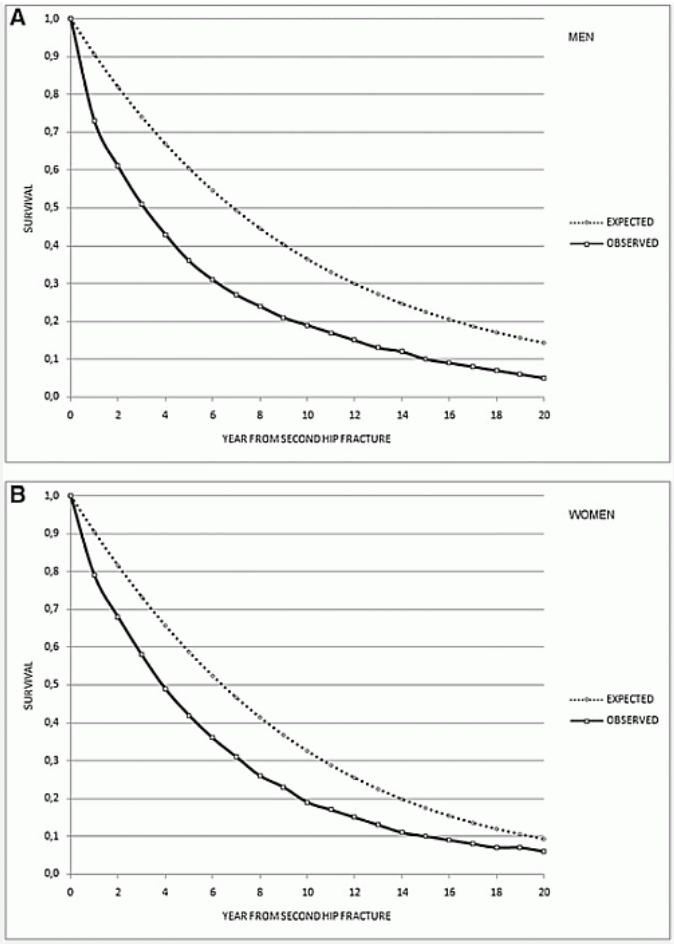

Fig. 10.4.134b Mortality after second HFx stratified according to sex compared with the mortality of the background population. Because of the large cohorts, CIs were too small to be presented on the curves. Reproduced from J Bone Miner Res 2009;24:1299-307 with permission of the American Society of Bone and Mineral Research.

10.4.135 Prediction of hip and other osteoporotic fractures from hip geometry in a large clinical cohort
Leslie WD, Pahlavan PS, Tsang JF, Lix LM
Osteoporos Int 2009;20:1767-74

Incident hip fractures (N=270) and nonhip osteoporotic fractures (N=1347) were identified during 3.7 years. Hip axis length (HAL) was greater in both hip and nonhip fracture cases than in nonfracture cases, whereas cross-sectional moment of inertia, cross-sectional area, and femoral strength index (SI) were all less. After adjustment for total hip BMD, HAL [hazard ratio (HR) 1.22 per SD increase, 95% CI 1.07-1.38] and SI (HR 1.21 per SD decrease, 95% CI 1.07-1.37) were independent predictors of hip fractures but not of nonhip fractures. When both HAL and SI were added to a model containing age and total hip BMD, there was a small improvement in hip fracture prediction (ROC area under the curve 0.832±0.013 vs. 0.823±0.013; P=0.001). HAL and SI made a small contribution to hip fracture prediction independent of age and BMD.

10.4.136 Which women should be selected for vertebral fracture assessment? Comparing different methods of targeting VFA
Middleton ET, Gardiner ED, Steel SA
Calcif Tissue Int 2009;85:203-10

1572 treatment-naive women over age 65 had undergone routine VFA screening and a VFscore was created. The risk factors associated with the presence of a fracture on VFA were age, femoral neck BMD, prior clinical fracture, and height loss/kyphosis. The VFscore derived from these factors had a 65.5% sensitivity and a 65.5% specificity. For equal resource requirements, the VFscore identified more women with fracture than using BMD category to target VFA. Compared to routinely screening all women, VFscore enabled a 30% reduction in the number of women undergoing VFA while still identifying >90% of women with a vertebral fracture. Overall, a large proportion of the population is required to undergo VFA in order to ensure that the majority of women with a vertebral fracture are selected for screening. The VFscore increased the efficiency of VFA screening to a modest degree compared to screening routinely or according to BMD category.

10.4.137 Genetic selection for fast growth generates bone architecture characterised by enhanced periosteal expansion and limited consolidation of the cortices but a diminution in the early responses to mechanical loading
Rawlinson SC, Murray DH, Mosley JR, Wright CD, Bredl JC, Saxon LK, Loveridge N, Leterrier C, Constantin P, Farquharson C, Pitsillides AA
Bone 2009;45:357-66

The authors compared the effects of fast and slow growth on bone strength and architecture in the tibiotarsi of embryonic and juvenile birds. Bones from chicks with divergent growth rates display equal resistance to applied loads, but weight correction revealed that the bones from juvenile fast growth birds are weaker, with reduced stiffness and lower resistance to fracture. Primary osteoblasts from slow growing juvenile birds proliferated more rapidly and had lower alkaline phosphatase activity. Bones from fast growing embryonic chicks display rapid radial expansion and incomplete osteonal infilling but, importantly, lack mechanical responsiveness. Fast embryonic and juvenile growth rates may predispose bone to particular architectures with increased fragility in the adult.

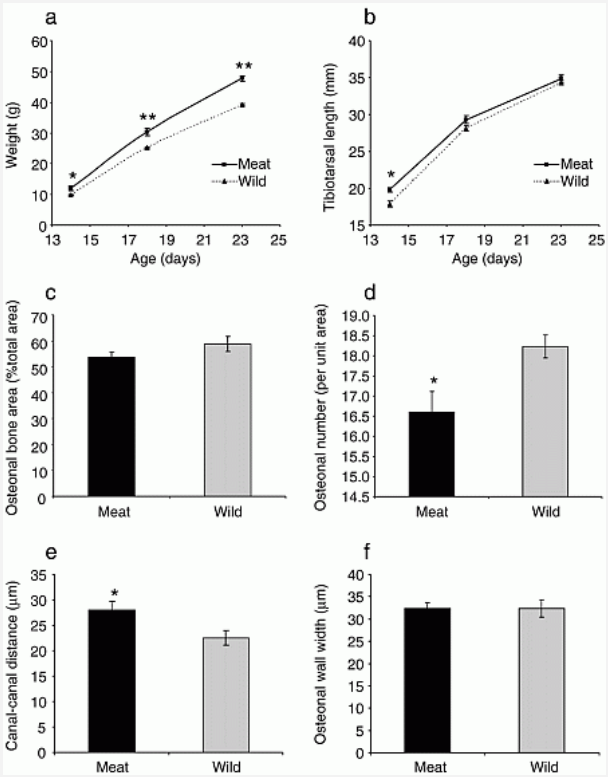

*Fig. 10.4.137 Cortical bone in embryonic meat-type chicks is more porous than in wildtype chicks. Analysis of bone organisation was evaluated in transverse sections of the mid-diaphyseal region of embryonic and post-hatch tibiotarsi from chickens commercially-selected fast growth for meat production (meat-type) compared to wildtype slower-growing strains. Total body weight (a) was greater in meat-type than in wild-type chicks at all embryonic and post-hatch stages examined, whilst at the time points studied tibiotarsal length (b) was only elevated in the meat-type vs. the wildtype chicks at 14 days post-fertilisation. Enhanced porosity of the meat-type chick cortex was evident in the reduced density of osteons (d) and greater canal-canal distances (e), without modification in bone area (c) or osteonalwall widths (f) when compared to wildtype chicks. Results are presented as mean±SEM (NS; not significant) and * denotes P<0.05 and **P<0.01. Reproduced from Bone, 45:357-66, Copyright (2009), with permission from Elsevier.*

10.4.138 Is QUS or DXA better for predicting the 10-year absolute risk of fracture?
Moayyeri A, Kaptoge S, Dalzell N, Bingham S, Luben RN, Wareham NJ, Reeve J, Khaw KT
J Bone Miner Res 2009;24:1319-25

From 1455 participants (703 men) 65-76 yr of age at baseline, 79 developed a fracture over 10.3±1.4 yr of follow-up. A 1 SD decrease in BMD was associated with a HR for fracture=2.26 (1.74-2.95) and a 1 SD decrease in BUA was 2.04 (1.55-2.69). Global measures of model fit showed relative superiority of the BMD model, whereas the area under the receiving operator characteristic (ROC) curve was slightly higher for the BUA model. Using both Cox models with BMD and BUA measures, we calculated exact 10-yr absolute risk of fracture for all participants and categorized them in groups of <5%, 5% to <15%, and ≥15%. Comparison of groupings based on two models showed a total reclassification of 28.8% of participants, with the greatest reclassification (approximately 40%) among the intermediate- and high-risk groups. QUS is comparable to DXA.

10.4.139 The effect of including quantitative heel ultrasound in models for estimation of 10-year absolute risk of fracture
Moayyeri A, Kaptoge S, Dalzell N, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT
Bone 2009;45:180-4

From 1455 participants (703 men) aged 65-76 years at baseline, 79 developed a fracture over 10.3±1.4 years. Global measures of model fit, area under ROC curve, and the Hosmer-Lemeshow statistic showed relative superiority of the model including BUA. Using each model, we calculated 10-year absolute risk of fracture for all participants and categorized them in groups of <5%, 5% to <15%, and ≥15%. Comparison of groupings showed a total reclassification of 16.6% of participants after inclusion of BUA with the greatest reclassification (30.7%) among the group with intermediate risk. Adding a QUS measurement to models based on clinical risk factors and BMD improves the predictive power of models.

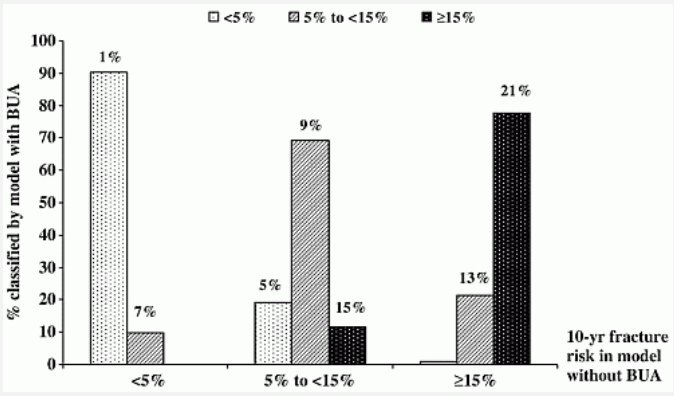

Fig. 10.4.139 Distribution of 10-year absolute fracture risk based on Cox proportional-hazard models with and without BUA

among 1455 EPIC-Norfolk study participants. Bars show the percentage of participants categorized to the specific risk bands using the model including BUA. The shading of the bars refers to the fracture risk from the model including BUA. The numbers on top of each bar show the observed fracture risk during the study period for that particular population. Reproduced from Bone, 45:180-4, Copyright (2009), with permission from Elsevier.

10.4.140 Tibial or hip BMD predict clinical fracture risk equally well: Results from a prospective study in 700 elderly Swiss women

Popp AW, Senn C, Franta O, Krieg MA, Perrelet R, Lippuner K
Osteoporos Int 2009;20:1393-9

During 1786 women-years of follow-up, 68 clinical fragility fractures occurred in 61 women. Older age and previous fracture were identified as risk factors for the present fractures. A decrease of 1 SD in BMD values yielded a 1.5-fold (HIP) to 1.8-fold (T-EPI) significant increase in clinical fragility fracture hazard ratio (adjusted for age and previous fracture). All measured sites had comparable performance for fracture prediction (area under the curve range from 0.63 [LS] to 0.68 [T-EPI]). Fracture risk prediction with BMD measurements at T-DIA and T-EPI is a valid alternative to BMD measurements at LS or HIP for patients in whom these sites cannot be accessed for clinical, technical or practical reasons.

10.4.141 Low calcaneal BMD and the risk of distal forearm fracture in women and men: A population-based case-control study

Atroshi I, Ahlander F, Billsten M, Ahlborg HG, Mellstrom D, Ohlsson C, Ljunggren O, Karlsson MK
Bone 2009;45:789-93

Patients 20-80 years of age with distal forearm fracture were invited to calcaneal BMD measurement; 270 women (81%) and 64 men (73%) participated. Of the fracture cohort, 254 women aged 40-80 years and 27 men aged 60-80 years were compared with population-based control cohorts of 171 women in the age groups 50, 60, 70 and 80 years and 75 men in the age groups 60, 70, and 80 years In women aged 40-80 years the prevalence of osteoporosis in the distal forearm fracture cohort was 34% and in the population-based controls was 25%; the age-adjusted prevalence ratio (PR) was 1.32 (95% CI 1.00-1.76). In the subgroup of women aged 60-80 years the age-adjusted prevalence ratio of osteoporosis was 1.28 (95% CI 0.95-1.71). In men aged 60-80 years the prevalence of osteoporosis in the fracture cohort was 44% and in the population-based controls was 8% (PR 6.31, 95% CI 2.78-14.4). The age-adjusted odds ratio for fracture associated with a 1 SD reduction in calcaneal BMD was in women aged 40-80 years 1.4 (95% CI 1.1-1.8), in the subgroup of women aged 60-80 years 1.2 (95% CI 0.95-1.6), and in men aged 60-80 years 2.6 (95% CI 1.7-4.1). Among those aged 60-80 years the area under the ROC curve was in women 0.56 (95% CI 0.49-0.63) and in men 0.80 (95% CI 0.70-0.80).

10.4.142 Repeat low-trauma fractures occur frequently among men and women who have osteopenic BMD

Langsetmo L, Goltzman D, Kovacs CS, Adachi JD, Hanley DA, Kreiger N, Josse R, Papaioannou A, Olszynski WP, Jamal SA
J Bone Miner Res 2009;24:1515-22

In 2179 men and 5269 women, 50-90 yr of age, over 8 yrs, 128 fractures occurred in men and 577 fractures in women; 25% of fractures in men and 40% in women were repeat fractures. Just over one half of first fractures occurred in those with osteopenic BMD (58% in men, 54% in women). Just under one half of repeat fractures also occurred in those with osteopenic BMD (42% in men, 47% in women). The incidence of repeat fracture was, in most cases, nearly double, but sometimes nearly quadruple, the incidence of first fracture within a given BMD risk category in both men and women. Repeat fractures contribute to overall fracture burden independent of BMD.

10.4.143 Combining bone resorption markers and heel quantitative ultrasound to discriminate between fracture cases and controls

Nanchen D, Cornuz J, Ruffieux C, Riesen W, Burckhardt P, Krieg MA
Osteoporos Int 2009;20:1695-703

In 368 women (mean age 76.2±3.2 years), 195 with low-trauma nonvertebral fractures and 173 without, matched for age, areas under the receiver operating-characteristic curve (AUC) for discriminative models of the fracture group, with 95% CI, were 0.62 (0.56-0.68) and 0.59 (0.53-0.65) for PYD and DPD, and 0.64 (0.58-0.69) and 0.65 (0.59-0.71) for Achilles+ and Sahara QUS, respectively. The combination of resorption markers and QUS added no discriminatory information to either alone with an AUC of 0.66 (0.60-0.71) for Achilles+ with PYD and 0.68 (0.62-0.73) for Sahara with PYD. Urinary bone resorption markers and QUS are equally discriminatory between nonvertebral fracture patients and controls. The combination of resorption markers and QUS is not better than either alone.

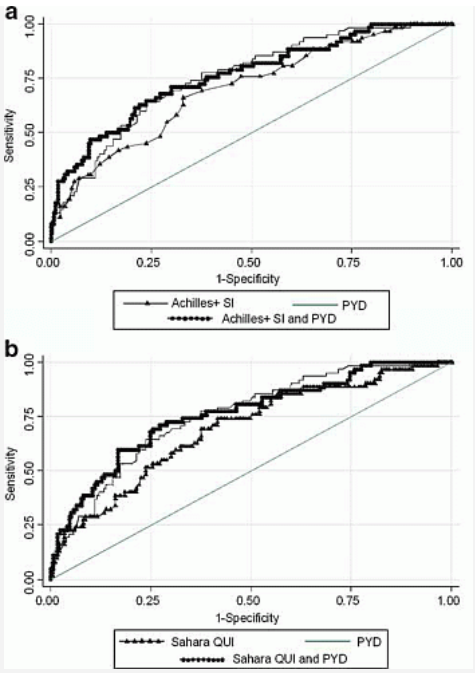

Fig. 10.4.143 Receiver operating characteristic (ROC) curves for the discrimination of hip fractures with heel quantitative ultrasounds and urinary marker of bone resorption. Achilles+ SI: stiffness index; PYD: pyridinoline; Sahara QUI: quantitative ultrasound index. (a) Combination of Achilles+ SI and PYD; (b) Combination of Sahara QUI and PYD. Reproduced from Osteoporos Int 2009;20:1695-1703 with permission from Springer.

10.4.144 Fractures after nursing home admission: Incidence and potential consequences
Rapp K, Lamb SE, Klenk J, Kleiner A, Heinrich S, Konig HH, Nikolaus T, Becker C
Osteoporos Int 2009;20:1775-83

Fractures at admission were measured in 93,424 women and men aged 65 years and over and newly admitted to nursing homes in Bavaria between 2001-2006. Fracture incidence was highest during the first months after admission to nursing homes and declined thereafter. This pattern was observed for all fracture sites, in women and men and in residents with different care needs. For example, fracture rates of the upper limb declined from 30.0 to 13.5/1000 person-years in the first 9 months after admission and for all fracture sites from 135.3 to 69.4/1000 person-years in a corresponding time period. Newly admitted residents have the highest fracture risk.

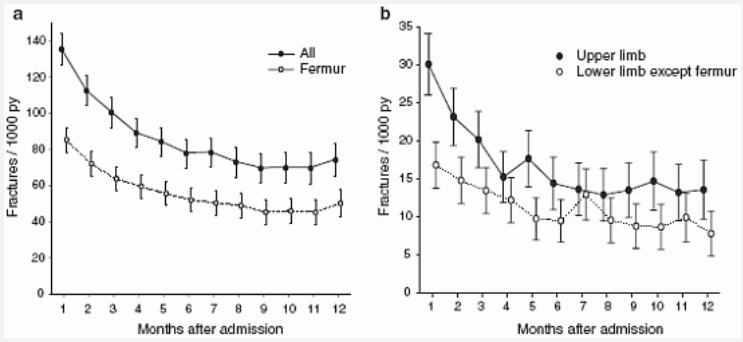

Fig. 10.4.144a Incidence rate of (a) all fractures (admitted to hospital) combined and of femoral fractures (admitted to hospital) and (b) of fractures (admitted to hospital) of the upper limb and the lower limb (except femur) as a function of time since admission to a nursing home in the cohort of residents admitted to nursing homes in Bavaria between 2001 and 2006. Reproduced from Osteoporos Int 2009;20:1775-83 with permission from Springer.

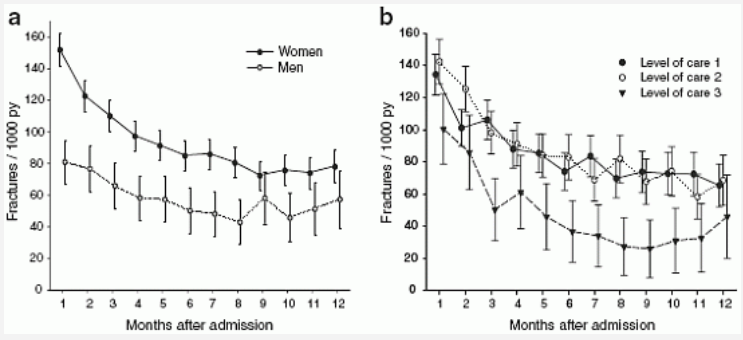

Fig. 10.4.144b Incidence rate of all fractures combined (admitted to hospital) stratified (a) by gender and (b) by care need (level of care) as a function of time since admission to a nursing home in the cohort of residents admitted to nursing homes in Bavaria between 2001 and 2006. Reproduced from Osteoporos Int 2009;20:1775-83 with permission from Springer.

10.4.145 Women and men with hip fractures have a longer femoral neck moment arm and greater

impact load in a sideways fall
Wang Q, Teo JW, Ghasem-Zadeh A, Seeman E
Osteoporos Int 2009;20:1151-6

Women and men with hip fractures have a longer moment arm of the force applied on the proximal femur during a sideways fall, a structural feature that may contribute to fracture risk. We studied 41 female and 22 male patients with hip fractures and 40 female and 17 male controls. Hip geometry was analyzed on the nonfracture hip in patients and left hip in controls using DXA There was no difference in areal BMD, hip axis length, femoral neck axis length, or neck-shaft angle between cases and controls. However, the moment arm of the force on the hip during a sideways fall was 7.3% and 9.5% longer resulting in 5.6% and 9.1% greater moment in such a fall in female and male cases relative to their respective controls (all p<0.056). Only the moment arm length in a sideways fall was associated with increased risk of hip fracture in females (odds ratio=1.91, 95%CI: 1.14-3.20 for each SD increase in moment arm length of sideways fall, p=0.02) and males (odds ratio=2.69, 95% CI: 1.19-6.09, p=0.01).

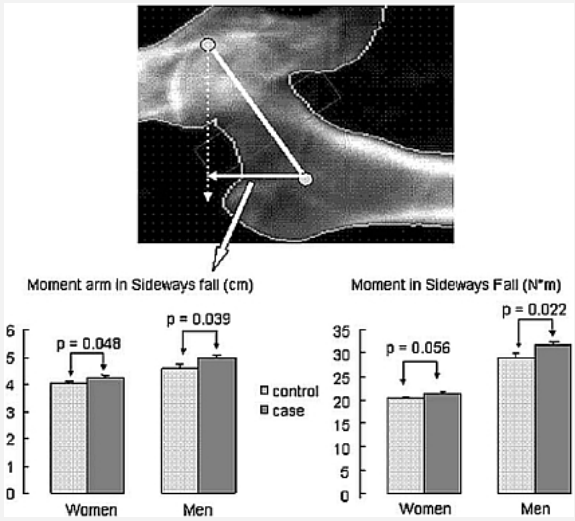

Fig. 10.4.145 Comparison of moment arm length (cm) and the moment (N m) in the sideways fall controlling for height and weight. Patients with hip fracture had longer moment arm and greater moment than controls in both sex. The error bar shows the SEM with adjustment of height and weight. Reproduced from Osteoporos Int 2009;20:1151-6 with permission from Springer.

10.4.146 Bone morphogenetic protein 7 (BMP7) gene polymorphisms are associated with inverse relationships between vascular calcification and BMD: The Diabetes Heart Study
Freedman BI, Bowden DW, Ziegler JT, Langefeld CD, Lehtinen AB, Rudock ME, Lenchik L, Hruska KA, Register TC, Carr JJ
J Bone Miner Res 2009;24:1719-27

Four single nucleotide polymorphisms (SNPs) in the BMP2 gene, 2 SNPs in BMP4, and 16 SNPs in BMP7 were tested for association with measures of VC using CT (coronary and carotid arteries, abdominal aorta), and BMD was measured using DXA and QCT in 920 European Americans from 374 Diabetes Heart Study families: 762 with type 2 diabetes. Association was observed between several measures of BMD and BMP7 rs17404303 (thoracic spine QCT p=0.03; lumbar spine QCT p=0.02; hip DXA p=0.06, dominant models). In addition, 6 of 16 BMP7 SNPs showed opposing effects on the bivariate PCA for VC and BMD (two-sided exact test, p=0.0143). Polymorphisms in BMP7 are associated with inverse relationships between bone mineralization and VC in the coronary, carotid, and abdominal aorta in a diabetes-enriched cohort of European Americans.

10.4.147 Low-fat, increased fruit, vegetable, and grain dietary pattern, fractures, and BMD: The Women's Health Initiative Dietary Modification Trial
McTiernan A, Wactawski-Wende J, Wu L, Rodabough RJ, Watts NB, Tylavsky F, Freeman R, Hendrix S, Jackson R
Am J Clin Nutr 2009;89:1864-76

Postmenopausal women (n=48,835) aged 50-79 y were randomized to Dietary Modification (40%, n=19,541) (daily goal: ≤20% energy as fat, ≥5 servings of vegetables and fruit, and ≥6 servings of grains) or to a no changes (60%; n=29,294). After 8.1 y, 215 women in the intervention group and 285 women in the comparison group (annualized rate: 0.14% and 0.12%, respectively) had a hip fracture (HR: 1.12; 95% CI: 0.94, 1.34). The intervention group (n=5423; annualized rate: 3.44%) had a lower rate of ≥2 falls than the comparison group (n=8695; annualized rate: 3.67%) (HR: 0.92; 95% CI: 0.89, 0.96). Those in the comparison group receiving hormone therapy had the lowest incidence of hip fracture. In a subset of 3951 women, hip BMD at years 3, 6, and 9 was 0.4-0.5% lower in the intervention group than in the comparison group (P=0.003). A low-fat and increased fruit, vegetable, and grain diet intervention modestly reduced the risk of multiple falls and slightly lowered hip BMD but did not change the risk of fractures.

10.4.148 Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: A 17-year follow-up from the Framingham Osteoporosis Study
Sahni S, Hannan MT, Blumberg J, Cupples LA, Kiel DP, Tucker KL
J Bone Miner Res 2009;24:1086-94

We evaluated associations of total and individual carotenoid intake (α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein+zeaxanthin) with incident hip fracture and nonvertebral osteoporotic fracture. 370 men and 576 women (mean age, 75±5 yr) from the Framingham Osteoporosis Study were followed for hip fracture until 2005 and nonvertebral fracture until 2003. 100 hip fractures occurred over 17 yr. Subjects in the highest tertile of total carotenoid intake had lower risk of hip fracture (p=0.02). Subjects with higher lycopene intake had lower risk of hip fracture (p=0.01) and nonvertebral fracture (p=0.02). A weak protective trend was observed for total beta-carotene for hip fracture alone, but associations did not reach statistical significance (p=0.10). These results suggest a protective role of several carotenoids for bone health in older adults.

10.4.149 Existing and potentially novel functional markers of vitamin D status: A systematic review
Seamans KM, Cashman KD
Am J Clin Nutr 2009;89:1997S-2008S

To review the effectiveness of 25(OH)D, PTH, bone turnover markers, BMD, and calcium absorption as biomarkers of vitamin D status, 36 vitamin D trial and 4 before-after studies were examined. Vitamin D supplementation raised 25(OH)D in all but one RCT, but the response was heterogeneous [weighted mean difference (WMD): 34.1 nmol/L; 95% CI: 28.9, 39.2; 32 RCTs; I^2=97%). Vitamin D lowered PTH (WMD: -0.29 pmol/L; 95% CI: -0.56, -0.02; 11 RCTs; I^2=29%), but not in the presence of calcium supplementation. There was a suggestion that whole-body or spine BMD may be a useful biomarker in older people. Bone turnover markers were not useful biomarkers of vitamin D status, but 4 before-after studies suggested that intestinal calcium absorption may respond to vitamin D status. 25(OH)D is a marker of vitamin D status.

10.4.150 Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men

Ensrud KE, Taylor BC, Paudel ML, Cauley JA, Cawthon PM, Cummings SR, Fink HA, Barrett-Connor E, Zmuda JM, Shikany JM, Orwoll ES
J Clin Endocrinol Metab 2009;94:2773-80

1279 men aged ≥65 years had 25(OH)D levels and BMD at baseline and repeat hip BMD 4.4 years later. After adjustment, the average loss in total hip BMD was 0.59%/year in men with D levels <15.0 ng/mL, -0.54%/year in men with D levels 15.0-19.9 ng/mL, -0.35%/year in men with)D levels 20.0-29.9 ng/mL, and -0.37%/year in men with 25(OH)D levels ≥30 ng/mL (p-trend=0.008 for multivariable model). Evidence supported an association in men ≥75 years (p-trend<0.001), not younger men. Men with 25(OH)D levels <20 ng/mL had greater rates of hip bone loss, but rates of loss were similar among men with higher levels.

10.4.151 25-hydroxy vitamin D levels in healthy premenopausal women: Association with bone turnover markers and BMD

Adami S, Bertoldo F, Braga V, Fracassi E, Gatti D, Gandolini G, Minisola S, Battista Rini G
Bone 2009;45:423-6

In 608 young healthy premenopausal women, 25(OH)D below 20 ng/ml was found in almost a third of the women. Its levels were inversely (P<0.001) related with age and body mass index (BMI kg/m^2) and directly with sunlight exposure during the summer, and latitude: i.e., the higher the latitude over Italy, the higher the 25(OH)D level. 25(OH)D levels, adjusted for age and BMI, were positively related with serum C-telopeptide of type I collagen, serum phosphate and spine BMD and negatively with serum PTH, serum magnesium, serum bone AP. Vitamin D deficiency is common in young healthy Italian women and particularly among those living in the southern part of the country. The most close determinants of vitamin D deficiency were BMI and sunlight exposure. Vitamin D insufficiency is associated with low spine BMD and increased bone AP even in young individuals.

10.4.152 Association of plasma vitamin D levels with adiposity in Hispanic and African Americans

Young KA, Engelman CD, Langefeld CD, Hairston KG, Haffner SM, Bryer-Ash M, Norris JM
J Clin Endocrinol Metab 2009;94:3306-13

The Insulin Resistance Atherosclerosis (IRAS) Family Study examined 917 Hispanics and 439 African Americans at baseline and again 5.3 years later (n=1081 at follow-up). 25(OH)D was inversely associated with BMI, VAT, and SAT in both populations at baseline. 25(OH)D was inversely associated with baseline VSR in African Americans (p=0.049), not Hispanics. $1,25(OH)_2D$ was inversely associated with BMI (p<0.0001, p=0.002) and VAT (p=0.0005, p=0.012) in Hispanics and African Americans, respectively, while $1,25(OH)_2D$ was inversely associated with SAT in Hispanics (p<0.0001) and with VSR in African-Americans (p=0.02). Adjusting for 25(OH)D attenuated these associations; $1,25(OH)_2D$ remained associated with BMI in both populations (p<0.05), and with SAT (p=0.004) in Hispanics. No associations between 5 year change in adiposity and 25(OH)D nor $1,25(OH)_2D$ were seen.

10.4.153 Determinants of 25-hydroxyvitamin D levels in African-American and Caucasian male veterans

Benjamin A, Moriakova A, Akhter N, Rao D, Xie H, Kukreja S, Barengolts E
Osteoporos Int 2009;20:1795-803

In this prospective cohort study, male veterans (n=307) were recruited. Among 232 African-American (AA) men (mean±SD), 25(OH)D (21.4±10.4 ng/ml) was lower and prevalence of insufficiency (80%) was higher than 75 Caucasians (C; 28.5±11.1 ng/ml and 53%, respectively, p<0.01 for both). Independent determinants (p<0.01 for all) of 25(OH)D included AA race, vitamin D supplements, BMI, dietary calcium intake, and smoking. Despite lower 25(OH)D levels in African-Americans, PTH levels were similar to those seen in Caucasians. There was a significant (p<0.02) negative linear association between 25(OH)D and PTH in African-American (r^2=0.05) and Caucasian (r^2=0.08) men, and there was no difference between the slopes of the relationship.

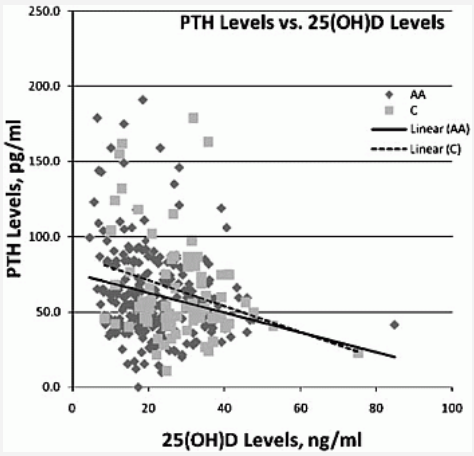

Fig. 10.4.153 Relationship between serum 25(OH)D and PTH. AA: African-American men, C: Caucasian men. There was a significant (p<0.02 for both) negative linear association between serum 25(OH)D and PTH in African-American (r^2=0.05) and Caucasian (r^2=0.08) men, and there was no difference between the slopes of the relationship. Reproduced from Osteoporos Int 2009;20:1795-803 with permission from Springer.

10.4.154 Heritability and environmental factors affecting vitamin D status in rural Chinese adolescent twins
Arguelles LM, Langman CB, Ariza AJ, Ali FN, Dilley K, Price H, Liu X, Zhang S, Hong X, Wang B, Xing H, Li Z, Liu X, Zhang W, Xu X, Wang X
J Clin Endocrinol Metab 2009;94:3273-81

226 male and female twins aged 13-20 years followed for 6 years has a mean (sd) 25(OH)D of 18.0(9.4)ng/ml. In males, 25(OH)D was 12.1(4.2)ng/ml in non-summer and 27.4(8.8)ng/ml in summer; in females, it was 10.1(4.1) ng/ml in non-summer and 19.5(6.3) ng/ml in summer. Male gender, summer, and high physical activity increased 25(OH)D. Overall, 68.9% of the variability in 25(OH) D level was attributable to additive genetic influence. Stratification by gender found that in males, 85.9% of the variability in 25(OH) D level was attributable to such influence, but in females, it was only 17%. There was a strong genetic influence on 25(OH)D level in males only.

10.4.155 Skeletal and hormonal responses to sunlight deprivation in Antarctic expeditioners
Iuliano-Burns S, Wang XF, Ayton J, Jones G, Seeman E
Osteoporos Int 2009;20:1523-8

Vitamin D insufficiency (<50 nmol/L) was observed in 85% of expeditioners by 6 months when serum calcium decreased and PTH increased (p<0.01). By 12 months, OC increased by 7.4±3.0% (p<0.05), and BMD decreased by 1.0±2.0% at the total proximal femur (p<0.05). For those with vitamin D sufficiency at baseline (>50 nmol/L), sunlight deprivation produced vitamin D insufficiency within 4 months unless baseline values were >100 nmol/L. Supplementation may be necessary for expeditioners with limited access to UV light.

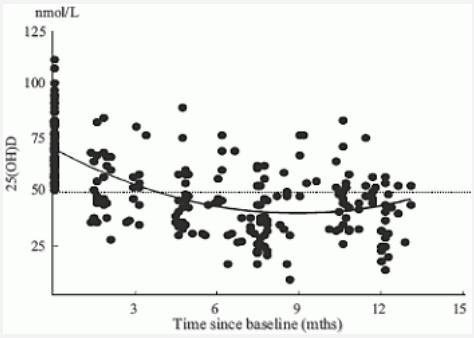

Fig. 10.4.155 Changes in serum 25(OH)D with duration of sunlight deprivation during an Antarctic winter in 52 adults who were vitamin D replete (>50 nmol/L) at baseline. Reproduced from Osteoporos Int 2009;20:1523-8 with permission from Springer.

10.4.156 Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women
Lippuner K, Johansson H, Kanis JA, Rizzoli R
Osteoporos Int 2009;20:1131-40

Osteoporotic fracture incidence was determined from national epidemiological data for hospitalised fractured patients from the Swiss Federal Office of Statistics in 2000 and results of a prospective Swiss cohort with almost 5000 fractured patients in 2006. Validated BMD-associated fracture risk was used together with national death incidence and risk tables to determine remaining lifetime and absolute 10-year fracture probabilities for hip and major osteoporotic (hip, spine, distal radius, proximal humerus) fractures. Major osteoporotic fractures incidence was 773 and 2078 per 100,000 men and women aged 50 and older. Corresponding remaining lifetime probabilities at age 50 were 20.2% and 51.3%. Hospitalisation for clinical spine, distal radius, and proximal humerus fractures reached 25%, 30% and 50%, respectively. Absolute 10-year probability of osteoporotic fracture increased with advancing age and decreasing BMD and was higher in women than in men.

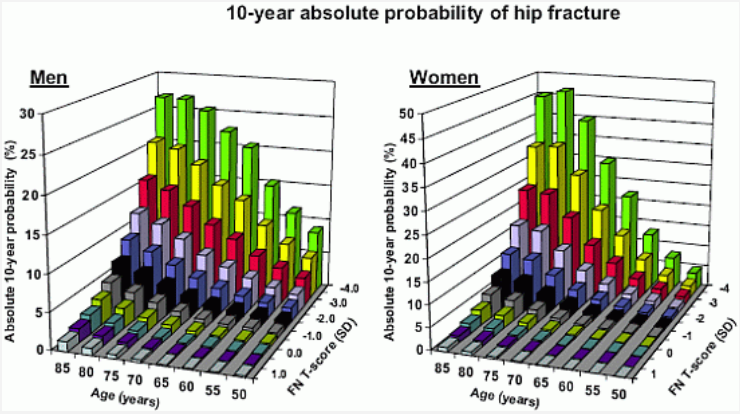

Fig. 10.4.156a Absolute 10-year probability of hip fracture (percent) by gender, age and femoral neck T-score. Based on Swiss fracture data from the SFOS, the Swiss OsteoCare cohort, death risk and incidence tables for Switzerland published by the WHO, BMD gradients of risk determined in ten international population-based cohorts validated for Switzerland and BMD normative data from US NHANES III. Reproduced from Osteoporos Int 2009;20:1131-40 with permission from Springer.

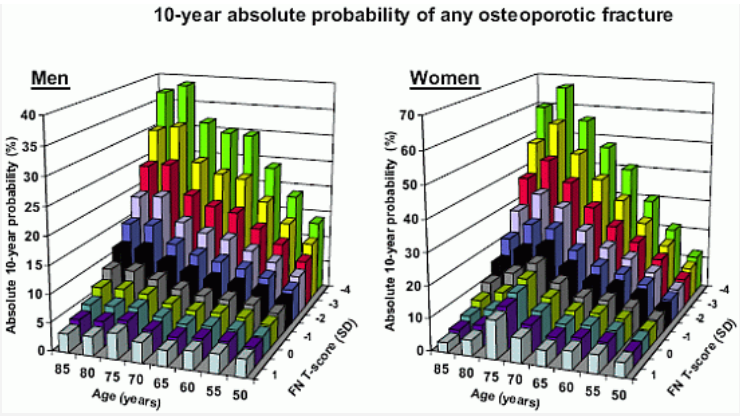

Fig. 10.4.156b Absolute 10-year probability for a major osteoporotic fracture (hip, clinical spine, distal radius or proximal humerus; percent) by gender, age and femoral neck T-score. Based on Swiss fracture data from the SFOS, the Swiss OsteoCare cohort, death risk and incidence tables for Switzerland published by the WHO, BMD gradients of risk determined in ten international population-based cohorts validated for Switzerland and BMD normative data from US NHANES III. Reproduced from Osteoporos Int 2009;20:1131-40 with permission from Springer.

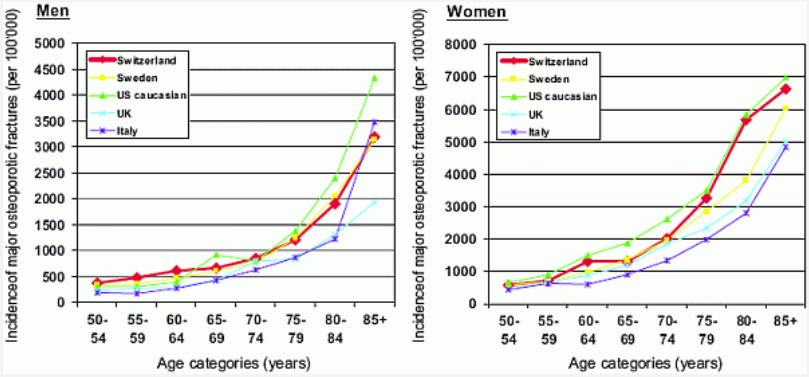

Fig. 10.4.156c Comparative incidence of major osteoporotic fractures (hip, spine, distal radius and proximal humerus) in number of fractures per 100,000 inhabitants. Reproduced from Osteoporos Int 2009;20:1131-40 with permission from Springer.

10.4.157 Prevalence and risk factors of radiographic vertebral fracture in postmenopausal Vietnamese women

Ho-Pham LT, Nguyen ND, Vu BQ, Pham HN, Nguyen TV

Bone 2009;45:213-7

Radiographs from 209 postmenopausal women aged between 50-85 years (average 62) showed 48 had at least one radiographic vertebral fracture; a prevalence of 23% (95%CI: 18-29%). Although fracture occurred in all vertebrae, most (83%) occurred at the L1-L5. Most occurred at one vertebra, and only 12% occurred at multiple vertebrae. The prevalence increased with age reaching 39% among those aged 70+ years. There was no association between vertebral fracture and back pain, fall history, and dietary calcium intake. In simple log-binomial regression analysis, higher risk of vertebral fracture was associated with advancing age (prevalence ratio [PR] per 10 years: 1.40; 1.16-2.05) and lower lumbar spine BMD (PR per SD: 1.51; 1.18-1.92). In multivariable analysis, the two factors remained independently associated with fracture risk, with the area under the receiver operating characteristic curve being 0.66. A quarter of postmenopausal women in Vietnam have a radiographic vertebral fracture, and this prevalence is as common as in Caucasian populations.

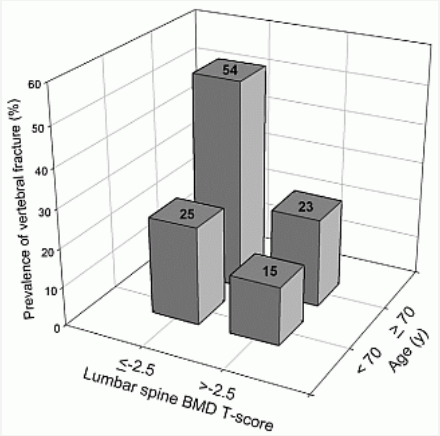

Fig. 10.4.157 Prevalence of radiographic vertebral fracture, stratified by LSBMD T-score and age. Reproduced from Bone, 45:213-7, Copyright (2009), with permission from Elsevier.

10.4.158 Estimated prevalence and patterns of presumed osteoporosis among older Americans based on Medicare data

Cheng H, Gary LC, Curtis JR, Saag KG, Kilgore ML, Morrisey MA, Matthews R, Smith W, Yun H, Delzell E

Osteoporos Int 2009;20:1507-15

Among 911,327 beneficiaries with 6 or 7 years of Medicare coverage, the overall prevalence of OP and associated fractures was 29.7%. Prevalence was four times higher for women than men, increased with age, and was two times higher for whites, Hispanic Americans, and Asian Americans than African Americans. Among people with OP-associated fracture claims, the proportion with an OP diagnosis was 49.7% overall (women, 57.1%; men, 21.9%) and was lower for men than women and for African Americans than other ethnic groups. The low proportion of beneficiaries who had an OP-associated fracture and also had an OP diagnosis, particularly among men and African American women, suggests suboptimal recognition and management of OP.

10.4.159 Greater osteoporosis educational outreach is desirable among Chinese immigrants in Chinatown, Chicago

Tan S, Ji L, Tsai J, Eng J, Ko HJ, Yau A, Edwards G, Bunta A, Edwards BJ
Osteoporos Int 2009;20:1517-22

The study population included 94 women with mean age of 51±9 years, mean length of residence in the United States of 9±7 years, and 73% (n=76) of whom were recent immigrants. Women expressed concern about the seriousness of osteoporosis and their relative susceptibility to osteoporosis. In particular, women with a prior fracture reported higher seriousness to osteoporosis. Nonetheless, women exhibited low health motivation and low awareness of the benefits of calcium and exercise. Bone densitometry results corresponded to a T-score of -1.2±1.5. Multiple regression analysis revealed that a younger age and longer length of residence in the USA were associated with higher BMD.

10.4.160 Ethnic differences in parathyroid hormone secretion and mineral metabolism in response to oral phosphate administration

Yan L, Schoenmakers I, Zhou B, Jarjou LM, Smith E, Nigdikar S, Goldberg GR, Prentice A
Bone 2009;45:238-45

Healthy people from UK (B), The Gambia (G) and China (C), 15 individuals from each sex and ethnic group, were studied. At baseline, PTH, $1,25(OH)_2D$ and turnover markers were higher in G than in B and C subjects ($P \leq 0.01$). Two hours after P loading, ionized calcium (iCa) decreased and PTH and plasma P (P) increased in all groups ($P \leq 0.01$, n.s. between groups). uP/Cr increased, the increase being greater in C than B and G on days 4 and 5 ($P \leq 0.01$). By day 5, fasting iCa was decreased and P increased in B and G ($P \leq 0.01$) but not in C subjects. Fasting PTH and uP/Cr increased in all groups. There were ethnic differences in changes in markers, but the relationship with changes in PTH was comparable between groups. Chinese showed a more rapid renal clearance of P than British and Gambian counterparts and there were differences between the groups in the skeletal response to P loading, but no evidence was found for resistance to the resorbing effects of PTH.

10.4.161 High BMD is associated with high body mass index

Morin S, Leslie WD
Osteoporos Int 2009;20:1267-71

In 16,500 women 50 years, higher BMI was associated with higher mean T-scores and Z-scores at all sites ($P<0.001$). The proportion of women with high BMD increased with each BMI category (P for trend <0.05). In women with a lumbar spine T-score of +2.5 or more, 43.5% were obese with BMI>30 kg/m^2 (55.6% for the femoral neck and 73.1% for the total hip). For women with a lumbar spine Z-score of +2.0 or more, 37.2% were obese (42.0% for the femoral neck and 50.9% for the total hip).

10.4.162 Fat mass is negatively associated with cortical bone size in young healthy male siblings

Taes YE, Lapauw B, Vanbillemont G, Bogaert V, De Bacquer D, Zmierczak H, Goemaere S, Kaufman JM
J Clin Endocrinol Metab 2009;94:2325-31

677 men (25-45 yr) with 296 pairs of brothers had total and regional fat mass inversely associated with areal bone mass and bone size, independent from lean mass (radius periosteal circumference beta: -0.29±0.04; $P<0.001$). Lean mass was positively associated with bone size but inversely with cortical density at both tibia and radius ($P<0.01$). The negative association between total fat mass and bone size was independent of sex steroids. Leptin but not adiponectin was inversely associated with bone size, but this was no longer significant after adjustment for body fat. Increased fat mass is associated with smaller bone size, challenging the view of a high bone mass index as a protective factor for osteoporosis, whereas lean mass was a consistent positive determinant of bone size.

10.4.163 Lipid levels: A link between cardiovascular disease and osteoporosis?

Buizert PJ, van Schoor NM, Lips P, Deeg DJ, Eekhoff EM
J Bone Miner Res 2009;24:1103-9

Epidemiological observations support a positive relationship between cardiovascular diseases (CVD) and osteoporosis, where cholesterol has been indicated to be a possible link. In 620 men and 635 women, 65-88 yr of age. No association was found between total cholesterol (TC) and QUS. Men and women in the highest quartile of high-density lipoprotein cholesterol (HDL-c) had a significantly lower QUS (men-VOS: $\beta=-20.8$, $p=0.00$; BUA: $\beta=-5.2$, $p=0.02$; women-VOS: $\beta=-18.6$, $p=0.00$) compared with men and women in the lowest quartile. An even stronger positive association was seen between TC/HDL-c ratio and QUS (men-VOS: $\beta=21.8$, $p=0.00$; BUA: $\beta=5.5$, $p=0.01$; women-VOS: $\beta=19.2$, $p=0.00$; BUA: $\beta=3.6$, $p=0.05$). The lipid profile that is favorable in the prevention of CVD (i.e., high levels of HDL-c and low TC/HDL-c ratio) is unfavorable for QUS. These results indicate that HDL-c levels do not explain the association between osteoporosis and CVD.

10.4.164 Effect of alcohol consumption on BMD and hormonal parameters in physically active male soldiers

Venkat KK, Arora MM, Singh P, Desai M, Khatkhatay I
Bone 2009;45:449-54

In 400 men from the armed forces (n=400), those with intake of >24 g/wk of alcohol had higher BMD at femur compared to nonalcohol consumers ($p=0.0001$) and a linear increase in mean femoral BMD over increasing categories of alcohol intake (p-trend<0.0001). Smoking was negatively associated with femoral BMD. In multiple regression analysis, age, BMI, alcohol consumption and smoking were independent predictors of femoral BMD, explaining 10.6% variance. At lumbar spine, age, height and BMI were independent predictors, explaining 9.4% variance in BMD. The concentrations of total testosterone, free testosterone, bioavailable testosterone and PTH were low ($p<0.0001$) whereas estradiol ($p=0.02$), free and bioavailable estradiol ($p<0.001$) were high in alcohol consumers compared to nonconsumers. In multiple regression analysis alcohol intake and height explained 5.5% variance in estradiol.

10.4.165 Moderate ingestion of alcohol is associated with acute ethanol-induced suppression of circulating CTX in a PTH-independent fashion

Sripanyakorn S, Jugdaohsingh R, Mander A, Davidson SL, Thompson RP, Powell JJ
J Bone Miner Res 2009;24:1380-8

Fasted volunteers (age, 20-47 yr) were given beer of different alcohol levels (<0.05-4.6%), solutions of ethanol or orthosilicic acid, and water±calcium chloride. Markers of bone formation were unchanged throughout the study for all solutions. CTX was reduced after ingestion of a 0.6 liters of ethanol solution (>2% ethanol; p=0.01), 0.6 liters of beer (<0.05-4.6% ethanol; p<0.02), or a solution of calcium (180 mg calcium; p<0.001), but only after calcium ingestion was the reduction in CTX preceded by a fall in PTH (p<0.001). Modeling indicated that the major, acute suppressive effects of moderate beer ingestion (0.6 liters) on CTX were caused by energy intake in the early phase (approximately 0-3 h) and a "nonenergy" ethanol component in the later phase (approximately 3 to >6 h). The early effect on bone resorption is well described after the intake of energy, mediated by glucagon-like peptide-2, but the late effect of moderate alcohol ingestion is novel, seems to be ethanol specific.

10.4.166 The effects of homocysteine and MTHFR genotype on hip bone loss and fracture risk in elderly women

Zhu K, Beilby J, Dick IM, Devine A, Soos M, Prince RL
Osteoporos Int 2009;20:1183-91

The effects of homocysteine and MTHFR genotype variation on hip BMD and fracture risk over 5 years in a cohort of 1213 community-dwelling women aged 70-85 years was assessed. The highest tertile of homocysteine was associated with a greater hip BMD loss over 4 years (-2.8%) compared to the middle (-1.6%) and lowest tertiles (-1.2%) (P<0.001). There was no effect of homocysteine on fracture prevalence or incidence. MTHFR gene variation was only weakly related to one of the bone outcome measures. In this study population, high homocysteine is associated with greater hip bone loss but not fracture risk.

10.4.167 Reduced bone perfusion in proximal femur of subjects with decreased BMD preferentially affects the femoral neck

Wang YX, Griffith JF, Kwok AW, Leung JC, Yeung DK, Ahuja AT, Leung PC
Bone 2009;45:711-5

Using dynamic contrast enhanced MR imaging, this study investigated perfusion of the proximal femur in subjects with normal BMD, low bone mass and osteoporosis. Study cohort comprised healthy elderly Hong Kong Chinese volunteers consisting of 107 males (74.4±4.2 years, mean±SD) and 135 females (73.9±4.3 years). Right proximal femur BMD measurement by DXA and MR perfusion imaging (maximum enhancement, E^{max} and enhancement slope, E^{slope}) of the femoral head, neck, and proximal shaft were carried out within a one month interval. Normal BMD, low bone mass and osteoporotic subjects accounted for 46.7%, 44.9%, and 8.4% of males; and 32.6%, 43.7%, and 23.7% of females. Perfusion indices showed that femoral head perfusion was less compared to the femoral shaft (E^{max} and E^{slope} indices of head region=28% of shaft region). Compared with normal BMD subjects, Esup>max of femoral head, neck, and proximal femur shaft were reduced by 15±5% (mean ±standard error); 40±4%; 15±5%, respectively, for low bone mass subjects, and 36±4%; 50±6%; 47±6%, respectively, for osteoporotic subjects. E^{slope} of femoral head, neck, and proximal femur shaft were reduced by 17±7%; 41±5%; 4±7% for low bone mass subjects and 50±5%, 62±5%, 34±8% for osteoporotic subjects. In low bone mass and osteoporotic subjects there was a tendency for perfusion in the femoral neck to reduce to a greater degree relative to that in the femoral head and shaft.

10.4.168 Serum estradiol is associated with volumetric BMD and modulates the impact of physical activity on bone size at the age of peak bone mass: A study in healthy male siblings

Lapauw BM, Taes Y, Bogaert V, Vanbillemont G, Goemaere S, Zmierczak HG, De Bacquer D, Kaufman JM
J Bone Miner Res 2009;24:1075-85

Healthy male siblings (n=677; 25-45 yr) had cross-sectional muscle area (CSMA) and bone parameters of radius (4% and 66% site) and tibia (66% site) assessed using pQCT. After controlling for age, weight, and height, free E_2 was associated with trabecular and cortical vBMD, negatively associated with endosteal circumference at the radius, and positively associated with cortical vBMD at the tibia. In addition, positive interactions between physical activity and serum E_2 were observed for bone size at the tibia. No associations between free T levels and pQCT bone parameters were found.

10.4.169 Antipsychotic use and the risk of hip/femur fracture: A population-based case-control study

Pouwels S, van Staa TP, Egberts AC, Leufkens HG, Cooper C, de Vries F
Osteoporos Int 2009;20:1499-506

Most cases were elderly (77.6% aged ≥70 years). There was an increased risk for hip/femur fracture associated with the use of antipsychotic drugs. The risk for current users (OR_{adj} 1.68 [1.43, 1.99]) was greater than with past use (OR_{adj} 1.33 [1.14, 1.56]; p=0.036). Current use of conventional antipsychotics (OR_{adj} 1.76 [1.48, 2.08]) but not atypical antipsychotics (OR_{adj} 0.83 [0.42, 1.65]) was associated with an increased risk.

10.4.170 Depression and low BMD: A meta-analysis of epidemiologic studies

Wu Q, Magnus JH, Liu J, Bencaz AF, Hentz JG
Osteoporos Int 2009;20:1309-20

Six case-controlled and eight cross-sectional studies met prestated inclusion criteria (N=10,523). Information on study design, participant characteristics, measurements of BMD and depression, and control for potential confounders was abstracted independently by two investigators using a standardized protocol. Overall, depression was associated with a decrease in mean BMD of spine (-0.053 g/cm^2 [95% CI -0.087 to -0.018 g/cm^2]) and hip (-0.052 g/cm^2 [95% CI -0.083 to -0.022 g/cm^2]). A substantially greater BMD decrease was observed in depressed women (-0.076 g/cm^2 in spine; -0.059 g/cm^2 in hip) and in cases of clinical depression (-0.074 g/cm^2 in spine; -0.080 g/cm^2 in hip). Depression is associated with low BMD, with a substantially greater BMD decrease in depressed women and in cases of clinical depression.

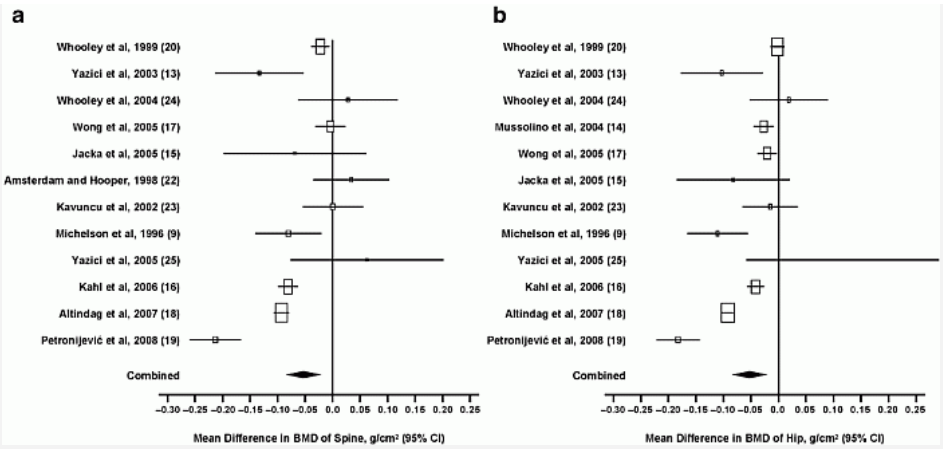

Fig. 10.4.170a Mean differences in BMD between depressed and nondepressed groups and corresponding 95% CIs for spine (a) and hip (b) in 12 studies. Reproduced from Osteoporos Int 2009;20:1309-20 with permission from Springer.

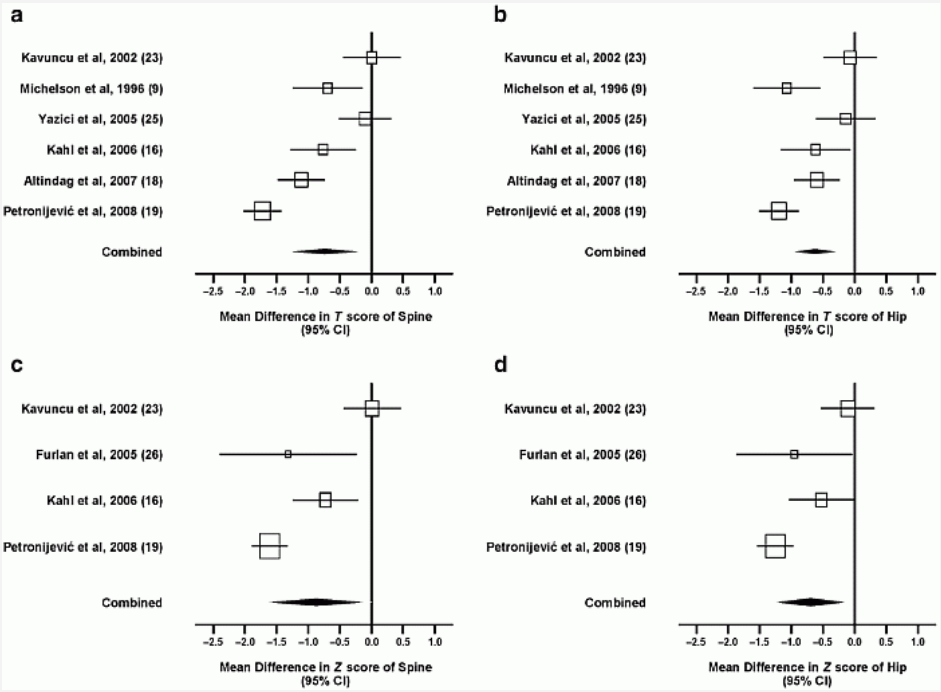

Fig. 10.4.170b Mean differences in T-score (a, b) and Z-score (c, d) between depressed and nondepressed groups and corresponding 95% CIs for spine and hip. Reproduced from Osteoporos Int 2009;20:1309-20 with permission from Springer.

10.4.171 Use of anti-depressants and the risk of fracture of the hip or femur

van den Brand MW, Samson MM, Pouwels S, van Staa TP, Thio B, Cooper C, Leufkens HG, Egberts AC, Verhaar HJ, de Vries F
Osteoporos Int 2009;20:1705-13

Cases (n=6763) were adult patients with a first hip/femur fracture. For each case, four controls (n=26,341) were matched by age, gender and geographic region. The risk of hip/femur fracture increased with current use of SSRIs (adjusted odds ratio (OR_{adj}) 2.35 [95% CI 1.94-2.84]) and TCAs (OR_{adj} 1.76 [95% CI 1.45-2.15]). The risk of hip/femur fracture declined after discontinuation of use. The risk of hip/femur fracture increased as the degree of 5-HTT inhibition of all anti-depressants increased from OR_{adj} 1.64 [95% CI 1.14-2.35] for drugs with low 5-HTT inhibition to OR_{adj} 2.31 [95% CI 1.94-2.76] for those with high 5-HTT inhibiting properties. SSRIs and TCAs increase hip/femur fracture risk.

10.4.172 Bone mass and structure in adolescents with type 1 diabetes compared to healthy peers

Saha MT, Sievanen H, Salo MK, Tulokas S, Saha HH
Osteoporos Int 2009;20:1401-6

In 48 adolescents, 26 girls and 22 boys, with type 1 diabetes, and for healthy peers matched for age, sex, body height and weight, and pubertal maturity, diabetes was associated with reduced bone mineral content (BMC) and smaller bone cross-sectional size. Diabetic boys seemed to be more affected than diabetic girls. Among the boys, the mean deficit in BMC of all measured skeletal sites was more than 10%, while among the girls it was less than 5%. In conclusion, type 1 diabetes is associated with reduced BMC and appears to affect bone cross-sectional size and cortical rigidity.

10.4.173 Associations between components of the metabolic syndrome vs. BMD and vertebral fractures in patients with type 2 diabetes

Yamaguchi T, Kanazawa I, Yamamoto M, Kurioka S, Yamauchi M, Yano S, Sugimoto T
Bone 2009;45:174-9

Visceral and subcutaneous fat areas (V and S) in 187 men (28-83 years) and 125 postmenopausal women (46-82 years) with type 2 diabetes showed men whose V was 100 cm^2 or more had lower urinary N-terminal crosslinked telopeptide of type I

collagen (p=0.005), higher FN-BMD (p=0.004), and lower prevalence of vertebral fractures (VFs) (p=0.04) than controls. Fat mass, V, S, and lean body mass correlated with FN-BMD in men and with lumbar (L) and FN-BMD in women. When adjusted for weight, these correlations became negative. Urinary C-peptide correlated with FN-BMD in both genders. Multivariate logistic regression identified V in men and urinary C-peptide in women as factors inversely associated with the presence of VFs [odds ratio (OR)=0.61 per SD increase, p=0.04, and OR=0.32, p=0.01, respectively]. Visceral fat in men and hyperinsulinemia in women may protect against VFs independent of weight, L-BMD, diabetes duration, or therapies.

10.4.174 Serum osteocalcin/bone-specific alkaline phosphatase ratio is a predictor for the presence of vertebral fractures in men with type 2 diabetes

Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Yano S, Sugimoto T
Calcif Tissue Int 2009;85:228-34

In 248 Japanese men with type 2 diabetes serum OC and OC/BAP ratio correlated negatively with HbA(1c) (P<0.01) and positively with IGF-I (P<0.01). OC/BAP ratio was inversely associated with the presence of vertebral fractures (odds ratio=0.695, P<0.05). This association was still significant after additional adjustment for lumbar or femoral neck BMD. Poor diabetic control and lower IGF-I level are linked to impaired bone formation and resultant reduction in OC/BAP ratio in men with type 2 diabetes.

10.4.175 Adiponectin is associated with changes in bone markers during glycemic control in type 2 diabetes mellitus

Kanazawa I, Yamaguchi T, Yamauchi M, Yamamoto M, Kurioka S, Yano S, Sugimoto T
J Clin Endocrinol Metab 2009;94:3031-7

50 Japanese patients with poorly controlled type 2 diabetes (iHbA1c 10.0±2.5%) were recruited. Bone specific alkaline phosphatase decreased with a mean change of -3.11 whereas osteocalcin (OC) increased with a mean change of 1.94 and undercarboxylated OC (ucOC)/OC ratio was decreased with a mean change of -0.15. Adiponectin level was not different before and after glycemic control, baseline adiponectin positively correlated with changes in OC, ucOC, and urinary N-terminal crosslinked telopeptide of type I collagen (uNTX). Changes in adiponectin were negatively correlated with changes in OC and uNTX. Changes in HbA1c were negatively correlated with changes in OC. Treatments for hyperglycemia enhance OC, and suggest that serum adiponectin before starting to compensate poorly controlled diabetics could predict the subsequent improvement of bone remodeling markers during glycemic control.

10.4.176 Effects of rhIGF-1 administration on surrogate markers of bone turnover in adolescents with anorexia nervosa

Misra M, McGrane J, Miller KK, Goldstein MA, Ebrahimi S, Weigel T, Klibanski A
Bone 2009;45:493-8

rhIGF-1 was administered at 30-40 μg/kg twice daily to 10 girls with AN 12-18 years old for 7-9 days. Ten age-matched girls with AN were followed without rhIGF-1 for a similar period. IGF-1, PINP and CTX levels were measured. rhIGF-1 caused an increase in IGF-1 from day 1 to day 4/5 (p<0.0001) and day 1 to day 8/9 (p<0.0001). PINP increased from day 1 to day 4/5 (p=0.004) and day 1 to day 8/9 (p=0.004), with a smaller increase from day 4/5 to day 8/9 (p=0.048). CTX levels did not change. No changes occurred in IGF-1 or PINP levels in girls not receiving rhIGF-1; however, CTX levels increased (p=0.01). Percent change in PINP was higher (p=0.02) and percent change in CTX was lower (p=0.006) in girls who received rhIGF-1 compared to those who did not receive any intervention. rhIGF-1 was well tolerated without hypoglycemia. Short-term administration of rhIGF-1 causes an increase in a surrogate bone formation markers in girls with AN without significant side effects.

10.4.177 Peptide YY in adolescent athletes with amenorrhea, eumenorrheic athletes and non-athletic controls

Russell M, Stark J, Nayak S, Miller KK, Herzog DB, Klibanski A, Misra M
Bone 2009;45:104-9

In 16 AA, 15 EA and 16 nonathletic controls 12-18 years old, PYY was higher in AA than EA (111±52 vs. 61±29 pg/ml, p<0.05), whereas adiponectin did not differ by group. Although activity scores did not differ, BMI was lower in AA than EA and a larger proportion (62.5% vs. 6.7%) reported disordered eating, indicating lower energy availability. PYY and adiponectin were independent predictors of testosterone in a regression model (p=0.01 and 0.04), but did not predict estradiol. PYY, not adiponectin, negatively predicted PINP (p=0.002) and lumbar bone mineral apparent density Z-scores (p=0.045). High PYY (but not adiponectin) differentiate AA from EA, and may be an important factor contributing to low bone density in athletes.

10.4.178 Alcohol alters whole body composition, inhibits bone formation, and increases bone marrow adiposity in rats

Maddalozzo GF, Turner RT, Edwards CH, Howe KS, Widrick JJ, Rosen CJ, Iwaniec UT
Osteoporos Int 2009;20:1529-38

Compared to ad libitum-fed age-matched controls, alcohol-fed rats weighed less and had lower lean mass, fat mass, and percent body fat, lower slow- and fast-twitch muscle mass, lower total body bone mineral content, and lower cancellous bone volume in the lumbar vertebra and proximal tibia. The effects of alcohol consumption on body composition were reduced when compared to the pair-fed control diet, indicating that caloric restriction was a comorbidity factor. In contrast, the effects of alcohol to decrease bone formation and serum leptin and IGF-I levels and to increase bone marrow adiposity appeared independent of caloric restriction.

10.4.179 Binge alcohol-induced bone damage is accompanied by differential expression of bone remodeling-related genes in rat vertebral bone

Callaci JJ, Himes R, Lauing K, Wezeman FH, Brownson K
Calcif Tissue Int 2009;84:474-84

Binge alcohol (3 g/kg, i.p.) was administered on 3 consecutive days each week, for 1 or 4 weeks, to adult male rats. Bone loss was observed after four binge alcohol cycles with a 23% decrease in cancellous BMD and 17% decrease in vertebral compressive strength (P<0.05). The expression of key bone formation-related marker genes such as osteocalcin and alkaline phosphatase were reduced (P<0.05) after acute binge alcohol exposure, and expression of regulators of osteoblast activity such as bone morphogenetic proteins and parathyroid hormone receptor displayed (P<0.05) decreased differential expression. The expression of sclerostin, was increased. The expression of NF-κβ ligand (RANKL) and interleukin-6 were

increased (P<0.05) and osteoprotegerin levels were decreased (P<0.05).

10.4.180 Etiopathogenesis of hepatic osteodystrophy in Wistar rats with cholestatic liver disease
Pereira FA, Facincani I, Jorgetti V, Ramalho LN, Volpon JB, Dos Reis LM, de Paula FJ
Calcif Tissue Int 2009;85:75-83

46 male Wistar rats: sham-operated (SO, n=23) and bile duct-ligated (BDL, n=23) were studied. Rats were killed on day 30 postoperatively. The maximal force at fracture and the stiffness of the midshaft femur were, respectively, 53% and 24% lower in BDL compared to SO. Histomorphometric measurements showed low cancellous bone volume and decreased cancellous bone connectivity in BDL, compatible with osteoporosis. This group also showed increased mineralization lag time, indicating disturbance in bone mineralization. Serum levels of IGF-I were lower in BDL (basal 1816±336 vs. 30 days 1062±191 ng/ml, P<0.0001). BDL also showed higher IGF-I expression in the liver tissue but lower IGF-I and GH receptor expression in growth plate cartilage than SO. BDL rats show reduced bone volume and decreased bone strength, as early as after one month of cholestasis.

10.4.181 May an altered hypothalamo-pituitary-adrenal axis contribute to cortical bone damage in primary hyperparathyroidism?
Gianotti L, Tassone F, Pia A, Bovio S, Reimondo G, Visconti G, Terzolo M, Borretta G
Calcif Tissue Int 2009;84:425-9

180 patients with PHPT and 56 subjects with incidentally discovered adrenal adenoma who served as controls. Serum morning cortisol and urinary cortisol were similar in PHPT patients and controls, whereas midnight cortisol was higher in PHPT patients (5.3±4.7 vs. 2.9±0.9 µg/dL, P=0.001). In this group, midnight cortisol correlated with age (r=0.27, P=0.008) and negatively with forearm (r=–0.36, P=0.003) and total-femur T-score (r=–0.30, P=0.02). Age (β=–0.29, P<0.0001), PTH (β=–0.33, P<0.0001), and midnight cortisol (β=–0.14, P<0.04) were independently associated with forearm T-score.

10.4.182 Hypothalamic suppression decreases bone strength before and after puberty in a rat model
Yingling V, Elle Saine M, Joshi R
Calcif Tissue Int 2009;84:485-93

Hypothalamic suppression was achieved by providing GnRH injections. Animals received injections for 25 days either before puberty (pre group) (age 23-46 days) or after puberty (post group) (age 65-90 days). The peak moment was lower in the pre and post GnRH-a groups compared with control. The percentage difference of the average peak moment and stiffness values from the respective age-matched control groups yielded a greater percentage difference in the pre group. The cortical area was less in the GnRH-a-treated groups, but no significant difference between the relative deficits between pre and post groups were found. Hypothalamic-pituitary-gonadal axis suppression before puberty resulted in a significantly larger deficit in mechanical strength compared with postpubertal animals.

10.4.183 Early acceleration phase and late stationary phase of remodeling imbalance in long bones of male rats exposed to long-standing acidemia: A 10-month longitudinal study using bone histomorphometry
Assapun J, Charoenphandhu N, Krishnamra N
Calcif Tissue Int 2009;85:1-9

Bone changes in male rats fed 1.5% NH(4)Cl in drinking water for up to 10 months to induce CMA with plasma pH of 7.2-7.3 showed decreases in BMD after 6 months of CMA, whereas histomorphometric analysis revealed a decrease in bone volume at week 2 after CMA induction. Exposure to CMA longer than 2 weeks decreased trabecular number, trabecular thickness, osteoblast surface, mineral apposition rate, and bone formation rate, while increasing trabecular separation, osteoclast surface, and eroded surface. Bone resorption was rapid during weeks 2-16 (acceleration phase) and thereafter persisted at a slower rate (stationary phase) until week 40. CMA reduced the total calcium content in bone and enhanced urinary calcium excretion.

10.4.184 Genetic hypercalciuric stone-forming rats have a primary decrease in BMD and strength
Grynpas M, Waldman S, Holmyard D, Bushinsky DA
J Bone Miner Res 2009;24:1420-6

Genetic hypercalciuric stone-forming (GHS) and control (Ctl) rats were fed a low (0.02% Ca, LCD) or a high Ca (1.2% Ca, HCD) diet for 6 wk. Urine Ca was greater in the GHS rats on both diets. GHS fed HCD had reduced cortical (humerus) and trabecular (L1-L5 vertebrae) BMD, whereas GHS rats fed LCD had a reduction in BMD similar to Ctl. GHS rats fed HCD had a decrease in trabecular volume and thickness, whereas LCD led to a approximately 20-fold increase in both osteoid surface and volume. GHS rats fed HCD had no change in vertebral strength (failure stress), ductibility (failure strain), stiffness (modulus), or toughness, whereas in the humerus, there was reduced ductibility and toughness and an increase in modulus, indicating that the defect in mechanical properties is mainly manifested in cortical, rather than trabecular, bone. GHS rat cortical bone is more mineralized than trabecular bone and LCD led to a decrease in the mineralization profile. Thus, the GHS rats, fed an ample Ca diet, have reduced BMD with reduced trabecular volume, mineralized volume, and thickness, and their bones are more brittle and fracture prone, indicating that GHS rats have an intrinsic disorder of bone that is not secondary to diet.

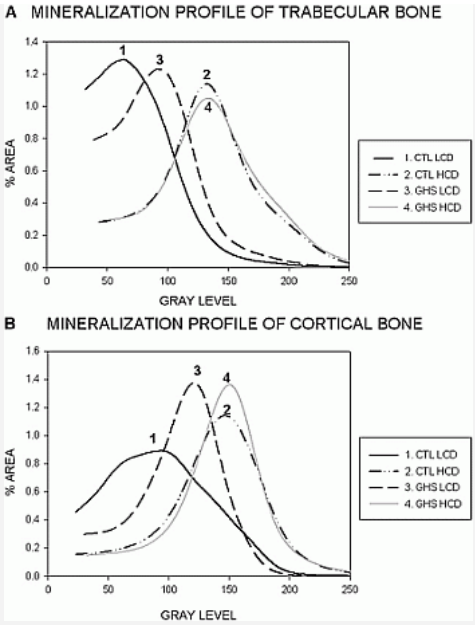

Fig. 10.4.184 Histograms of mineralization profile for trabecular bone (A) and cortical bone (B). Higher gray level (shift of curve to right) indicated an increased level of mineralization. Increased width of curve indicates increased degree of heterogenicity. Reproduced from J Bone Miner Res 2009;24:1420-6 with permission of the American Society of Bone and Mineral Research.

10.4.185 Type 1 diabetes in young rats leads to progressive trabecular bone loss, cessation of cortical bone growth, and diminished whole bone strength and fatigue life
Silva MJ, Brodt MD, Lynch MA, McKenzie JA, Tanouye KM, Nyman JS, Wang X
J Bone Miner Res 2009;24:1618-27

Fischer 344 and Sprague Dawley rats (12 wk of age) were injected with vehicle (Control) or streptozotocin (Diabetic). Rats were killed after 12 wk. Trabecular osteopenia was caused by bone loss: volumetric BMD decreased in diabetic rats not controls. Cortical osteopenia was caused by premature arrest of cortical expansion: cortical area did not increase after 4-8 wk in diabetic rats but continued to increase in controls. µCT showed a 60% reduction in proximal tibial trabecular BV/TV in diabetic vs. control rats, moments of inertia of the ulnar and femoral diaphysis were reduced approximately 30%. Monotonic bending tests indicated that ulna and femora from diabetic animals were 25% less stiff and strong vs. controls. Estimates of material properties indicated no changes in elastic modulus or ultimate stress but 10% declines in yield stress for diabetic bone. These changes were associated with a 50% increase in the nonenzymatic collagen crosslink pentosidine. Cyclic testing showed diminished fatigue life in diabetic bones at the structural (force) level but not at the material (stress) level.

10.4.186 Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative observational study
Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z
J Bone Miner Res 2009;24:1369-79

10.4.187 Racial difference in the correlates of bone mineral content/density and age at peak among reproductive-aged women
Berenson AB, Rahman M, Wilkinson G
Osteoporos Int 2009;20:1439-49

10.4.188 Variation in fracture rates by country may not be explained by differences in bone mass
Eklund F, Nordstrom A, Neovius M, Svensson O, Nordstrom P
Calcif Tissue Int 2009;85:10-6

10.4.189 Short-term relationship between meteorological variables and hip fractures: An analysis carried out in a health area of the Autonomous Region of Valencia, Spain (1996-2005)
Tenias JM, Estarlich M, Fuentes-Leonarte V, Iniguez C, Ballester F
Bone 2009;45:794-8

10.4.190 The association between socioeconomic status and osteoporotic fracture in population-based adults: A systematic review
Brennan SL, Pasco JA, Urquhart DM, Oldenburg B, Hanna F, Wluka AE
Osteoporos Int 2009;20:1487-97

10.4.191 Vitamin D status and common risk factors for bone fragility as determinants of quantitative ultrasound variables in a nationally representative population sample
Kauppi M, Impivaara O, Maki J, Heliovaara M, Marniemi J, Montonen J, Jula A
Bone 2009;45:119-24

10.4.192 Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects
Tarcin O, Yavuz DG, Ozben B, Telli A, Velioglu Ogunc A, Yuksel M, Toprak A, Yazici D, Sancak S, Deyneli O, Akalin S
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.4.193 Prevalence and risk factors of low BMD and 25-hydroxyvitamin D status in young healthy epileptic adult patients in a tropical Asian country taking antiepileptic drug
Phabphal K, Geater A, Leelawattana R, Sathirapunya P, Sattawatcharawanich S, Limapichat K
Bone 2009;45:232-7

10.4.194 Bone mineral density in estrogen-deficient young women
Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM
J Clin Endocrinol Metab 2009;94:2277-83

10.4.195 Vertebral fractures in males with type 2 diabetes treated with rosiglitazone
Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, Vescovi PP, Giustina A
Bone 2009;45:784-8

10.4.196 Effect of GLP-1 treatment on bone turnover in normal, type 2 diabetic, and insulin-resistant states
Nuche-Berenguer B, Moreno P, Esbrit P, Dapia S, Caeiro JR, Cancelas J, Haro-Mora JJ, Villanueva-Penacarrillo ML
Calcif Tissue Int 2009;84:453-61

10.4.197 Calcium malabsorption does not cause secondary hyperparathyroidism
Nordin BE, Morris HA, Horowitz M, Coates PS, O'Loughlin PD, Need AG
Calcif Tissue Int 2009;85:31-6

10.4.198 Mecp2 deficiency decreases bone formation and reduces bone volume in a rodent model of Rett syndrome
O'Connor RD, Zayzafoon M, Farach-Carson MC, Schanen NC
Bone 2009;45:346-56

10.4.199 Diphenylhydantoin inhibits osteoclast differentiation and function through suppression of NFATc1 signaling
Koide M, Kinugawa S, Ninomiya T, Mizoguchi T, Yamashita T, Maeda K, Yasuda H, Kobayashi Y, Nakamura H, Takahashi N, Udagawa N
J Bone Miner Res 2009;24:1469-80

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Corticosteroid Therapy

10.4.200 Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: A 12-month randomized, placebo-controlled clinical trial

Stoch SA, Saag KG, Greenwald M, Sebba AI, Cohen S, Verbruggen N, Giezek H, West J, Schnitzer TJ
J Rheumatol 2009;36:1705-14

In a 12-month, multicenter, randomized, double-blind, trial with 114 and 59 patients in received alendronate 70 mg once weekly (ALN OW) or placebo respectively, at 12 months, there was an increase in the ALN OW group for lumbar spine (2.45%), trochanter (1.27%), total hip (0.75%), and total body (1.70%) in BMD. Comparing ALN OW vs. placebo at 12 months, a significant treatment difference for the mean percentage change from baseline was observed for lumbar spine (2.92%; p ≤0.001), trochanter (1.66%; p=0.007), and total hip (1.19; p=0.008) BMD.

10.4.201 Transgenic disruption of glucocorticoid signaling in mature osteoblasts and osteocytes attenuates K/BxN mouse serum-induced arthritis in vivo

Buttgereit F, Zhou H, Kalak R, Gaber T, Spies CM, Huscher D, Straub RH, Modzelewski J, Dunstan CR, Seibel MJ
Arthritis Rheum 2009;60:1998-2007

To investigate the impact of osteoblast-targeted disruption of GC signaling on joint inflammation, cartilage damage, and bone metabolism in the K/BxN mouse serum transfer model of autoimmune arthritis mutants with transgenic overexpression of 11β-hydroxysteroid dehydrogenase type 2 had arthritis induced at 5-weeks of age. Acute arthritis developed in both transgenic and WT mice treated with K/BxN mouse serum. The arthritis and inflammatory activity were attenuated in transgenic mice. Bone turnover and bone volume remained unchanged in arthritic transgenic mice, while WT mice exhibited stimulated bone resorption, suppressed osteoblast activity, and reduced bone volume, compatible with the known effects of active inflammation on bone. Circulating levels of proinflammatory cytokines tended to be lower in arthritic transgenic mice than in control transgenic mice. Disruption of GC signaling in osteoblasts attenuates K/BxN mouse serum-induced autoimmune arthritis in mice.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Treatment

10.4.202 Factors predicting osteoporosis treatment initiation in a regionally based cohort

Cranney A, Tsang JF, Leslie WD
Osteoporos Int 2009;20:1621-5

8689 women age ≥50 years, who had not been dispensed any osteoporosis treatment (OTx) medication in the year prior to baseline BMD, were identified from a regionally based database in the Province of Manitoba, Canada, and OTx initiation rates were analyzed. 44% of women were dispensed OTx in the year after BMD. OTx initiation increased progressively as BMD T-scores decreased (8.2% normal, 41.0% osteopenic, 78.5% osteoporotic, p-for-trend<0.0001). There was a gradient response to OTx initiation, rather than step increases at conventional T-score intervention thresholds. BMD was strongly associated with OTx (p<0.0001) while age, weight, and fracture in the last year were not. Physicians rely heavily on BMD T-score to decide on OTx initiation.

10.4.203 Treating osteoporosis in Canada: What clinical efficacy data should be considered by policy decision makers?

Adachi JD, Kennedy CC, Papaioannou A, Ioannidis G, Leslie WD, Walker V
Osteoporos Int 2009;20:1785-93

This paper contrasts fracture reduction estimates for risedronate utilizing efficacy data from two approaches to meta-analysis: summary data vs. individual patient data. Using a Markov state-transition model, we compared fractures averted over 3 years in a hypothetical cohort by inputting fracture risk reduction estimates (risedronate vs. placebo) from two data sources (summary data vs. IPD). The cohort consisted of 100,000 Canadian women, age ≥65 years with osteoporosis and prevalent morphometric vertebral fracture. Nonvertebral fractures averted with risedronate were: 3571 and 6584 per 100,000 women for summary data and IPD, respectively. For vertebral fractures, the numbers were 8552 and 10,127. When IPD vs. summary data was used, an additional 3013 more nonvertebral fractures and 1575 vertebral fractures were averted. Relative risk estimates from IPD analyses were the best choice for modelling fracture outcomes when applied in a specified high-risk population.

10.4.204 Value of routine monitoring of BMD after starting bisphosphonate treatment: Secondary analysis of trial data

Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, Bauer DC
BMJ 2009;338:b2266

To assess the value of monitoring response to bisphosphonate by densitometry, 6459 postmenopausal women with low BMD in FIT were studied and showed mean effect of 3 years alendronate was to increase hip BMD by 0.030 g/cm^2. There was some between-person variation but this was small in size compared with within-person variation. Alendronate is estimated to result in increases in hip bone density ≥0.019 g/cm^2 in 97.5% of patients. Monitoring BMD in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary. Routine monitoring should be avoided in this early period after bisphosphonate treatment is commenced.

10.4.205 Adherence to weekly oral bisphosphonate therapy: Cost of wasted drugs and fractures

Sheehy O, Kindundu C, Barbeau M, LeLorier J
Osteoporos Int 2009;20:1583-94

The cost of wasted drugs is $25.87 per patient initiated in the primary prevention cohort and $30.52 in the secondary prevention cohort. If all patients had been compliant, 110 fractures would have been avoided in the primary prevention cohort and 19 fractures in the secondary prevention cohort. The cost of these avoidable fractures per patient initiated on BP therapy was $62.95 in primary prevention cohort and $330.84 in secondary prevention cohort. This study confirms that poor adherence to oral BPs leads to a significant waste of money and avoidable fractures.

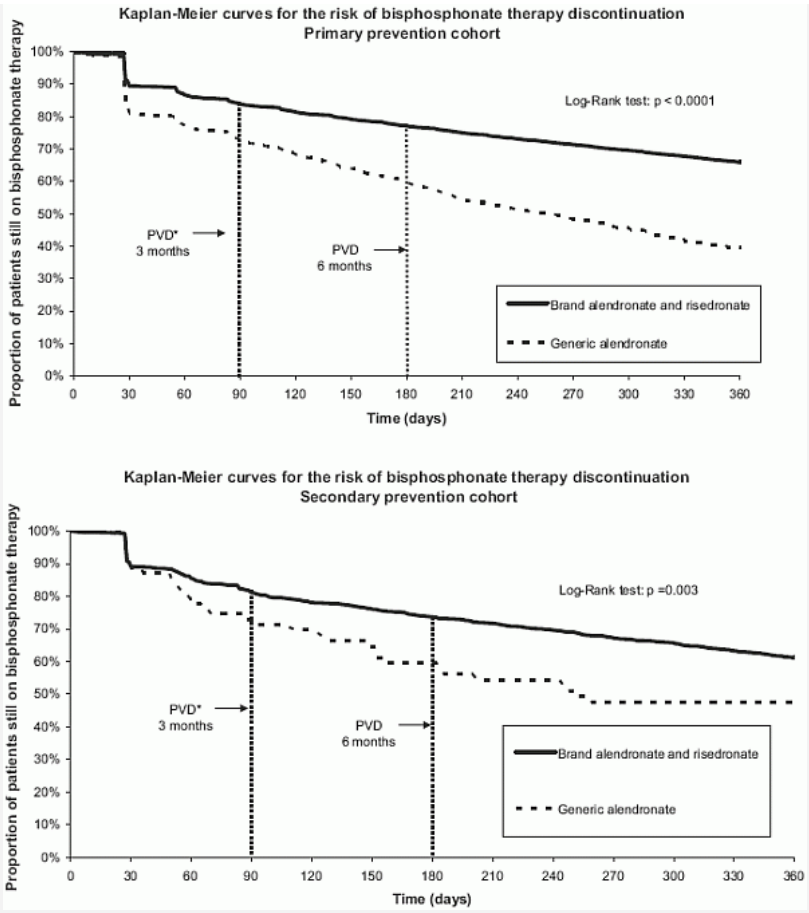

Fig. 10.4.205 Kaplan-Meier curves for the risk of early discontinuation during the year following index date (first filled prescription of bisphosphonate) for the primary and the secondary prevention cohorts. Point of visual divergence: point of time where the cumulative incident curves of active treatment compared to placebo started to diverge. The cumulative incident curves were obtained from the RCTs. Reproduced from Osteoporos Int 2009;20:1583-94 with permission from Springer.

10.4.206 Differences in persistence among different weekly oral bisphosphonate medications

Sheehy O, Kindundu CM, Barbeau M, LeLorier J

Osteoporos Int 2009;20:1369-76

Patients newly initiated on branded risedronate, branded alendronate, or generic alendronate once weekly were selected from the Regie de l'Assurance Maladie du Quebec databases. The cohort included patients with and without a previous OP fracture. The study cohort included 32,804 patients. After one year, a significant difference in persistence on oral BP therapy was found. The patients started on branded risedronate were 11% more likely to stop OP therapy than patients started on branded alendronate. Risk of discontinuation doubled in patients initiated with generic alendronate compared to patients started on branded alendronate. Male gender was associated with a 25% increase risk of early discontinuation.

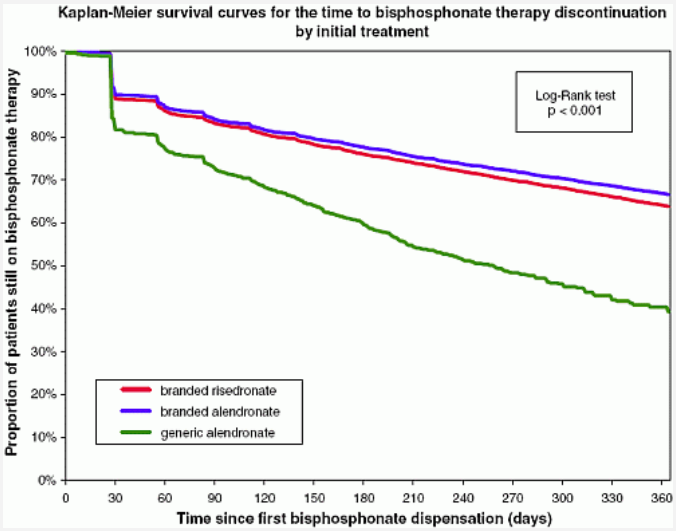

Fig. 10.4.206 Kaplan-Meier curves for the risk of early discontinuation during the year following index date (first dispensation of bisphosphonate). Reproduced from Osteoporos Int 2009;20:1369-76 with permission from Springer.

10.4.207 Association of low-energy femoral fractures with prolonged bisphosphonate use: A case control study

Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM

Osteoporos Int 2009;20:1353-62

In a retrospective case-control study of postmenopausal women presenting with low-energy femoral fractures from 2000-2007, 41 subtrochanteric and femoral shaft fracture cases were identified and matched by age, race, and BMI to one intertrochanteric and femoral neck fracture each. Bisphosphonate use was observed in 15 of the 41 subtrochanteric/shaft cases, compared to 9 of the 82 intertrochanteric/femoral neck controls (Mantel-Haenszel odds ratio (OR), 4.44 [95% CI 1.77-11.35]; P=0.002). A common X-ray pattern was identified in ten of the 15 subtrochanteric/shaft cases on a bisphosphonate. This X-ray pattern was highly associated with bisphosphonate use (OR, 15.33 [95% CI 3.06-76.90]; P<0.001). Duration of bisphosphonate use was longer in subtrochanteric/shaft cases compared to both hip fracture controls groups (P=0.001).

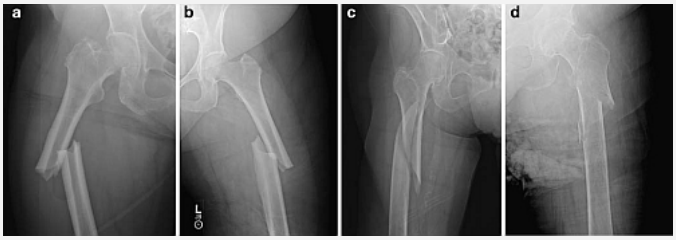

Fig. 10.4.207a Representative radiographs of subtrochanteric/shaft cases on a bisphosphonate with evidence of the simple with thick cortices pattern with comparison radiographs of subtrochanteric/shaft fracture cases not on a bisphosphonate. (a, b) Representative radiographs of ten of the 41subtrochanteric/shaft cases that were associated with bisphosphonate use. Prominent cortical thickening near the fracture site and beaking of the cortex on one side can be seen. (a) An 83-year-old women with a 9-year history of alendronate use. (b) A 61-year-old woman with a 9-year history of alendronate use. (c, d) Representative radiographs of subtrochanteric/shaft fractures in women not on bisphosphonate. Fractures are more complex in nature, cortical thickening is minimal, and there is no identifiable beaking at the fracture site. These fractures are not consistent with our definition of the characteristic X-ray pattern associated with prolonged bisphosphonate use. (c) An 83-year-old woman with no history of bisphosphonate use. (d) A 60-year-old woman with no history of bisphosphonate use. Reproduced from Osteoporos Int 2009;20:1353-62 with permission from Springer.

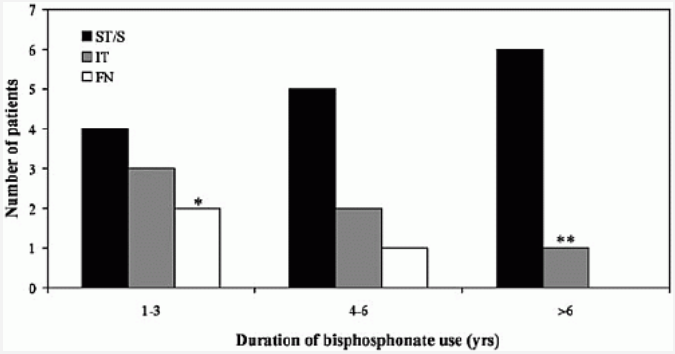

*Fig. 10.4.207b Distribution of all fractures associated with bisphosphonate use. All fractures associated with bisphosphonate use were grouped by the type of femoral fracture and displayed according to duration of bisphosphonate use. Black bars represent subtrochanteric/shaft (ST/S) fractures, gray bars represent intertrochanteric (IT) fractures, and white bars represent femoral neck (FN) fractures. Kruskal-Wallis oneway variance analysis of the duration of bisphosphonate use in patients in all three groups yielded P=0.001. Time on a bisphosphonate differed for subtrochanteric/shaft fractures as compared to both intertrochanteric (P=0.01) and femoral neck fractures (P=0.001). There was no significant difference between time on a bisphosphonate between intertrochanteric and femoral neck fractures (P=0.3). *One patient in this group was taking risedronate. **This patient was taking etidronate for 5 years and then took alendronate for 2 years. Reproduced from Osteoporos Int 2009;20:1353-62 with permission from Springer.*

10.4.208 Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: A case series

Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, Novack D
Calcif Tissue Int 2009;85:37-44

In a retrospective analysis of patients presenting with a history of low-energy cortical fractures (femoral shaft, pelvis, rib, metatarsal, and ankle), who received bisphosphonates for at least two consecutive years 15 of 54 patients who underwent bone biopsy. Of these, 10 patients had findings of suppressed trabecular bone remodeling, as demonstrated by lack of double tetracycline labels. There were no significant differences in bone density, clinical features, and biochemical features between those with suppressed turnover and the other five subjects with normal remodeling. However, the low turnover group had received bisphosphonates (primarily alendronate) for a longer duration (6.5±0.6 vs. 3.9±0.8 years, P=0.02). Thus, about two-thirds of patients presenting with cortical fractures while on long-term treatment with bisphosphonates had suppressed turnover.

10.4.209 Comparative gastrointestinal safety of weekly oral bisphosphonates

Cadarette SM, Katz JN, Brookhart MA, Sturmer T, Stedman MR, Levin R, Solomon DH
Osteoporos Int 2009;20:1735-47

A total of 10,420 new users were studied, mean age=79 years (SD, 6.9), and 95% women. We observed 31 hospitalizations for upper gastrointestinal bleed (0.91 per 100 person-years) within 120 days of treatment. Adjusting for covariates, there was no difference in hospitalization for upper gastrointestinal bleed among those treated with risedronate compared with alendronate (HR, 1.12; 95%CI, 0.55-2.28). Risedronate switching rates were lower; otherwise, no differences were observed for secondary or composite outcomes. No important difference in gastrointestinal safety between weekly oral bisphosphonates was found.

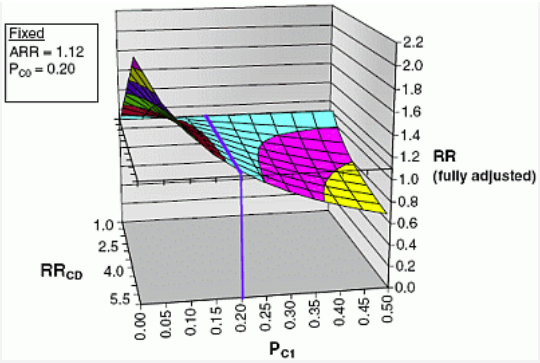

Fig. 10.4.209 Sensitivity analysis of residual confounding using the array approach for our primary outcome (hospitalization for upper gastrointestinal bleed). ARR: apparent exposure relative risk, i.e., the relative risk (hazard ratio) observed in the current study (risedronate versus alendronate), fixed at 1.12. P_{C0} prevalence of counfounder among unexposed (alendronate), fixed at 20% in this example. P_{C1} prevalence of confounder among exposed (risedronate) group, varied from 0% to 50% in the figure. RR_{CD} association between confounder and disease outcome, varied from 1.0 to 5.5 in figure. RR fully adjusted or "true" exposure relative risk. Blue line: no confounding present, prevalence of confounder same among alendronate and risedronate recipients. Reproduced from Osteoporos Int 2009;20:1735-47 with permission from Springer.

10.4.210 Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: A register-based national cohort study

Abrahamsen B, Eiken P, Eastell R

J Bone Miner Res 2009;24:1095-102

Two national register-based studies were performed: (1) cross-sectional study (N=11,944) comparing age, exposure, and trauma between different types of proximal femur fractures and (2) matched cohort study in patients with prior nonhip fractures (N=5187+10,374), testing the hypothesis that the increase in the risk of subsequent atypical femur fractures exceeded the increase in typical hip fractures. 7% of patients with atypical fractures were aln exposed, and the same was found for typical hip fractures. In the cohort study, the HR for subtrochanteric/diaphyseal fracture with ALN was 1.46 (0.91-2.35, p=0.12) compared with 1.45 (1.21-1.74, p<0.001) for hip fracture after adjustment for comorbidity and comedications. The risk was reduced by adherence, and the ratio between hip and subtrochanteric/diaphyseal femur fractures was identical in ALN-treated patients and the controls. The authors infer that subtrochanteric/diaphyseal femur fractures share the epidemiology and treatment response of classical hip fractures and are best classified as osteoporotic fractures.

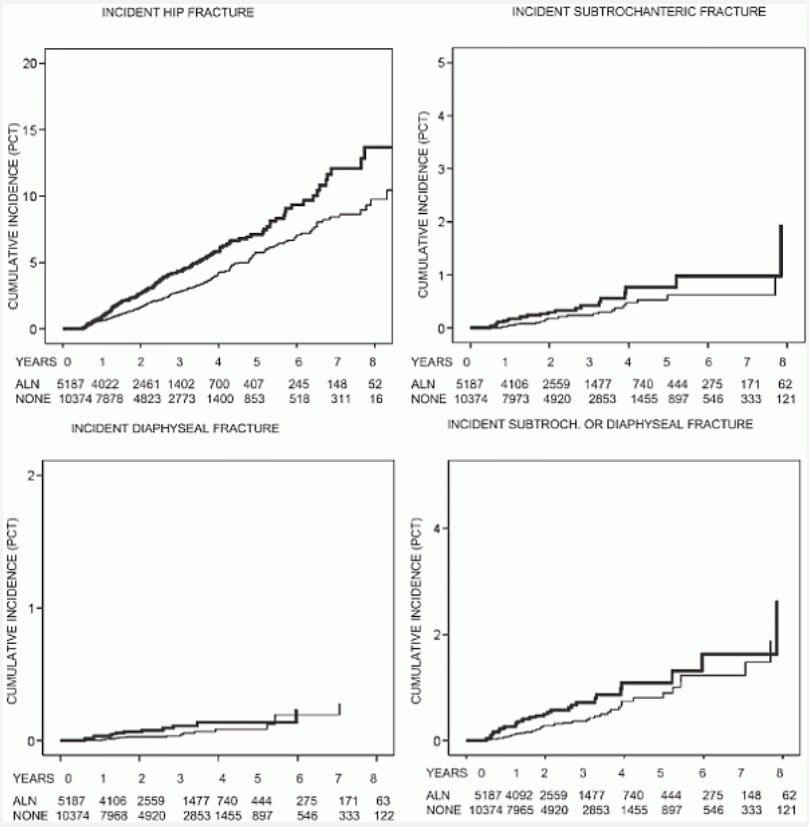

Fig. 10.4.210a Cumulative incidence of classical (hip) and nonclassical (subtrochanteric and diaphyseal) femur fractures in alendronate exposed patients and matched controls. The mean observation period was 2.5 yr. Please refer to Table 2 for baseline demographics and Table 3 for fracture-free survival analysis. Note the proportional increase in the risk of both typical and atypical fractures in the alendronate cohort. Reproduced from J Bone Miner Res 2009;24:1095-102 with permission of the American Society of Bone and Mineral Research.

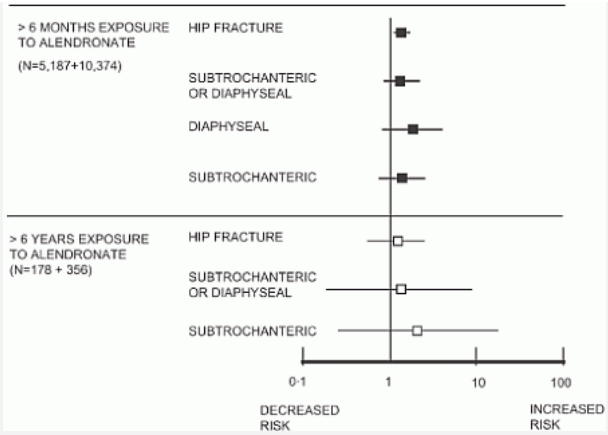

Fig. 10.4.210b Summary of results of the restricted cohort study. HR for fracture (mean and 95% CI) by fracture type and alendronate exposure. Cox regression analysis adjusted for number of different drugs (ATC codes) redeemed in past year, oral glucocorticoid use in past year (0/1), and Charlson comorbidity index, age, and sex. Bottom of figure indicates a subgroup analysis for highly adherent alendronate users with MPR>80% and a treatment duration of at least 6 yr. Reproduced from J Bone Miner Res 2009;24:1095-102 with permission of the American Society of Bone and Mineral Research.

10.4.211 Vitamin D insufficiency does not affect response of BMD to alendronate
Antoniucci DM, Vittinghoff E, Palermo L, Black DM, Sellmeyer DE
Osteoporos Int 2009;20:1259-66

To determine whether vitamin D insufficiency at initiation of alendronate therapy for low BMD affects treatment efficacy, 1000 postmenopausal women randomly selected from the vertebral fracture arm (n=2027) of the placebo-controlled Fracture Intervention Trial of alendronate. Participants were randomly assigned to placebo (50%) or alendronate and most (83%) to calcium (500 mg/day) and cholecalciferol (250 IU/day). We measured serum 25-hydroxy vitamin D (25OHD) at enrollment, then categorized baseline vitamin D status according to 25OHD concentration (≤10 ng/ml=deficient; >10 but ≤30 ng/ml=insufficient; >30 ng/ml=sufficient) and used linear regression to compare the effects of alendronate treatment among these categories. At baseline, participants were vitamin D sufficient (14%), insufficient (83%), and deficient (2%). BMD response to therapy at total hip or spine did not vary by vitamin D status at baseline (p for heterogeneity=0.6).

10.4.212 Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: Clues to the mechanism of increased bone fragility
Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE
J Bone Miner Res 2009;24:1736-40

A patient with rheumatoid arthritis and multiple risk factors for fractures was treated with alendronate for 8 yr and developed spontaneous bilateral subtrochanteric/diaphyseal fractures. Bone biopsies obtained form the iliac crest and the femur showed decreased bone formation with increased bone resorption at the femur.

10.4.213 Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: A randomized double-blind, placebo-controlled trial
Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, Obermayer-Pietsch BM, Pilz S, Dimai HP, Prenner G, Tscheliessnigg KH, Hauge E, Portugaller RH, Dobnig H
J Bone Miner Res 2009;24:1335-44

35 male cardiac transplant recipients received ibandronate (IBN) 2 mg intravenously every 3 mo or placebo (CTR). In the IBN group, 13% sustained a new morphometric vertebral fracture compared with 53% in the CTR (absolute RR 40%; relative RR 75%; p=0.04). BMD remained unchanged with IBN but in the CTR group decreased at the spine by 25% and at the femoral neck by 23% over 1-yr. sCTX and TRACP 5b increased in the CTR group and decreased in the IBN group. Osteocalcin and bone-specific alkaline phosphatase levels showed, after a similar decrease over the first 3 mo in both groups, a marked rise in the CTR and declining levels in the IBN patients. Three paired biopsies were available from each group. A difference in the relative change of eroded surface (68% in the CTR vs. -23% in the IBN group, p<0.05) occurred. Intravenous IBN reduced fractures, preserved bone mass after CTP.

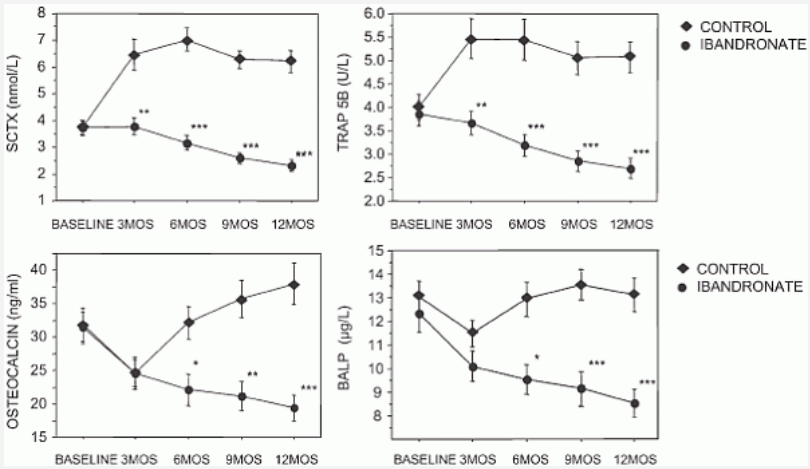

*Fig. 10.4.213a Changes of bone turnover markers (mean±SD) of the control (CTR) and ibandronate (IBN) group over the 1-yr posttransplantation period. *p<0.05, **p<0.01, and ***p<0.005 vs. CTR. Reproduced from J Bone Miner Res 2009;24:1335-44*

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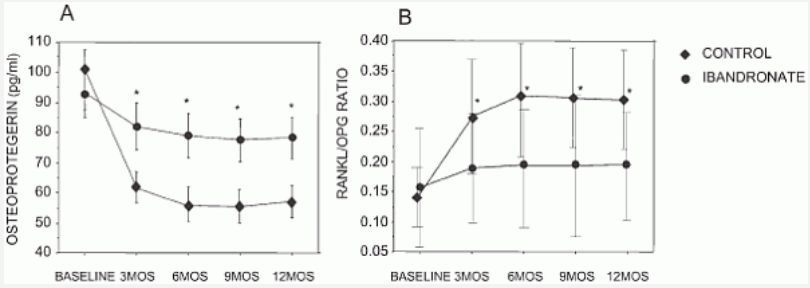


*Fig. 10.4.213b (A) Changes of OPG levels of the control (CTR) and ibandronate (IBN) group over the 1-yr post-transplantation period. (B) Respective changes of RANKL/OPG ratio (mean±SD). *p<0.01 vs. CTR. Reproduced from J Bone Miner Res 2009;24:1335-44 with permission of the American Society of Bone and Mineral Research.*

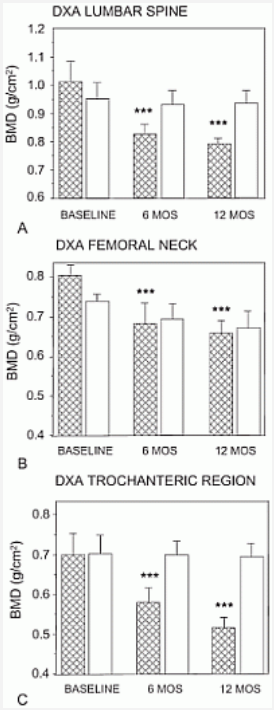


*Fig. 10.4.213c Changes in BMD (g/cm^2) of the control group (patterned bars) and the ibandronate-treated patients (white bars) at (A) the lumbar spine, (B) the femoral neck site, and (C) the trochanteric region. ***p<0.0001 vs. CTR group. Reproduced from J Bone Miner Res 2009;24:1335-44 with permission of the American Society of Bone and Mineral Research.*

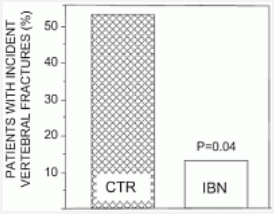


Fig. 10.4.213d Percentage of patients in the CTR (patterned bar) and in the ibandronate treatment group (white bar) who sustained a new vertebral fracture. Reproduced from J Bone Miner Res 2009;24:1335-44 with permission of the American Society of Bone and Mineral Research.

10.4.214 Monthly ibandronate suppresses serum CTX-I within 3 days and maintains a monthly fluctuating pattern of suppression

Binkley N, Silverman SL, Simonelli C, Santiago N, Kohles JD, Dasic G, Sunyecz JA

Osteoporos Int 2009;20:1595-601

This randomized, double-blind, placebo-controlled study evaluated the rapidity of onset and pattern of suppression of the bone resorption marker serum CTX-I in women with postmenopausal osteoporosis (PMO) who received once-monthly oral ibandronate. Women diagnosed with PMO received once-monthly oral ibandronate (150 mg) or placebo for 6 months. This study enrolled 67 women: 49 received ibandronate, 17 received placebo, and one took no study drug. At day 3, median reduction in serum CTX-I from baseline was 70.2% with ibandronate and 6.0% with placebo (difference, -64.2%; 95% confidence interval, -80.3% to -46.2%; p<0.0001). In women receiving ibandronate, serum CTX-I levels remained consistently below baseline, exhibiting a regular monthly fluctuating pattern of suppression over 6 months. Ibandronate was well tolerated.

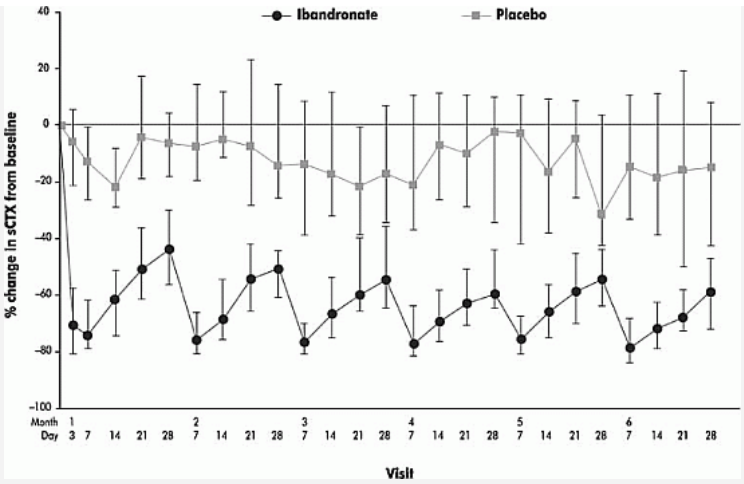


Fig. 10.4.214a Median relative change (±95%CI) in serum CTX-I from baseline over 6 months. Differences between treatment groups at each time point were significant (all p-values <0.01; ITT population). Serum CTX-I serum C-terminal crosslinking telopeptide of type I collagen, ITT: intent-to-treat. Reproduced from Osteoporos Int 2009;20:1595-601 with permission from Springer.

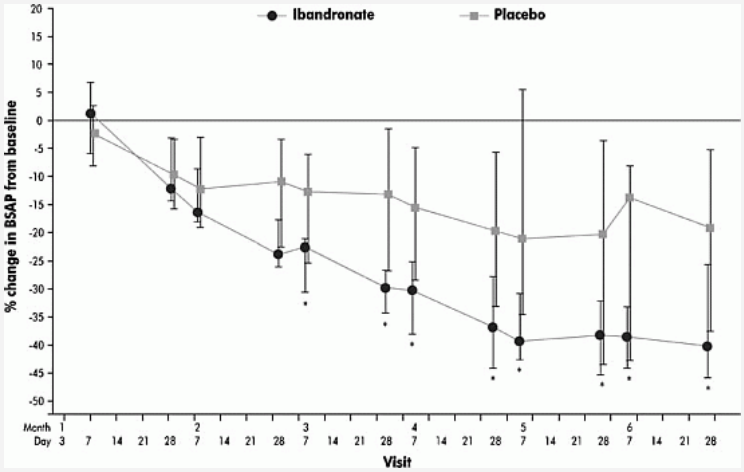


*Fig. 10.4.214b Median relative change (±95%CI) in bone ALP from baseline over 6 months (ITT population). Bone ALP bonespecific alkaline phosphatase, ITT: intent-to-treat. *p<0.05, significant difference between the treatment groups. Reproduced from Osteoporos Int 2009;20:1595-601 with permission from Springer.*

10.4.215 Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: A randomized placebo-controlled double-blind study
Matsumoto T, Hagino H, Shiraki M, Fukunaga M, Nakano T, Takaoka K, Morii H, Ohashi Y, Nakamura T
Osteoporos Int 2009;20:1429-37

Minodronate increases BMD in postmenopausal osteoporotic patients. To examine antifracture efficacy and safety, a randomized, double-blind, placebo-controlled trial was conducted in 704 postmenopausal women (55-80 years) with 1-5 vertebral fractures and low BMD. Subjects were randomly assigned to receive daily oral 1 mg minodronate (n=359) or placebo (n=345) for 24 months, with daily supplements of 600 mg calcium and 200 IU vitamin D3. Daily 1 mg minodronate for 24 months reduced the risk of vertebral fractures by 59% (95% CI, 36.6-73.3%). Furthermore, when fractures during the first 6 months were eliminated, the risk of vertebral fractures from 6-24 months was reduced by 74% in minodronate-treated group. Minodronate treatment also reduced height loss. Bone turnover markers were suppressed by about 50% after 6 months of minodronate treatment and remained suppressed thereafter.

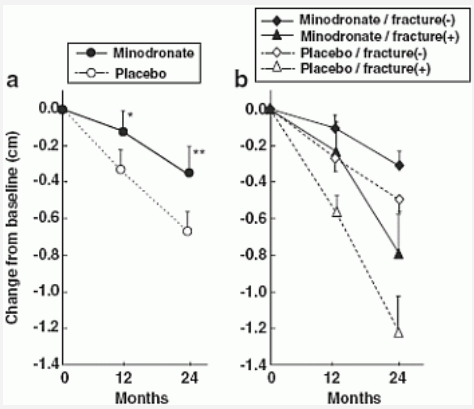


*Fig. 10.4.215a Effect of daily oral 1 mg minodronate for 24 months on height changes of osteoporotic patients. (a) Minodronate treatment significantly reduced height reduction at both 12 months (*p<0.05) and 24 months (**p<0.01). (b) Height changes in minodronate-treated patients with (closed triangle, n=27) or without (closed diamond, n=242) vertebral fracture, and placebo-treated patients with (open triangle, n=61) or without vertebral fracture (open diamond, n=200) are shown. Data are means±SE. Reproduced from Osteoporos Int 2009;20:1429-37 with permission from Springer.*

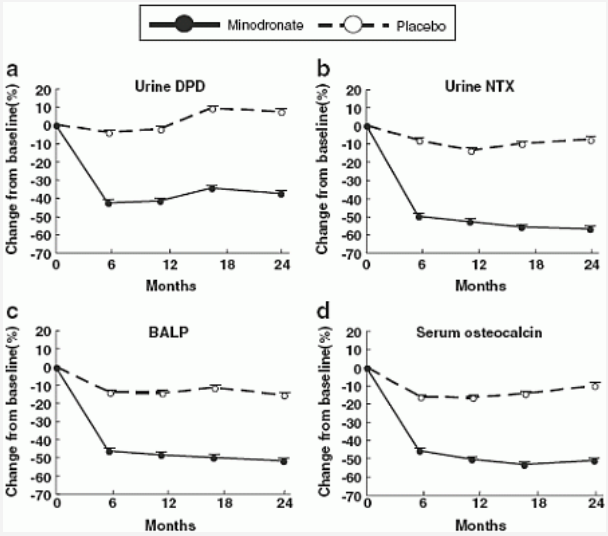


Fig. 10.4.215b Effect of daily oral 1 mg minodronate for 24 months on the changes in bone turnover markers in osteoporotic patients. Data are means±SE. Reproduced from Osteoporos Int 2009;20:1429-37 with permission from Springer.

10.4.216 Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): A multicentre, double-blind, double-dummy, randomised controlled trial
Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, Papanastasiou P, Ferreira A, Hartl F, Fashola T, Mesenbrink P, Sambrook PN
Lancet 2009;373:1253-63

This one-year randomised, double-blind, double-dummy, noninferiority study of 54 centres compared 5 mg zoledronic acid (ZA) vs. 5 mg oral risedronate (RIS) in 833 patients. A subgroup treated for more than 3 months (272 patients on ZA and 273 on RIS), and the prevention subgroup of those treated for less than 3 months (144 patients on each drug). ZA was noninferior and superior to RIS for increase of spine BMD (least-squares mean 4.06% [SE 0.28] vs. 2.71% [SE 0.28], mean difference 1.36% [95% CI 0.67-2.05], p=0.0001) and prevention (2.60% [0.45] vs. 0.64% [0.46], 1.96% [1.04-2.88], p<0.0001) subgroups at 12 months. Adverse events were more frequent in patients given ZA due to transient symptoms during the first 3 days after infusion. A single 5 mg intravenous infusion of ZA is noninferior, possibly more effective, and more acceptable to patients than is 5 mg of RIS daily for prevention and treatment of bone loss associated with glucocorticoid use.

10.4.217 Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture
Eriksen EF, Lyles KW, Colon-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, Hyldstrup L, Recknow C, Nordsletten L, Lavecchia C, Hu H, Boonen S, Mesenbrink P
J Bone Miner Res 2009;24:1308-13

2127 patients (1065 treatment, 1062 placebo; mean age, 75 yr; 76% women and 24% men) were given zoledronic acid or placebo within 90 days after surgery and annually, with a median follow-up time of 1.9 yr. Median time to first dose after hip fracture surgery was 6 wk. Posthoc analyses by 2-wk intervals showed a significant total hip BMD response and a consistent reduction of overall clinical fractures and mortality in patients receiving the first dose 2-wk or later after surgery. We concluded that administration of zoledronic acid to patients suffering a low trauma hip fracture 2 wk or later after surgical repair increases hip BMD, induces reductions in the risk of subsequent clinical vertebral, nonvertebral, and hip fractures, and mortality.

10.4.218 Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis
Delmas PD, Munoz F, Black DM, Cosman F, Boonen S, Watts NB, Kendler D, Eriksen EF, Mesenbrink PG, Eastell R
J Bone Miner Res 2009;24:1544-51

Annual infusions of zoledronic acid 5 mg reduced BTMs: median decrease of 50% for β-C-terminal telopeptides of type I collagen (βCTX), 30% for bone alkaline phosphatase (ALP), and 56% for procollagen type 1 amino-terminal propeptide (PINP). The mean level of BTMs decreased in treated patients but remained within the premenopausal range. The percentage of zoledronic acid treated patients with values below the premenopausal reference range at all time points was 1.7%, 17.8%, and 19% for bone ALP, CTX, and PINP, respectively. The third injection of zoledronic acid resulted in 60% reduction of βCTX within 9-11 days, followed by a gradual increase, indicating the persistence of osteoclastic bone resorption. The association between changes in BTMs and fracture incidence was assessed in 1132 patients who had PINP measurements at baseline and 1 yr. There was no association between low PINP levels at 1 yr and increased fracture incidence.

10.4.219 Teriparatide and raloxifene reduce the risk of new adjacent vertebral fractures in postmenopausal women with osteoporosis. Results from two randomized controlled trials
Bouxsein ML, Chen P, Glass EV, Kallmes DF, Delmas PD, Mitlak BH
J Bone Joint Surg Am 2009;91:1329-38

Of 1226 untreated postmenopausal women with one or more prevalent vertebral fractures at baseline, 196 (16.0%) had 292 new fractures during the two years, with 108 (8.8%) of the 1226 women having at least one fracture adjacent to a prevalent fracture. Of the 292 new vertebral fractures, 136 (47%) were adjacent to a previous fracture. The risk of a new adjacent vertebral fracture was 2.5-fold higher than the risk of a new nonadjacent fracture (4.03% compared with 1.59%). The incidence of new adjacent vertebral fractures increased with both the number and the severity of prevalent vertebral fractures. Teriparatide reduced the risk of any new, new adjacent, and new nonadjacent vertebral fractures by 72%, 75%, and 70%, respectively, compared with the rates in the placebo group. Similarly, compared with the placebo, raloxifene reduced the risk of any new vertebral fracture, new adjacent vertebral fracture, and new nonadjacent vertebral fracture by 54%, 54%, and 53%, respectively.

10.4.220 Effects of teriparatide retreatment in osteoporotic men and women
Finkelstein JS, Wyland JJ, Leder BZ, Burnett-Bowie SA, Lee H, Juppner H, Neer RM
J Clin Endocrinol Metab 2009;94:2495-501

Subjects in a 30-month trial comparing alendronate, teriparatide or both were studied. Teriparatide was stopped then administered to all subjects. Posterior-anterior and lateral spine BMD increased 12.5±1.5% and 16.9±1.7%, respectively during the first 12 months of teriparatide and 5.2±0.8% and 6.2±1.8%, respectively during retreatment (P<0.001 and P=0.001). Increases in osteocalcin (P<0.001), PINP (P<0.001), and N-telopeptide (P<0.001) were greater during the first teriparatide administration. The response to teriparatide is attenuated when re-administered after a 12-month hiatus.

10.4.221 Improvements in vertebral body strength under teriparatide treatment assessed in vivo by finite element analysis: Results from the EUROFORS study
Graeff C, Chevalier Y, Charlebois M, Varga P, Pahr D, Nickelsen TN, Morlock MM, Gluer CC, Zysset PK
J Bone Miner Res 2009;24:1672-80

In 44 postmenopausal women with osteoporosis, FE models based on high-resolution CT (HRCT) of T12 were evaluated. Highly significant improvements in all analyzed variables as early as 6 mo after teriparatide. After 24 mo, bone strength in compression was increased by 28.1±4.7% (SE), in bending by 28.3±4.9%, whereas app. BV/TV was increased by 54.7±8.8%, vBMD by 19.1±4.0%, and areal BMD of L1-L4 by 10.2±1.2%. When comparing standardized increases, FE changes were larger than those of densitometry and not different from app. BV/TV. The size of regions at high risk for local failure was reduced with teriparatide. Treatment leads to bone strength increases for different loading conditions of close to 30%. FE is a suitable tool for monitoring anabolic treatment in groups or individual patients and offers additional information about local failure modes. FE variables showed a higher standardized response to changes than BMD measurements.

10.4.222 Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment
Watts NB, Miller PD, Kohlmeier LA, Sebba A, Chen P, Wong M, Krohn K
J Bone Miner Res 2009;24:1125-31

Decreases of >4% FN BMD were less common in women receiving TPTD (10%) vs. PL (16%, p<0.05), yet women on TPTD who lost FN BMD had reductions in VF risk (RR=0.11; 95% CI=0.03-0.45). VF risk reduction with TPTD was similar across categories of FN BMD change from baseline at 12 mo (loss >4%, loss 0-4%, gain 0-4%, or gain >4%; interaction p=0.40). Irrespective of FN BMD loss or gain, TPTD-treated women had increases in LS BMD and PINP.

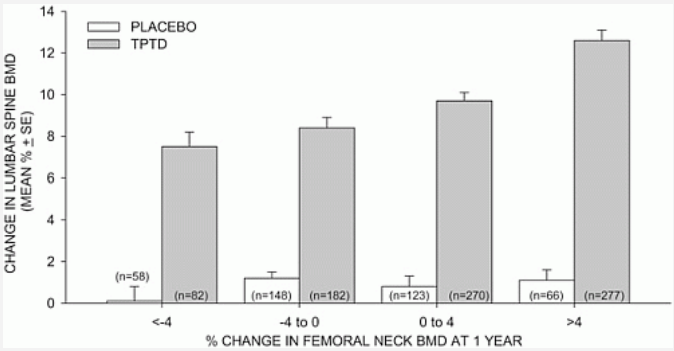


Fig. 10.4.222a Changes in LS BMD in women treated with PL or TPTD by category of percent change in FN BMD at 1 yr. All TPTD treatment groups had significant increases in LS BMD compared with PL and from baseline, irrespective of the percent change in FN BMD. Reproduced from J Bone Miner Res 2009;24:1125-31 with permission of the American Society of Bone and Mineral Research.

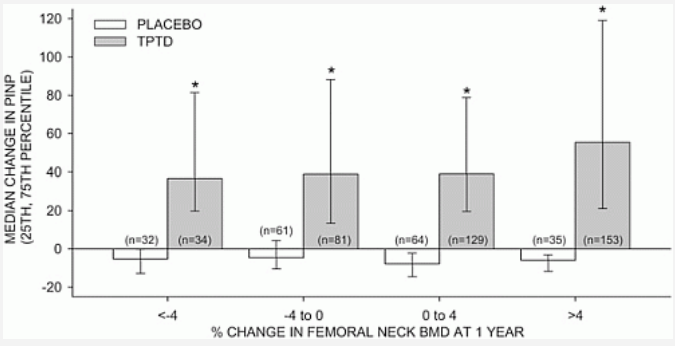


*Fig. 10.4.222b Median change in the bone formation marker PINP at 3 mo in women treated with PL or TPTD by category of percent change in FN BMD at 1 yr. Compared with PL and baseline, all groups treated with TPTD had significant increases in PINP, irrespective of loss or gain in FN BMD. *p<0.05 between groups. Reproduced from J Bone Miner Res 2009;24:1125-31 with permission of the American Society of Bone and Mineral Research.*

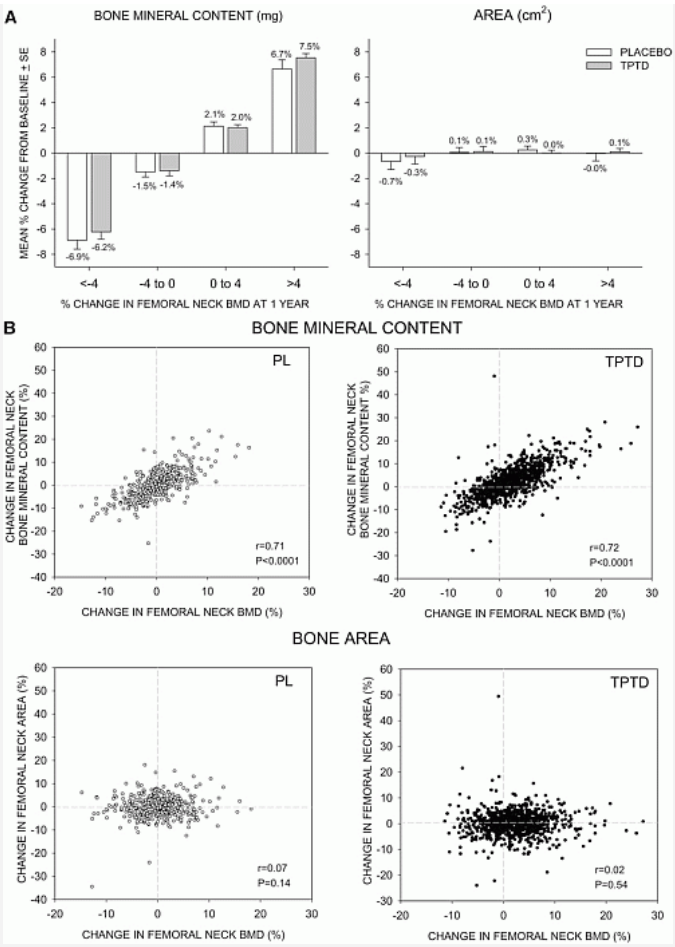


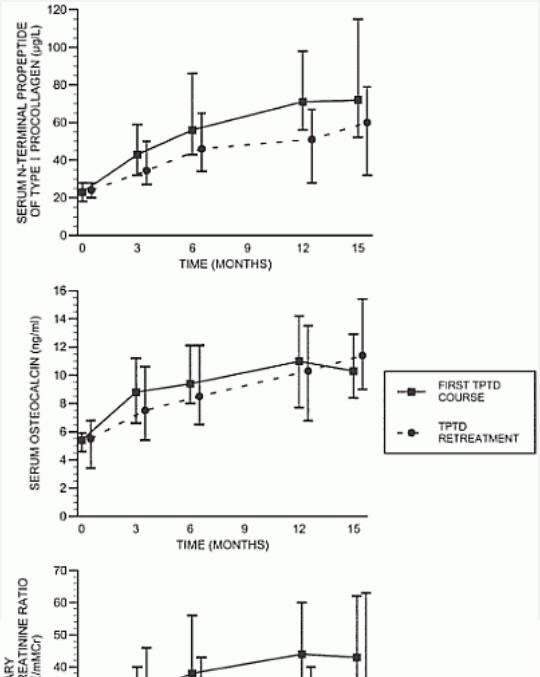
Fig. 10.4.222c Changes in BMC and area at the FN in women treated with PL or TPTD by category of percent change in FN BMC at 1 yr. (A) Change in FN BMD was apparently caused by change in BMC, because the area was unchanged. (B) In both the PL and TPTD groups, individual FN BMD values were significantly correlated with BMC but not with area. Reproduced from J Bone Miner Res 2009;24:1125-31 with permission of the American Society of Bone and Mineral Research.

10.4.223 Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate

Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R

J Bone Miner Res 2009;24:1110-5

To determine whether a retreatment with teriparatide produces similar biochemical and BMD changes as seen during the first course, 126 women on alendronate for ≥1 yr were randomized to continue alendronate and receive teriparatide, cyclic teriparatide (3-mo cycles), or alendronate for 15 mo. Of the 72 patients who completed the original regimen, 49 completed a 12-mo follow-up on continued alendronate alone. At that time, 32 patients, who remained at high risk of future fracture, were recruited into the retreatment and 27 completed another course of teriparatide for 15 mo (including 15 from the original treatment group and 12 from the original cyclic group). Bone formation indices (propeptide of type I procollagen and osteocalcin) increased with median 3-mo increments of 120% and 72% above baseline during the original course and 60% and 40% above baseline during retreatment, respectively. Mean spine BMD increments were 6.2% after the first daily course and 4.7% after retreatment and 4.1% after the first course of cyclic teriparatide and 4.9% after retreatment. Retreatment stimulates bone formation and increases spine BMD to a similar extent as seen during the original teriparatide course.



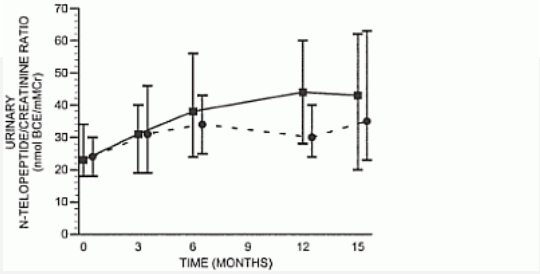


Fig. 10.4.223a Median (IQR) biochemical levels during the first TPD course and during TPTD retreatment for the original daily group over 15 mo, respectively. There were no differences between the biochemical changes for OC or NTX between the first TPTD course and TPTD retreatment, but the increment for PINP was slightly lower during the TPTD retreatment vs. the first TPTD course (p=0.04). Reproduced from J Bone Miner Res 2009;24:1110-5 with permission of the American Society of Bone and Mineral Research.

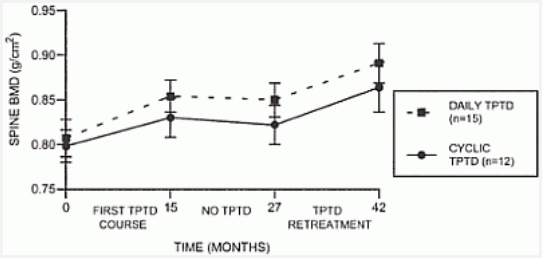


Fig. 10.4.223b Mean spine BMD throughout the original TPTD course and the TPTD retreatment for the original daily (n=15) and cyclic (n=12) groups for all subjects who completed the full 42-mo protocol. Increments were significantly above baseline for the spine during the first TPTD course and retreatment in both groups (p≤0.02 for both). There were no significant differences between increments seen during the first TPTD course and retreatment TPTD course in either of the groups. Reproduced from J Bone Miner Res 2009;24:1110-5 with permission of the American Society of Bone and Mineral Research.

10.4.224 Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: Differences between stopping and continuing the antiresorptive agent

Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV, Krege JH
J Clin Endocrinol Metab 2009;[Epub ahead of print]

Postmenopausal women with osteoporosis receiving alendronate or raloxifene had teriparatide added or were switched to teriparatide for 18 months. In the alendronate group, increases in BTM were less in the Add vs. Switch [PINP (64 v 401%); ALP (15 v 71%); βCTX (27 v 250%); all P<0.001]. At 6 months, total hip BMD increased more in the Add v switch (1.4 v -0.8%, P=0.002). In the Add vs. Switch group, 18 month BMD increments were higher in the spine (8.4 v 4.8%, P=0.003) and total hip (3.2 v 0.9%, P=0.02), but not femoral neck (2.7 v 2.3%, P=0.75). In the raloxifene group, increases in BTM were also smaller in the Add vs. Switch [6 month PINP (131 v 259%, P<0.001), bone ALP (31 v 44%, P=0.035), and βCTX (67 v 144%, P=0.001)]. At 6 months, total hip BMD increase was greater in the Add vs. Switch group (1.8 v 0.5%, P=0.028). At 18 months, increases in lumbar spine (9.2 v 8.1%), total hip (2.8 v 1.8%) and femoral neck (3.8 v 2.2%) were not different. Greater bone turnover increases were achieved by switching to teriparatide, while greater BMD increases were achieved by adding teriparatide.

10.4.225 Raloxifene and risk for stroke based on the Framingham stroke risk score

Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D
Am J Med 2009;122:754-61

RUTH enrolled 10,101 women; MORE enrolled 7705 women. A Framingham Stroke Risk Score (FSRS) was calculated for those with no prior cerebrovascular events (n=16,858) and predicted an increased stroke risk in the placebo groups. There was no difference in nonfatal strokes between the raloxifene and placebo groups in MORE or RUTH. In RUTH, women with FSRS <13 showed no increase in raloxifene-associated fatal stroke risk (HR 1.08; 0.49-2.37). Those with FSRS ≥13 had a 75% increased risk of raloxifene-associated fatal stroke (HR 1.75; 95% CI, 1.01-3.02). In MORE 80% had a FSRS <13 and no increase in fatal (HR 0.57; 95% CI, 0.19-1.68) stroke risk. Risk of fatal stroke associated with raloxifene was greater in women at high stroke risk.

10.4.226 Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis

Recker RR, Marin F, Ish-Shalom S, Moricke R, Hawkins F, Kapetanos G, de la Pena MP, Kekow J, Farrerons J, Sanz B, Oertel H, Stepan J
J Bone Miner Res 2009;24:1358-68

Daily s/c teriparatide (n=39, 20 µg/d) or oral strontium ranelate (SrR, n=40, 2 g/d) in postmenopausal women with osteoporosis were compared using bone biopsies from 29 patients in the teriparatide group and 22 in the SrR group after 6 mo. On trabecular surfaces mineral apposition rate were 7.73±1.48% for teriparatide and 5.25±1.15% for SrR (p=NS) and at the endocortical level were 17.22±3.06% and 9.70±2.07%, respectively (p=0.052). Cortical porosity was 5.40±0.41% in the teriparatide and 4.14±0.40% in the SrR group (p=0.037). Teriparatide increased markers of bone formation and resorption, reaching significance for PINP after 1 mo (+57%, p<0.001). SrR induced small, but significant, reductions from baseline in PINP at 3 (-14%, p=0.005) and 6 mo (-19%, p<0.001) and in βCTX at 1 and 3 mo (-11%, for both, p<0.05). There were more patients with adverse events after SrR (70%) than teriparatide (41%) treatment (p=0.013).

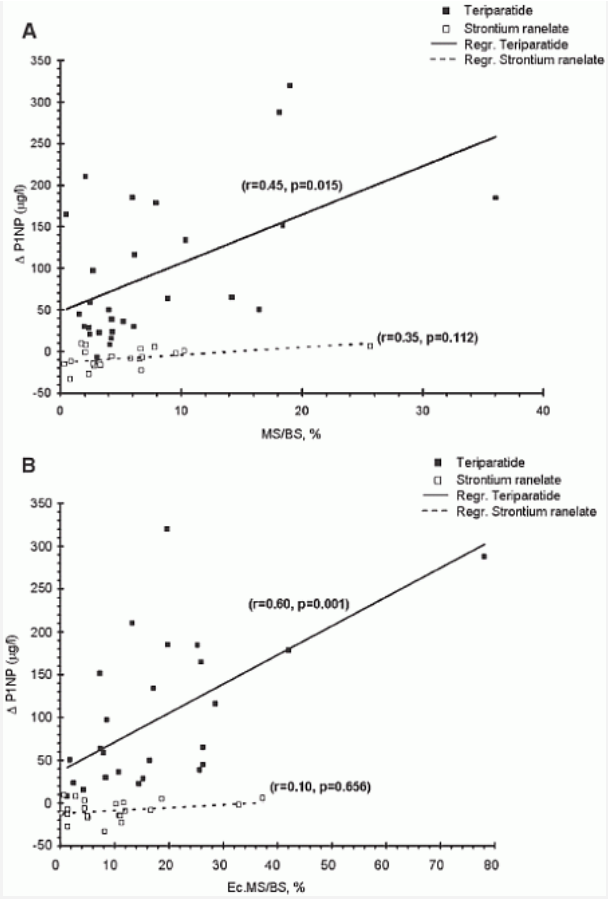


Fig. 10.4.226 Correlation between MS/BS at 6 mo and the change from baseline to month 6 for PINP (ΔPINP) in (A) trabecular, and (B) endocortical bone. Reproduced from J Bone Miner Res 2009;24:1358-68 with permission of the American Society of Bone and Mineral Research.

10.4.227 Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis

Meunier PJ, Roux C, Ortolani S, Diaz-Curiel M, Compston J, Marquis P, Cormier C, Isaia G, Badurski J, Wark JD, Collette J, Reginster JY

Osteoporos Int 2009;20:1663-73

A total of 1649 postmenopausal osteoporotic women were randomized to strontium ranelate or placebo for 4 years, followed by a 1-year treatment-switch period for half of the patients. Over 4 years, risk of vertebral fracture was reduced by 33% (risk reduction=0.67, p<0.001). Among patients with two or more prevalent vertebral fractures, risk reduction was 36% (p<0.001). QoL, assessed by the QUALIOST®, was better (p=0.025), and patients without back pain were greater (p=0.005) with strontium ranelate than placebo over 4 years. Lumbar BMD increased over 5 years in patients who continued with strontium ranelate, while it decreased in patients who switched to placebo.

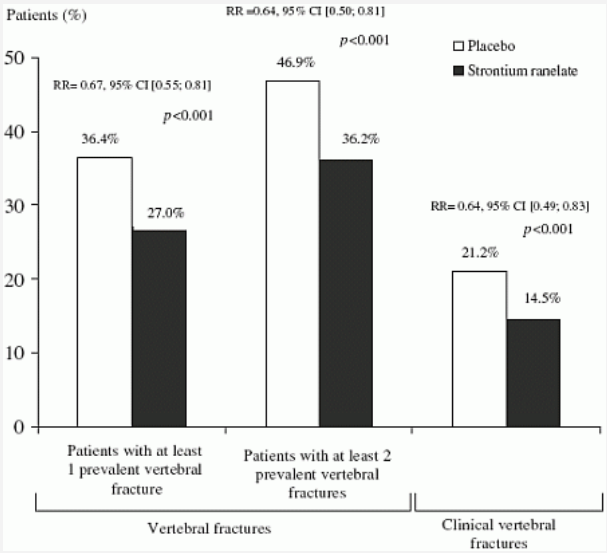


Fig. 10.4.227a The proportion of patients who experienced new vertebral fracture(s) during the M0-M48 period. Reproduced from Osteoporos Int 2009;20:1663-73 with permission from Springer.

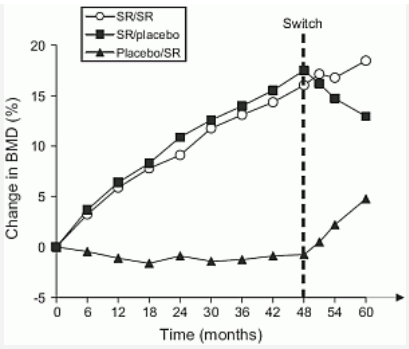


Fig. 10.4.227b Changes in BMD at the lumbar L2-L4 site with time throughout the trial. Treatment switch at 48 months is indicated by vertical dashed line. Reproduced from Osteoporos Int 2009;20:1663-73 with permission from Springer.

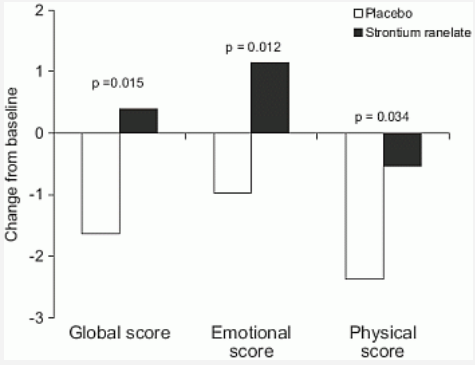


Fig. 10.4.227c Changes from baseline to last evaluation (baseline-endpoint) during the M0-M48 treatment period in quality of life assessed by QUALIOST® global score, emotional score, and physical score in the ITT population on treatment (ANCOVA). p-value difference versus the placebo group. Reproduced from Osteoporos Int 2009;20:1663-73 with permission from Springer.

10.4.228 Efficacy and safety of 2 g/day of strontium ranelate in Asian women with postmenopausal osteoporosis

Liu JM, Wai-Chee Kung A, Pheng CS, Zhu HM, Zhang ZL, Wu YY, Xu L, Meng XW, Huang ML, Chung LP, Hussain NH, Sufian SS, Chen JL
Bone 2009;45:460-5

329 women from China, Hong Kong and Malaysia were randomized. The baseline characteristics were similar in the treatment and placebo groups: mean age of 66.2±6.5 years, time since menopause 17.6±7.2 years. In the full analysis set (FAS, N=302), the mean baseline lumbar L2-L4 BMD was 0.715±0.106 g/cm^2 in the strontium ranelate group and 0.708±0.109 g/cm2 in the placebo group. The mean baseline femoral neck BMD was 0.575±0.074 g/cm^2 and 0.566±0.069 g/cm^2, respectively, and mean total hip BMD was 0.642±0.080 g/cm^2 and 0.631±0.088 g/cm^2, respectively. The overall compliance was 91.4% in the study drug group, and 97.4% in the placebo group. After one year, the lumbar spine, femoral neck and total hip BMD in the treated group was increased by 3-5% as compared to placebo. Strontium ranelate was well tolerated. The most frequently reported emergent adverse events were comparable in both groups (60.4% vs. 60.0%), with majority being mild gastrointestinal disorders.

10.4.229 Effect of long-term treatment with strontium ranelate on bone strontium content

Barenholdt O, Kolthoff N, Nielsen SP
Bone 2009;45:200-6

Bone strontium was measured by a DPA method. 32 osteoporotic female patients volunteered to participate in a 3-year open study of the effect on bone Sr. The group was treated with 2 g SrR/day, 17 of the group had received treatment for 4-5 years. DXA BMD and DPA of the relative bone strontium hydroxy apatite termed %Sr (SrHA/(CaHA+SrHA)) were done simultaneously ultradistally (UD) on the nondominant radius every 6 months and 3-6 months after treatment stop. The highest relative Sr content was found in patients who had been treated for 7-8 years. The variability was pronounced; a mean of 1.1% Sr was measured at the end of treatment. No effect was demonstrated on distal radius relative bone Ca hydroxyapatite. Bone strontium uptake and retention data were compatible with a power function model. Withdrawal of SrR resulted in a decline in bone Sr, but 73% Sr and 67% Sr, respectively, remained in UD-radius 3 and 6 months after drug withdrawal. The rise in bone Sr content measured by DPA as well as BMD measured by DXA was most marked initially. After the treatment was stopped, bone Sr decreased rapidly only during the first months. In UD-radius, the apparent BMD corrected for the influence of %Sr measured by DPA. showed a slight decline like in an untreated population. Strontium-containing drugs may influence DXA bone mineral measurements several years after treatment withdrawal. According to the power function model the skeletal retention 3 and 6 months after stopping the treatment would average 66% and 58%, respectively, after 3 years of treatment, and 76% and 70%, respectively, after 8 years of treatment.

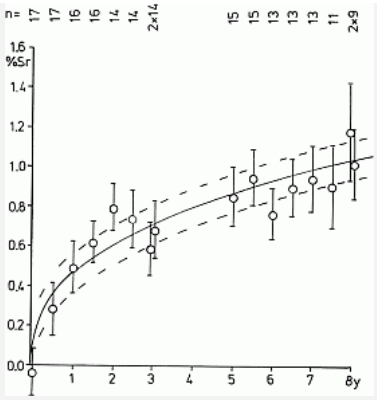


Fig. 10.4.229a %Sr at the ultradistal radius at different time point during treatment with strontium ranelate. n denotes number of patients. Fully drawn line: values according to power function. Interrupted lines: SEE. Reproduced from Bone, 45:200-6, Copyright (2009), with permission from Elsevier.

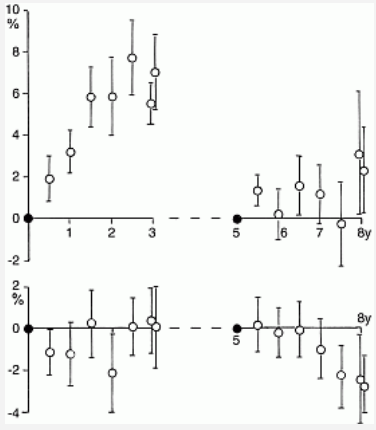


Fig. 10.4.229b Upper panel: relative change (in %) in measured BMD in the ultradistal radius (DXA). Values compared to first BMD value (●) Groups as in above figure. Lower panel: values expressed as BMD corrected for the influence of Sr. Mean and SD. Corrections carried out for the individual patients. Reproduced from Bone, 45:200-6, Copyright (2009), with permission from Elsevier.

10.4.230 Denosumab for prevention of fractures in postmenopausal women with osteoporosis
Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C
N Engl J Med 2009;361:756-65

7868 women between 60 and 90 years with T-score of less than -2.5 at the spine or total hip were randomly assigned to 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. Denosumab reduced new vertebral fracture; 2.3% in vs. 7.2% in placebo (RR, 0.32; 0.26 to 0.41; P<0.001) - decrease of 68%, reduced the risk of hip fracture, 0.7% vs. 1.2% in placebo (HR, 0.60; 95% CI, 0.37 to 0.97; P=0.04) - a decrease of 40% and reduced the risk of nonvertebral fracture, 6.5% vs. 8.0% in placebo (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01) - a decrease of 20%.

10.4.231 The same annual dose of 292,000 IU of vitamin D3 (cholecalciferol) on either daily or four monthly basis for elderly women: 1-year comparative study of the effects on serum 25(OH) D3 concentrations and renal function
Pekkarinen T, Valimaki VV, Aarum S, Turpeinen U, Hamalainen E, Loyttyniemi E, Valimaki MJ
Clin Endocrinol (Oxf) 2009;[Epub ahead of print]

800 IU daily or 97,333 IU four monthly of vitamin D3 resulting in the equal annual dose of 292,000 IU were assessed in a randomized, double-blind, double-dummy parallel group comparison in 40 women aged 69.3-78.8 years. 25(OH)D3 increased more in daily than in 4-months group (P<0.0001). All in the daily group and 67% in 4-months group had 25(OH)D3 above 50 nmol/L at 12 months; the target level of 75 nmol/L was reached by 47% and 28%, respectively.

10.4.232 Changes in 25-hydroxyvitamin D3 to oral treatment with vitamin D3 in postmenopausal females with osteoporosis
Hoeck HC, Li B, Qvist P
Osteoporos Int 2009;20:1329-35

In 131 postmenopausal females screened for participation in an osteoporosis trial, the 25-hydroxyvitamin D3 concentration was <60 nmol/L. They were treated with 25 (n=22), 50 (n=19), 75 (n=19), 100 (n=41) or 200 µg (n=30) of vitamin D3 daily for at least 10 days. In the females treated with 25, 50, 75, 100 and 200 microg of vitamin D3 daily the 25-hydroxyvitamin D3 increased from 32.4±2.7 (mean±SEM) to 50.8±2.9, from 46.7±2.8 to 65.8±2.6, from 41.6±2.7 to 67.4±2.9, from 46.7±1.4 to 64.4±2.2 and from 42.1±2.0 to 71.2±2.8 nmol/L, respectively (p<0.001). S-calcium increased but within the reference range (p<0.006). Oral vitamin D3 safely increased 25-hydroxyvitamin D3 in all females above 60 nmol/L.

10.4.233 High-dose oral vitamin D3 supplementation in the elderly
Bacon CJ, Gamble GD, Horne AM, Scott MA, Reid IR
Osteoporos Int 2009;20:1407-15

This randomized double-blind trial compares responses to three high-dose vitamin D3 regimens and estimates optimal 25-hydroxyvitamin D (25OHD) levels, from changes in PTH, and procollagen type I amino-terminal propeptide (PINP) in relation to baseline 25OHD. 63 elderly participants were randomized to three regimens of vitamin D supplementation: a 500,000 IU loading dose; the loading dose plus 50,000 IU/month; or 50,000 IU/month. The Loading and Loading+Monthly groups showed increases in 25OHD of 58±28 nmol/L from baseline to one month. Thereafter, levels gradually declined to plateaus of 69 ±5 nmol/L and 91±4 nmol/l, respectively. In the Monthly group, 25OHD reached a plateau of ~80±20 nmol/L at 3-5 months. PTH and PINP were only suppressed by vitamin D treatment in those with baseline 25OHD levels <50 and <30 nmol/L, respectively. Large loading doses of vitamin D3 rapidly and safely normalize 25OHD levels in the frail elderly. Monthly dosing is similarly effective and safe, but takes 3-5 months for plateau 25OHD levels to be reached.

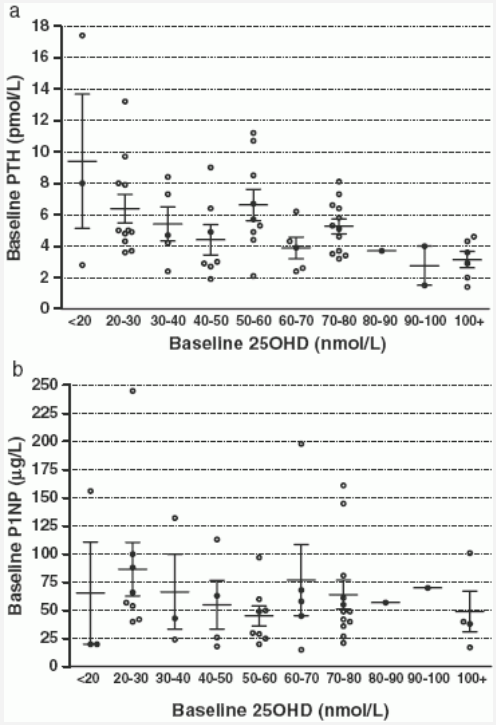


Fig. 10.4.233a Relationships between baseline 25OHD and (a) PTH and (b) procollagen type I amino-terminal propeptide (PINP). Data are mean±SEM. Reproduced from Osteoporos Int 2009;20:1407-15 with permission from Springer.

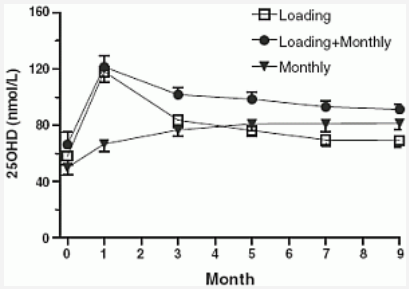


Fig. 10.4.233b Effects of three regimens of supplementation with vitamin D3 on serum levels of 25OHD. There was a significant difference between groups in levels of 25OHD (P<0.001), and in the areas under the curves (P=0.02). Data are mean ±SEM. Reproduced from Osteoporos Int 2009;20:1407-15 with permission from Springer.

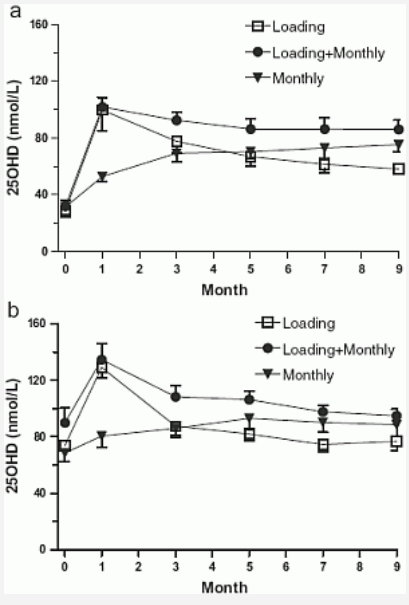


Fig. 10.4.233c Effects of three regimens of supplementation with vitamin D3 on serum levels of 25OHD, according to whether baseline concentrations of 25OHD were (a) below, or (b) above 50 nmol/L. In both cohorts, there were significant timetreatment interactions in the 25OHD response (P<0.001; a: $F_{(10,99)}$=11, b: $F_{(105,130)}$=63). Data are mean±SEM. Reproduced from Osteoporos Int 2009;20:1407-15 with permission from Springer.

10.4.234 High-dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency

von Restorff C, Bischoff-Ferrari HA, Theiler R

Bone 2009;45:747-9

Over 4 months, we 33 elderly with severe vitamin D deficiency (25(OH)D<25 nmol/l) on admission to acute care aged 80.5 years (SD±6.1). All were treated with a single oral dose of 300,000 IU D3 with 500-1000 mg calcium per day. Baseline 25(OH)D were 15 nmol/l (SD±5.5). Mean 25(OH)D increased to 81.4 nmol/l (SD±29.7) at 3 months (29 patients) and were still 69.0 nmol/l (SD ±17.9) at 6 months (26 patients). Mean serum calcium levels were 2.24 mmol/l (SD±0.11) at baseline, 2.28 mmol/l (SD±0.18) at 3 months, and 2.28 mmol/l (SD±0.13) at 6 months. Two patients with mild hypercalcemia (2.69 mmol/l) at 3 months had normal values at 6 months.

10.4.235 Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal North American women

Binkley N, Harke J, Krueger D, Engelke J, Vallarta-Ast N, Gemar D, Checovich M, Chappell R, Suttie J

J Bone Miner Res 2009;24:983-91

Low vitamin K is associated with low BMD. A menaquinone, menatetrenone (MK4), may reduce fracture risk. To evaluate the impact of phylloquinone or MK4 on turnover and BMD in a double-blind, placebo-controlled study, 381 postmenopausal women received phylloquinone (1 mg daily), MK4 (45 mg daily), or placebo for 12 months. All received calcium and vitamin D3. Phylloquinone and MK4 reduced serum undercarboxylated osteocalcin but not BSALP or NTX. No effect of phylloquinone or MK4 on lumbar spine or proximal femur BMD or proximal femur geometric parameters was observed. This study does not support a role for vitamin K in osteoporosis prevention among healthy, postmenopausal, North American women receiving calcium and vitamin D supplementation.

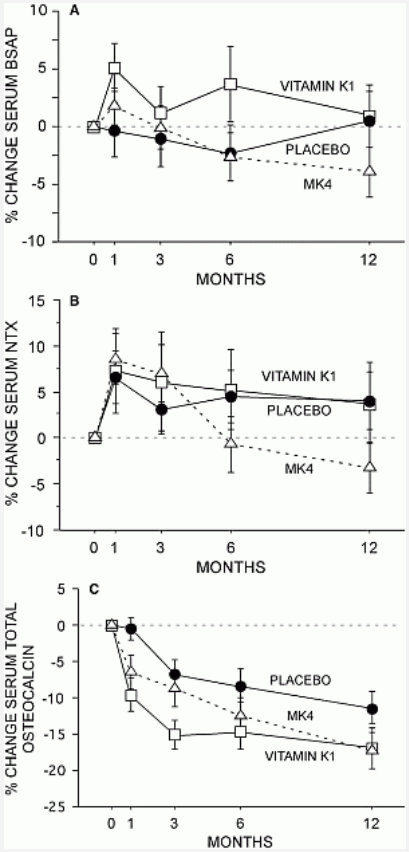


Fig. 10.4.235a Bone turnover. No effect of phylloquinone or MK4 was observed on serum BSALP (A) or serum NTX (B). Serum osteocalcin declined in all groups (C). Specifically, total osteocalcin declined (p<0.001) over the 1-yr study duration by 11.4% in the placebo group. In comparison with placebo, slightly greater declines (p<0.05) were observed for the two treatment groups. Data (mean±SE) presented for study completers. Reproduced from J Bone Miner Res 2009;24:983-91 with permission of the American Society of Bone and Mineral Research.

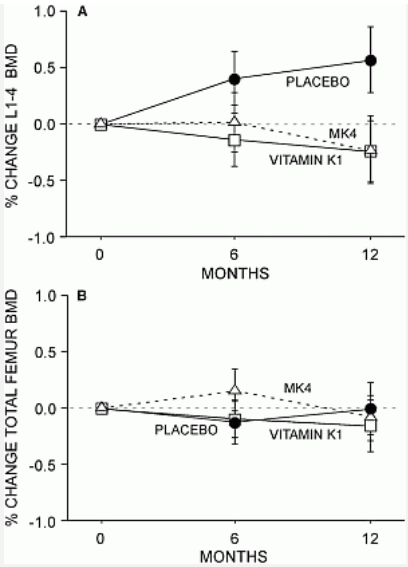


Fig. 10.4.235b BMD. No effect of either phylloquinone or MK4 was observed at the L1-L4 spine (A) or left total proximal femur (B). Data (mean±SE) presented for study completers. Reproduced from J Bone Miner Res 2009;24:983-91 with permission of the American Society of Bone and Mineral Research.

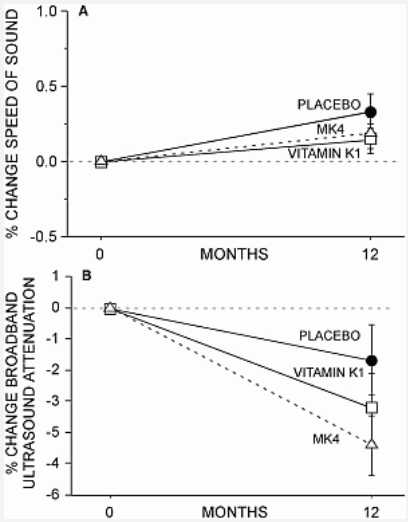


Fig. 10.4.235c Calcaneal ultrasound parameters. No effect of either phylloquinone or MK4 was observed on SOS (A) or BUA (B). Data (mean±SE) reported for 208 study completers; 71, 67, and 70 in the placebo, phylloquinone, and MK4 groups, respectively. Reproduced from J Bone Miner Res 2009;24:983-91 with permission of the American Society of Bone and Mineral Research.

10.4.236 Transdermal nitroglycerin therapy may not prevent early postmenopausal bone loss
Wimalawansa SJ, Grimes JP, Wilson AC, Hoover DR
J Clin Endocrinol Metab 2009;94:3356-64

Nitric oxide (NO) donors may reduce bone loss. To evaluate if NO donor, nitroglycerin prevents postmenopausal bone loss a 3-yr blinded, single-center, placebo-controlled clinical trial 186 postmenopausal women aged 40-65 years, stratified by BMD and years since menopause received nitroglycerin ointment (22.5 mg as Nitrobid®, or placebo ointment for 3 years. After 36 months, changes of -2.1% in the active group (n=88) and -2.5% in the placebo group (n=82) in lumbar spine BMD were seen (NS). Secondary outcomes also did not differ by intervention.

10.4.237 Milk ribonuclease-enriched lactoferrin induces positive effects on bone turnover markers in postmenopausal women
Bharadwaj S, Naidu AG, Betageri GV, Prasadarao NV, Naidu AS
Osteoporos Int 2009;20:1603-11

Milk ribonuclease (RNase) promotes angiogenesis and lactoferrin (LF) to stimulate bone formation by osteoblasts. We examine the effect of RNase-enriched LF supplement on the bone health of 38 healthy, postmenopausal women, aged 45-60 years randomized into placebo or RNAse-enriched-LF (R-ELF). R-ELF supplementation demonstrated a decrease in urine Dpd levels by 14% (19% increase for placebo) and serum NTX maintained at 24% of the baseline (41% for placebo), while serum BAP and OC levels showed a 45% and 16% elevation (25% and 5% for placebo). R-ELF supplementation demonstrated a statistically reduction in bone resorption markers and increase in bone formation markers.

10.4.238 A short treatment with an antibody to sclerostin can inhibit bone loss in an ongoing model of colitis
Eddleston A, Marenzana M, Moore AR, Stephens P, Muzylak M, Marshall D, Robinson MK
J Bone Miner Res 2009;24:1662-71

Scl-AbI did not reduce the weight loss or histological changes associated with colitis but did prevent inflammation-induced bone loss. Scl-AbI treated animals had a higher femoral BMD (+27%, $p<0.05$) than control antibody (Cntrl-Ab) treated animals. In a

second experiment, Scl-AbI was delayed until colitis had developed, by which time the mechanical properties of femurs in colitic animals were worse (maximum load, -26%, p<0.05; energy, -37%, p<0.05; ultimate strength, -33%, p<0.05; elastic modulus, -17%, p<0.05). Scl-AbI halted bone loss and reversed the decline of both intrinsic and extrinsic mechanical properties of the femur such that, after 19 days, the bone mechanical properties in the Scl-AbI treated animals were not different from those of noncolitic controls. Serum markers of bone formation and resorption suggested that the antibody to sclerostin stimulated osteoblast activity and inhibited osteoclast-mediated bone resorption.

10.4.239 External hip protectors are effective for the elderly with higher-than-average risk factors for hip fractures

Koike T, Orito Y, Toyoda H, Tada M, Sugama R, Hoshino M, Nakao Y, Kobayashi S, Kondo K, Hirota Y, Takaoka K
Osteoporos Int 2009;20:1613-20

76 homes with 672 ambulatory but frail elderly women. In the intervention group, 19 hip fractures occurred (54.0/1,000 person-years), whereas 39 hip fractures occurred in the control group (78.8/1,000 person-years). Hazard ratio of hip fracture in the intervention group was 0.56 (95%CI, 0.31-1.03; p=0.06) after adjusting for risk factors. In subgroup analysis, hip protectors were more effective for prevention of hip fractures in residents with fall history (n=202; HR, 0.375; 95%CI, 0.14-0.98; p=0.05) and BMI ≤19.0 (n=206; HR, 0.37; 95%CI, 0.14-0.95; p=0.04). Overall compliance with use of hip protectors was 79.7%.

10.4.240 Clinical and radiological comparison of unipedicular vs. bipedicular balloon kyphoplasty for the treatment of vertebral compression fractures

Song BK, Eun JP, Oh YM
Osteoporos Int 2009;20:1717-23

The authors compared the pre- and postoperative compression ratios (CRs), kyphotic angles (KAs), and visual analogue scale (VAS) scores of the patients in the unipedicular and bipedicular kyphoplasty groups. The clinical and radiological results of unipedicular kyphoplasty were as good as those of bipedicular kyphoplasty. Percutaneous balloon kyphoplasty is a therapeutic option for patients with painful osteoporotic vertebral compression fractures (VCFs). In 45 patients who underwent balloon kyphoplasty a unipedicular approach was used in 15 and a bipedicular approach in 30 patients. The CR, KA, and 100-point VAS score for pain were measured pre- and postoperatively in each patient. There was no significant difference in restoration of the CR (p=0.376) and KA (p=0.888) between the unipedicular and bipedicular kyphoplasty groups. The patients in the unipedicular group showed greater improvement in VAS score than those in the bipedicular group (p<0.001). Unipedicular balloon kyphoplasty is as good as bipedicular balloon kyphoplasty.

10.4.241 Evaluation of pharmaceuticals with a novel 50-hour animal model of bone loss

Tomimori Y, Mori K, Koide M, Nakamichi Y, Ninomiya T, Udagawa N, Yasuda H
J Bone Miner Res 2009;24:1194-205

Rapid bone loss by administration of soluble RANKL (sRANKL) to mice was used to evaluate antiosteoporosis drugs. sRANKL decreased BMD within 50 h in a dose-dependent manner. The marked decrease in femoral trabecular BMD shown by pQCT and the 3D images obtained by μCT were indistinguishable from those observed in the OVX model. Serum biochemical markers of bone turnover such as Ca, C-telopeptide of type I collagen (CTX), and TRACP5b were increased in a dose-dependent manner. The sRANKL model is the simplest, fastest, and easiest of all osteoporosis models and could be useful in the evaluation of drug candidates for osteoporosis.

10.4.242 Cancer treatment dosing regimens of zoledronic acid result in near complete suppression of mandible intracortical bone remodeling in beagle dogs

Allen MR, Kubek DJ, Burr DB
J Bone Miner Res 2009;[Epub ahead of print]

In beagle dogs, monthly zoledronic acid (ZOL, 0.067 mg/kg i.v.); or oral alendronate for 3 months, reduced remodeling ZOL (-95%) compared to VEH; by 6 months ZOL had produced 99% suppression compared to VEH. ZOL also suppressed remodeling in the rib cortex at 3 (-83%) and 6(-85%) months compared to VEH; tibia cortex bone formation rate was nonsignificantly lower with ZOL treatment (-68 to -75%). Remodeling suppression greater than in ALN-treated animals at both the mandible and rib; ALN and VEH were not different at any of the sites. Compared across skeletal sites, the absolute level of remodeling suppression with ZOL-treatment was greater at those sites with higher remodeling while the percent reduction was similar among the site

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10.4.243 Determination of rat vertebral bone compressive fatigue properties in untreated intact rats and zoledronic-acid-treated, ovariectomized rats

Brouwers JE, Ruchelsman M, Rietbergen B, Bouxsein ML
Osteoporos Int 2009;20:1377-84

35-week-old Wistar rats were divided into SHAM-OVX (n=7) and OVX with ZOL treatment (n=5; single injection, 20 μg/kg b.w. s.c.). After 16 weeks, vertebral trabecular microarchitecture and cortical thickness were determined using μCT. Vertebrae were cyclically compressed in load-control at 2 Hz starting at 0.75% apparent strain. A line parallel to the apparent strain curve was drawn at 0.5% higher offset, after which the intersection was defined as the time to failure and the apparent strain at failure. Data were compared using Student's t-test. Morphology and fatigue properties were the same in both groups. Samples failed between 10 min and 15 h. Force-displacement curves displayed typical fatigue behavior. Displacement increased over time due to mostly creep and to decreasing secant stiffness. ZOL-treated OVX rats have similar vertebral fatigue properties as SHAM-OVX controls.

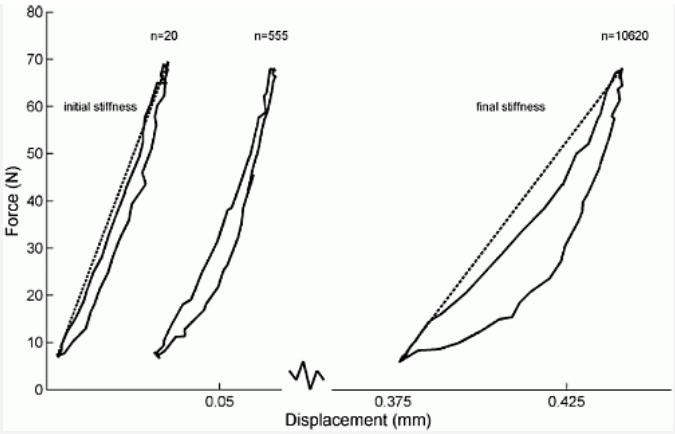

Fig. 10.4.243a Three representative force-displacement cycles throughout the testing period: 20, 55, and 10,620 cycles for a typical sample. Force-displacement cycles display typical fatigue behavior characterized by decreasing secant stiffness, increasing hysteresis, and increasing nonlinearity. Displacement increases over time due to mostly creep and to a lower extent, a decreasing secant stiffness. Reproduced from Osteoporos Int 2009;20:1377-84 with permission from Springer.

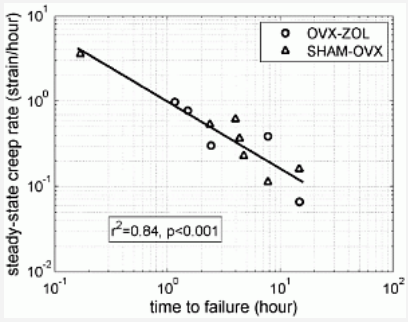

Fig. 10.4.243b Steady-state creep rate plotted against time to failure for all samples on a log-log scale. A significant inverse linear correlation was found between log of the time to failure and log of the steadystate creep rate (r^2=0.84, p<0.001). Reproduced from Osteoporos Int 2009;20:1377-84 with permission from Springer.

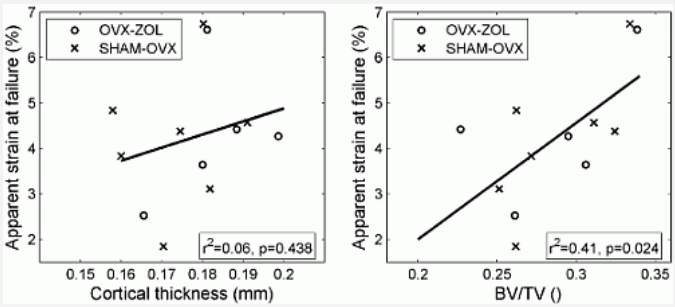

Fig. 10.4.243c A nonsignificant and a significant correlation between, respectively, cortical thickness and apparent strain at failure and BV/TV and apparent strain at failure. Reproduced from Osteoporos Int 2009;20:1377-84 with permission from Springer.

10.4.244 Strontium ranelate improves bone strength in ovariectomized rat by positively influencing bone resistance determinants

Bain SD, Jerome C, Shen V, Dupin-Roger I, Ammann P

Osteoporos Int 2009;20:1417-28

Adult female Sprague Dawley rats were OVX, then treated daily for 52 weeks with 125, 250, or 625 mg strontium ranelate/kg. Bone strength, mass, microarchitecture, turnover, and intrinsic quality were assessed. Strontium ranelate prevented ovariectomy-induced deterioration in mechanical properties with energy necessary for fracture completely maintained vs. SHAM at 625 mg/kg/day, which corresponds to the clinical dose. This was related to a dose-dependent effect on bone volume, higher trabeculae number, and lower trabecular separation in strontium ranelate vs. OVX. Load and energy required to induce lamella deformation were higher with strontium ranelate than in OVX and in SHAM, indicating that the bone formed with strontium ranelate is able to withstand greater damage before fracture. Bone formation was maintained high or even increased in strontium ranelate as shown by mineralizing surfaces and alkaline phosphatase while strontium ranelate led to reductions in deoxypyridinoline. Strontium ranelate administered at 625 mg/kg/day for 52 weeks prevented OVX-induced biomechanical properties deterioration by influencing the determinants of bone strength: it prevented bone loss and microarchitecture degradation in association with an effect on intrinsic bone quality.

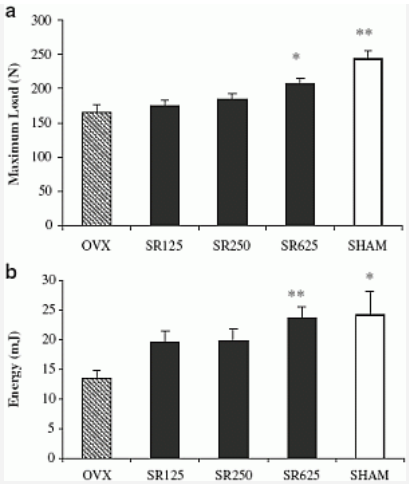

*Fig. 10.4.244a (a) Maximum load (in newtons) and (b) energy (in millijoules) of L5 lumbar vertebra obtained by a compression test in OVX rats treated with strontium ranelate at 125, 250, and 625 mg/kg/day for 52 weeks. Values represent the mean±SD; n=20-27 animals per group. *p<0.05 compared to OVX control group; **p<0.01 compared to OVX control group. Reproduced from Osteoporos Int 2009;20:1417-28 with permission from Springer.*

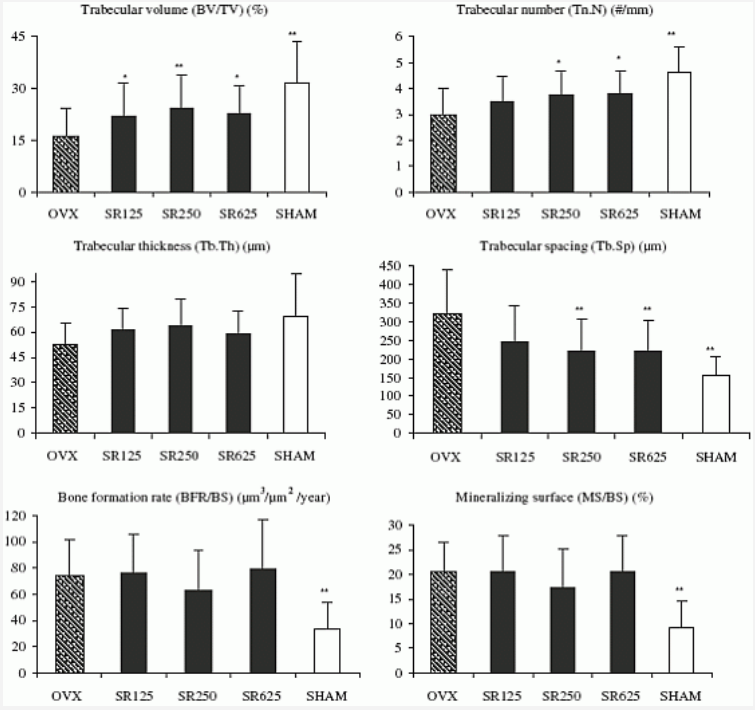

*Fig. 10.4.244b L3 lumbar vertebra 2-D histomorphometry indices in OVX rats treated with strontium ranelate. Values are expressed as the mean±SD; n=20-27 animals per group. *p<0.05 compared to OVX; ** p<0.01 compared to OVX. Reproduced from Osteoporos Int 2009;20:1417-28 with permission from Springer.*

10.4.245 One year of transgenic overexpression of osteoprotegerin in rats suppressed bone resorption and increased vertebral bone volume, density, and strength

Ominsky MS, Stolina M, Li X, Corbin TJ, Asuncion FJ, Barrero M, Niu QT, Dwyer D, Adamu S, Warmington KS, Grisanti M, Tan HL, Ke HZ, Simonet WS, Kostenuik PJ

J Bone Miner Res 2009;24:1234-46

Overexpression of OPG reduced osteoclasts and turnover, and increased peak load in vertebrae. Femurs from OPG-Tg rats were of normal length, osteopetrotic changes, reduced periosteal perimeter (-6%) and reduced bending strength. Serum OPG in WT rats showed no correlations with bone turnover, mass, or strength, whereas the supraphysiological serum OPG in OPG-Tg rats correlated negatively with bone turnover and positively with vertebral bone mass and strength.

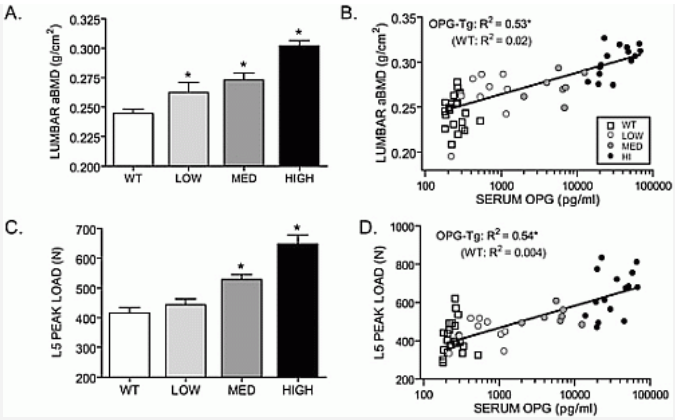

*Fig. 10.4.245a Areal BMD and peak load of the lumbar spine. (A) aBMD of L1-L5 was analyzed by DXA before the necropsy of 1-yr old WT (n=23) and OPG-Tg rats (n=32). Transgenic groups were binned by serum OPG level. Areal BMD increased concentration dependently with increasing levels of serum OPG (*p<0.05). (B) Serum OPG correlated positively with lumbar aBMD in OPG-Tg rats but not in WT controls. Regression line represents OPG-Tg rats only (*p<0.05). (C) Destructive compressive testing of L5 showed concentrationdependent increases in peak load with increasing levels of serum OPG. *Significantly different from WT littermates, p<0.05. (D) Serum OPG correlated positively with lumbar peak load in OPG-Tg rats but not in WT controls. Regression line represents OPG-Tg rats only (*p<0.05). Reproduced from J Bone Miner Res 2009;24:1234-46 with permission of the American Society of Bone and Mineral Research.*

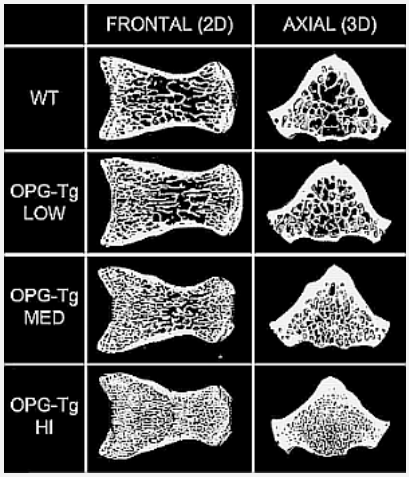

Fig. 10.4.245b Representative μCT images of fifth lumbar vertebrae (L5). Transgenic rats were binned by serum OPG levels. Representative surface rendered images were selected based on the median values for whole vertebra vBMC within each group. The frontal 2D sections (18 μm thick) were thresholded. The axial 3D isosurface-rendered images consist of 20 slices (a 360-μm-thick region) from the center of the vertebral body and were thresholded. Reproduced from J Bone Miner Res 2009;24:1234-46 with permission of the American Society of Bone and Mineral Research.

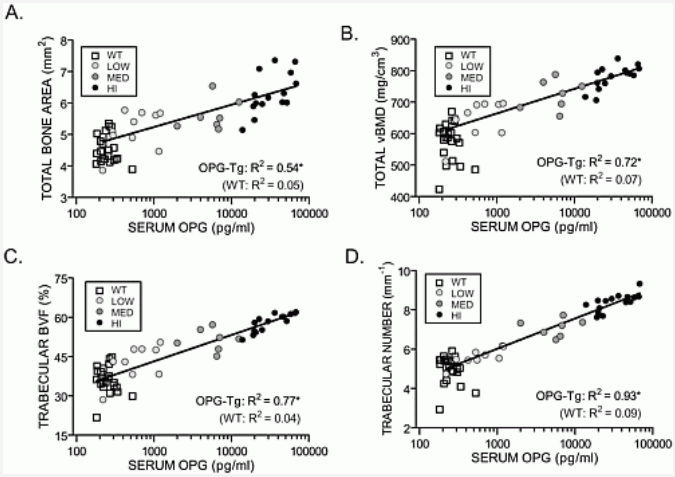

*Fig. 10.4.245c Correlations of serum OPG levels with μCT parameters. Serum OPG levels in OPG-Tg rats correlated positively with (A) total bone area, (B) total volumetric BMD (vBMD), (C) trabecular bone volume fraction (BVF), and (D) trabecular number. R^2 values are presented for individual regressions of WT and OPG-Tg rats. The regression lines shown in each panel are for OPG-Tg rats only (*all p<0.001), because no significant correlations were found in wildtype (WT) controls. Reproduced from J Bone Miner Res 2009;24:1234-46 with permission of the American Society of Bone and Mineral Research.*

10.4.246 Prevention of glucocorticoid-induced bone loss in mice by inhibition of RANKL
Hofbauer LC, Zeitz U, Schoppet M, Skalicky M, Schuler C, Stolina M, Kostenuik PJ, Erben RG
Arthritis Rheum 2009;60:1427-37

8-month-old male homozygous hRANKL-knockin mice received 2.1 mg/kg of prednisolone or placebo daily over 4 weeks, phosphate buffered saline or denosumab (10 mg/kg s.c twice weekly). Prednisolone induced loss of vBMD. suppressed bone formation and increased bone resorption, as shown by increases in TRAP-positive osteoclasts, TRAP-5b protein in

bone extracts, serum levels of TRAP-5b, and urinary excretion of deoxypyridinoline. Denosumab prevented bone loss. RANKL inhibition by denosumab prevents glucocorticoid-induced loss of bone mass and strength in hRANKL-knockin mice.

10.4.247 Low-intensity electrical stimulation counteracts the effects of ovariectomy on bone tissue of rats: Effects on bone microarchitecture, viability of osteocytes, and nitric oxide expression
Lirani-Galvao AP, Chavassieux P, Portero-Muzy N, Bergamaschi CT, Silva OL, Carvalho AB, Lazaretti-Castro M, Delmas PD
Calcif Tissue Int 2009;84:502-9

Low intensity electrical stimulation (LIES) has been used for bone repair. Osteocytes probably play a role in mediating this physical stimulus and they could act as transducers through the release of biochemical signals, such as nitric oxide (NO). Thirty rats (200-220 g) were divided into 3 groups: SHAM, OVX, and OVX subjected to LIES (OVX+LIES) for 12 weeks. OVX rats showed ($p<0.05$ vs. SHAM) decreased bone volume (10% vs. 25%) and trabecular number (1.7 vs. 3.9), and increased eroded surfaces (4.7% vs. 3.2%) and mineralization surfaces (15.9% vs. 7.7%). In contrast, after LIES, all these parameters were different from OVX but not different from SHAM. eNOS and iNOS were similarly expressed in subperiosteal regions of tibiae cortices of SHAM, not expressed in OVX, and similarly expressed in OVX+LIES when compared to SHAM. In OVX, the percentage of apoptotic osteocytes (24%) was increased when compared to SHAM (11%) and OVX+LIES (8%). Our results suggest that LIES counteracts some effects of OVX on bone tissue preserving bone structure and microarchitecture, iNOS and eNOS expression, and osteocyte viability

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10.4.248 Intermittent PTH administration stimulates pre-osteoblastic proliferation without leading to enhanced bone formation in osteoclast-less c-fos(-/-) mice
Luiz de Freitas PH, Li M, Ninomiya T, Nakamura M, Ubaidus S, Oda K, Udagawa N, Maeda T, Takagi R, Amizuka N
J Bone Miner Res 2009;24:1586-97

This study aimed to investigate the behavior and ultrastructure of osteoblastic cells after intermittent PTH and attempted to elucidate the role of osteoclasts on the mediation of PTH-driven bone anabolism. Structural and kinetic parameters related to bone formation increased in PTH-treated wildtype, whereas in the osteoclast-deficient c-fos(-/-) mice, there were no differences between groups. In wildtype and knockout mice, PTH increases in the number of cells double-positive for alkaline phosphatase and BrdU, suggesting active pre-osteoblastic proliferation. Ultrastructure showed two major preosteoblastic subtypes: one rich in endoplasmic reticulum (ER), the hypER cell, and other with fewer and dispersed ER, the misER cell. The latter constituted the most abundant preosteoblastic phenotype after PTH in the wildtype mice. In c-fos(-/-) mice, misER cells were present on the bone surfaces but did not seem to be actively producing matrix. Several misER cells were shown to be positive for EphB4 and were eventually seen rather close to osteoclasts in the PTH-administered wildtype mice. Absence of osteoclasts in c-fos(-/-) mice might hinder PTH-driven bone anabolism and that osteoclastic presence may be necessary for full osteoblastic differentiation and enhanced bone formation seen after intermittent PTH.

10.4.249 Secreted frizzled related protein 1 is a target to improve fracture healing
Gaur T, Wixted JJ, Hussain S, O'Connell SL, Morgan EF, Ayers DC, Komm BS, Bodine PV, Stein GS, Lian JB
J Cell Physiol 2009;220:174-81

Secreted frizzled related protein 1 (sFRP1) is a Wnt antagonist. In vivo deletion of sFRP1 function improves fracture repair by promoting early bone union and increased mechanical strength, increased intramembranous bone formation with bone bridging by 14 days, and early bone remodeling during the 28-day fracture repair process in the sFRP1(-/-) mice. sFRP1 loss-of-function accelerates healing by directing mesenchymal stem cells into the osteoblast lineage via the canonical pathway. Hence sFRP1(-/-) mouse progenitor cells are shifted directly into the osteoblast lineage. Antagonist to specifically inhibit sFRP1 represents a safe target for stimulating fracture repair and bone formation in metabolic bone disorders, osteoporosis and aging.

10.4.250 The Global Longitudinal Study of Osteoporosis in Women (GLOW): Rationale and study design
Hooven FH, Adachi JD, Adami S, Boonen S, Compston J, Cooper C, Delmas P, Diez-Perez A, Gehlbach S, Greenspan SL, LaCroix A, Lindsay R, Netelenbos JC, Pfeilschifter J, Roux C, Saag KG, Sambrook P, Silverman S, Siris E, Watts NB, Anderson FA, Jr.
Osteoporos Int 2009;20:1107-16

10.4.251 Osteoporosis management among residents living in long-term care
Giangregorio LM, Jantzi M, Papaioannou A, Hirdes J, Maxwell CJ, Poss JW
Osteoporos Int 2009;20:1471-8

10.4.252 Effectiveness of a community-based osteoporosis education and self-management course: A wait list controlled trial
Francis KL, Matthews BL, Van Mechelen W, Bennell KL, Osborne RH
Osteoporos Int 2009;20:1563-70

10.4.253 Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck BMD
Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, Cummings SR, Delmas PD, Palermo L, Mesenbrink P, Cauley JA
J Clin Endocrinol Metab 2009;94:3215-25

10.4.254 Pamidronate-induced kidney injury in a patient with metastatic breast cancer
Nagahama M, Sica DA
Am J Med Sci 2009;338:225-8

10.4.255 Histologic and histomorphometric features of bisphosphonate-related osteonecrosis of the jaws: An analysis of 31 cases with confocal laser scanning microscopy
Favia G, Pilolli GP, Maiorano E
Bone 2009;45:406-13

10.4.256 Antiresorptive effects of phytoestrogen supplements compared to estradiol or risedronate in postmenopausal women using 41Ca methodology
Weaver CM, Martin BR, Jackson GS, McCabe GP, Nolan JR, McCabe LD, Barnes S, Reinwald S, Boris ME, Peacock M
J Clin Endocrinol Metab 2009;[Epub ahead of print]

10.4.257 The effects of anti-resorptive therapies and estrogen withdrawal in adult scoliosis measured by sub-segmental vertebral BMD analysis
Routh RH, Lee KM, Burshell AL, Nauman EA
Bone 2009;45:193-9

10.4.258 Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/or alfacalcidol in postmenopausal Japanese women
Gorai I, Tanaka Y, Hattori S, Iwaoki Y
J Bone Miner Metab 2009;[Epub ahead of print]

10.4.259 Effects of calcium supplementation on body weight and adiposity in overweight and obese adults: A randomized trial
Yanovski JA, Parikh SJ, Yanoff LB, Denkinger BI, Calis KA, Reynolds JC, Sebring NG, McHugh T
Ann Intern Med 2009;150:821-9, W145-6

10.4.260 Rho GTPase signaling and PTH 3-34, but not PTH 1-34, maintain the actin cytoskeleton and antagonize bisphosphonate effects in mouse osteoblastic MC3T3-E1 cells
Kazmers NH, Ma SA, Yoshida T, Stern PH
Bone 2009;45:52-60

10.4.261 Parathyroid hormone suppresses osteoblast apoptosis by augmenting DNA repair
Schnoke M, Midura SB, Midura RJ
Bone 2009;45:590-602

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Exercise

10.4.262 Targeted exercises against hip fragility

Nikander R, Kannus P, Dastidar P, Hannula M, Harrison L, Cervinka T, Narra NG, Aktour R, Arola T, Eskola H, Soimakallio S, Heinonen A, Hyttinen J, Sievanen H

Osteoporos Int 2009;20:1321-8

Using 3D magnetic resonance imaging, we scanned the proximal femur of 91 female athletes, and 20 referents. Cortical thickness at the inferior, anterior, superior, and posterior regions of the femoral neck was evaluated. For the inferior cortical thickness, only the high-impact group differed (approximately 60%, p=0.012) from the reference group, while for the anterior cortex, both the high-impact and odd-impact groups differed (approximately 20%, p=0.042 and p=0.044, respectively). Also, the posterior cortex was approximately 20% thicker (p=0.014 and p=0.006, respectively) in these two groups. Odd-impact exercise-loading was associated, similar to high-impact exercise-loading, with 20% thicker cortex around the femoral neck.

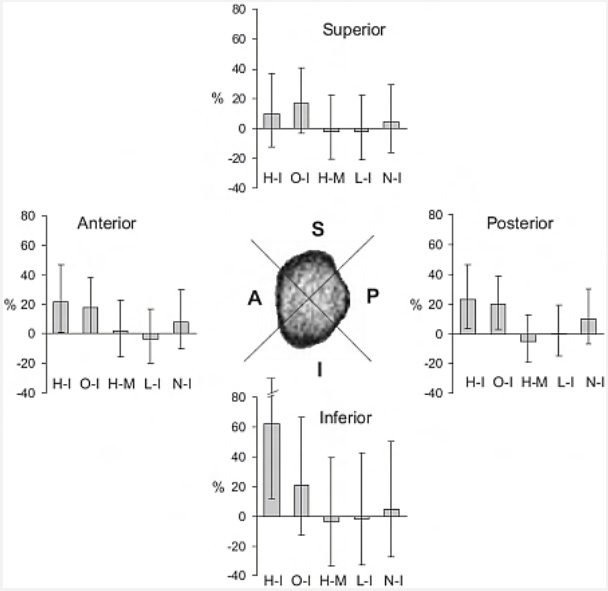

Fig. 10.4.262 Body height-, weight-, and age-adjusted percentage differences in the inferior, anterior, superior, and posterior cortical thickness of the femoral neck between the exerciseloading groups and the reference group (the 0% line indicates the mean of the reference group). The bars indicate the mean difference and the whiskers 95% CIs. If zero is not included in the confidence interval, the difference is statistically significant. H-I: Highimpact, O-I: odd-impact, H-M: high-magnitude, L-I: low-impact, and N-I: non-impact exerciseloading. I: Inferior, A: anterior, S: superior, and P: posterior. Reproduced from Osteoporos Int 2009;20:1321-8 with permission from Springer.

10.4.263 Preventative effect of exercise against falls in the elderly: A randomized controlled trial

Iwamoto J, Suzuki H, Tanaka K, Kumakubo T, Hirabayashi H, Miyazaki Y, Sato Y, Takeda T, Matsumoto H

Osteoporos Int 2009;20:1233-40

68 elderly ambulatory volunteers were randomly divided into two groups: the exercise and control groups. The daily exercise, which consisted of calisthenics, body balance training (tandem standing, tandem gait, and unipedal standing), muscle power training (chair-rising training), and walking ability training (stepping), were performed 3 days/week only in the exercise group. No exercise was performed in the control group. After the 5-month exercise program, the indices of the flexibility, body balance, muscle power, and walking ability improved in the exercise group. The incidence of falls was lower in the exercise group than in the control group (0.0% vs. 12.1%, P=0.0363). The exercise program was safe and well tolerated.

10.4.264 Long-term leisure time physical activity and properties of bone: A twin study

Ma H, Leskinen T, Alen M, Cheng S, Sipila S, Heinonen A, Kaprio J, Suominen H, Kujala UM

J Bone Miner Res 2009;24:1427-33

Long-term leisure time physical activity (LTPA) and bone properties in twin pairs discordant for activity for at least 30 yr was studied in 16 middle-aged (50-74 yr) same-sex twin pairs (7 MZ and 9 DZ pairs). Paired differences were studied. Active members of MZ twin pairs had larger cortical bone cross-sectional area (intrapair difference: 8%, p=0.006), thicker cortex (12%, p=0.003), and greater moment of inertia (I_{max}, 20%, p=0.024) at the tibia shaft than their inactive co-twins. At the distal tibia, trabecular BMD (12%, p=0.050) and compressive strength index (18%, p=0.038) were also higher in physically active MZ pair members than their inactive co-twins. The trends were similar, but less consistently so, in DZ pairs. LTPA during adulthood strengthens bones in a site-specific manner, that is, the long bone shaft has a thicker cortex, and thus higher bending strength, whereas the distal bone has higher trabecular density and compressive strength. These results suggest that LTPA has a potential causal role in decreasing the long-term risk of osteoporosis and thus preventing osteoporotic fractures.

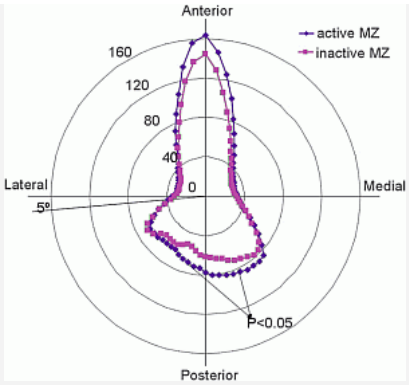

Fig. 10.4.264 Polar bone mass distribution of active and inactive MZ twin pairs discordant for physical activity. p-values for difference in the bone mass of specific sectors between active and inactive members of twin pairs. Reproduced from J Bone Miner Res 2009;24:1427-33 with permission of the American Society of Bone and Mineral Research.

10.4.265 Bone, muscle, and physical activity: Structural equation modeling of relationships and genetic influence with age

Lang DH, Conroy DE, Lionikas A, Mack HA, Larsson L, Vogler GP, Vandenbergh DJ, Blizard DA, McClearn GE, Sharkey NA
J Bone Miner Res 2009;24:1608-17

This study used structural equation modeling (SEM) to explore the extent to which select genetic loci manifest their pleiotropic effects through functional adaptations. Quantitative trait locus (QTL) analysis was used to identify regions of chromosomes that simultaneously influenced skeletal mechanics, muscle mass, and/or activity-related behaviors in young and aged B6xD2 second-generation (F_2) mice of both sexes. The SEM approach provided the means to numerically decouple the musculoskeletal effects of mechanical loading from the effects of other physiological processes involved in locomotion and physical activity. Muscle mass was a better predictor of bone mechanics in young females, whereas mechanical loading was a better predictor of bone mechanics in older females. An activity-induced loading factor predicted the mechanical behavior of hindlimb bones in older males; contrarily, load-free locomotion (i.e., the remaining effects after removing the effects of loading) negatively predicted bone performance. QTLs on chromosomes 4, 7, and 9 seem to exert some of their influence on bone through actions consistent with Wolff's Law.

10.4.266 Effect of impact exercise on bone metabolism

Vainionpaa A, Korpelainen R, Vaananen HK, Haapalahti J, Jamsa T, Leppaluoto J
Osteoporos Int 2009;20:1725-33

In a 12-month population-based, controlled exercise trial in 120 women (age 35-40 years) randomly assigned to an exercise (EG; n=60) or a control (CG; n=60). The exercise regimen consisted of supervised high-impact exercises three times per week. 12 months of impact exercise did not reveal any effects in turnover whereas serum PTH decreased more in the EG than in the CG (-11.2 vs. -2.2 pg/mL; p=0.03). The change in PTH was dose dependent and most clearly seen in subjects with 96-130 daily impacts at 2.5-5.3 g (e.g., running or jumping). Impact exercise lowers PTH.

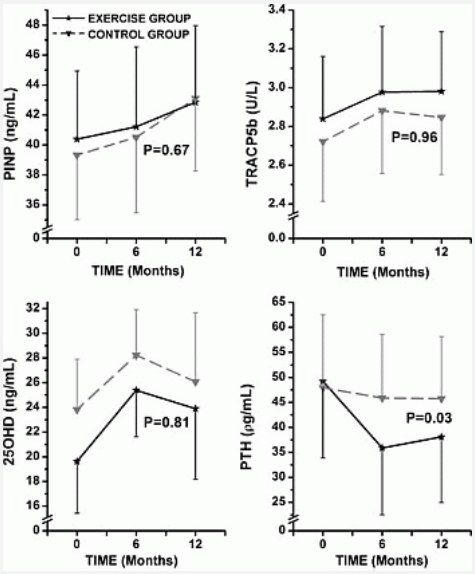

Fig. 10.4.266a Parameters of bone metabolism during the study and the significance of the difference between the groups in the repeatedmeasures ANCOVA. Bars represent 95% CIs (N=76). PINP procollagen type I amino-terminal propeptide, TRACP5b tartrate resistant acid phosphatase 5b, 25OHD serum 25-hydroxyvitamin D (1 ng/mL=2.5 nmol/L), PTH: intact parathyroid hormone. Reproduced from Osteoporos Int 2009;20:1725-33 with permission from Springer.

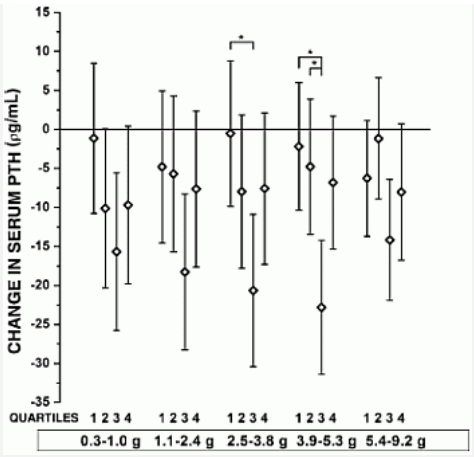

*Fig. 10.4.266b Mean 12-month change in intact PTH in quartiles of physical activity. The quartiles are defined by the number of daily impacts at each acceleration level in pooled groups (N=16 per quartile). Error bars represent 95% CIs. g: acceleration of gravity (9.81 m/s^2), *p<0.05. Reproduced from Osteoporos Int 2009;20:1725-33 with permission from Springer.*

10.4.267 Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on BMD in older men: A randomised controlled trial

Kukuljan S, Nowson CA, Bass SL, Sanders K, Nicholson GC, Seibel MJ, Salmon J, Daly RM

Osteoporos Int 2009;20:1241-51

This 12-month randomised controlled trial assessed whether calcium-vitamin-D3-fortified milk could enhance the effects of a multi-component exercise program on BMD in older men. Men (n=180) aged 50-79 years were randomised into: (1) exercise +fortified milk; (2) exercise; (3) fortified milk; or (4) controls. Exercise consisted of high intensity progressive resistance training with weight-bearing impact exercise. Men assigned to fortified milk consumed 400 mL/day of low fat milk providing an additional 1000 mg/day calcium and 800 IU/day vitamin D3. Femoral neck (FN), total hip, lumbar spine and trochanter BMD and body composition (DXA), muscle strength 25-hydroxyvitamin D and PTH were assessed. There were no exercise-by-fortified milk interactions. Exercise resulted in a 1.8% net gain in FN BMD relative to no-exercise (p<0.001); lean mass (0.6 kg, p<0.05) and muscle strength (20-52%, p<0.001) also increased in response to exercise. For lumbar spine BMD, there was a net 1.4-1.5% increase in all treatment groups relative to controls (all p<0.01). There were no main effects of fortified milk at any skeletal site. A multi-component community-based exercise program was effective for increasing FN BMD in older men, but calcium-vitamin D3 did not enhance the response.

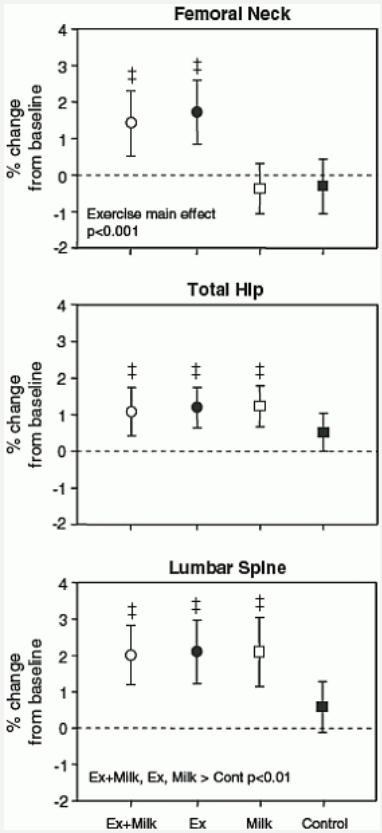

Fig. 10.4.267a Mean unadjusted percentage change (95% CI) in femoral neck, total hip and lumbar spine (L1-L4) aBMD in the Ex +Milk (n=45), Ex (n=46), Milk (n=45) and control groups (n=44). At the femoral neck, there was a significant main effect of exercise (p<0.001). The increase in L1-L4 aBMD in the treatment groups was significantly greater than the increases in the control group (all p<0.01). ‡p<0.001 within-group change from baseline. Reproduced from Osteoporos Int 2009;20:1241-51 with permission from Springer.

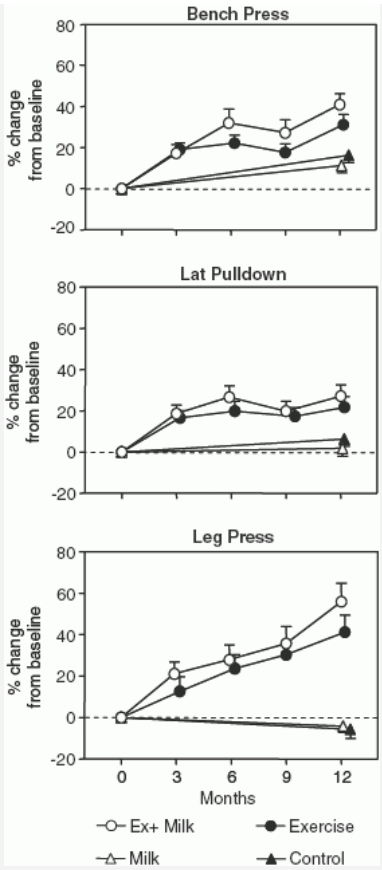

Fig. 10.4.267b Mean percentage changes (±SE) from baseline for upper body (bench press), back (lat. pull down) and lower body (leg press) muscle strength according to treatment group. Exercise resulted in significant increases in all strength measures relative to both baseline and the non-exercise group (main effects, p<0.001). Reproduced from Osteoporos Int 2009;20:1241-51 with permission from Springer.

10.4.268 Effect of antioxidants combined to resistance training on BMD in elderly women: A pilot study
Chuin A, Labonte M, Tessier D, Khalil A, Bobeuf F, Doyon CY, Rieth N, Dionne IJ
Osteoporos Int 2009;20:1253-8

The purpose of this study was to determine the effects of antioxidant supplements combined to resistance training on BMD in healthy elderly women. 34 postmenopausal women (66.1±3.3 years) were randomized in four groups (placebo, n=7; antioxidants, n=8; exercise and placebo, n=11; and exercise and antioxidants, n=8). The 6-month intervention consisted in antioxidant supplements (600 mg vitamin E and 1000 mg vitamin C daily) or resistance exercise (3x/week). We observed a significant decrease in the placebo group for lumbar spine BMD (pre, 1.01±0.17 g/cm^2; post, 1.00±0.16 g/cm^2; P<0.05, respectively) while it remained stable in all other groups. No changes were observed for femoral neck BMD. Antioxidant vitamins may offer some protection against bone loss in the same extent as resistance exercise although combining both does not seem to produce additional effects.

10.4.269 Isokinetic resistance training increases tibial bending stiffness in young women
Miller LE, Nickols-Richardson SM, Wootten DF, Ramp WK, Steele CR, Cotton JR, Carneal JP, Herbert WG
Calcif Tissue Int 2009;84:446-52

The mechanical response tissue analyzer measures long bone bending stiffness (EI), which predicts bone breaking strength. 52 women, aged 18-26 years, performed concentric (CON, n=30) or eccentric (ECC, n=22) isokinetic resistance training with the nondominant leg three times per week for 20 weeks. Both training groups increased CON (15-21%) and ECC (17-31%) peak torque vs. the untrained leg. Tibial EI increased in the entire cohort (26%) and in each training group (CON 34%, ECC 16%) vs. the untrained tibia. Tibial BMC and BMD increased in the trained and untrained tibiae, with no differences between limbs. No differential tibial EI or bone mineral outcomes were observed between the CON and ECC training groups. CON and ECC isokinetic resistance training increased tibial EI, but not BMC or BMD, in young women.

10.4.270 Bone mass and geometry of the tibia and the radius of master sprinters, middle and long distance runners, race-walkers and sedentary control participants: A pQCT study
Wilks DC, Winwood K, Gilliver SF, Kwiet A, Chatfield M, Michaelis I, Sun LW, Ferretti JL, Sargeant AJ, Felsenberg D, Rittweger J
Bone 2009;45:91-7

Peripheral quantitative computed tomography (pQCT) of the tibia and radius was performed in 106 sprinters, 52 middle distance runners, 93 long distance runners and 49 race-walkers competing at master championships, aged 35-94 years and 75 controls. Tibia diaphyseal vBMC, cortical area and polar moment of resistance were largest in sprinters, followed in descending order by middle and long distance runners, race-walkers and controls. When compared to controls, the differences were >13% in male and >23% in female sprinters (p<0.001). Similarly, the periosteal circumference in the tibia shaft was larger in male and female sprinters by 4% and 8%, respectively. Epiphyseal group differences were predominantly found for trabecular vBMC in both male and female sprinters, who had 15% and 18% larger values, respectively, than controls (p<0.001). In contrast, cortical vBMD in the tibia was the reverse, and only few group differences were found between athletes and control people for the radius. Greater skeletal size may allow larger muscle forces, and bias towards engagement in athletics. Musculoskeletal forces related to running can induce skeletal adaptation and enhance bone strength.

10.4.271 Effects of repetitive loading on bone mass and geometry in young male tennis players: A quantitative study using MRI
Ducher G, Daly RM, Bass SL
J Bone Miner Res 2009;24:1686-92

43 male pre-, peri-, and postpubertal competitive tennis players 10-19 yr of age were studied. In prepubertal boys, BMC was 17% greater in the playing compared with nonplaying arm ($p<0.001$), which was accompanied by a 12-21% greater cortical area, because of greater periosteal expansion than medullary expansion at the midhumerus and periosteal expansion associated with medullary contraction at the distal humerus. Compared with prepuberty, the side-to-side differences in BMC (27%) and cortical area (20-33%) were greater in peripuberty ($p<0.01$). No differences were found between peri- and postpuberty despite longer playing history in the postpubertal players. The osteogenic response to loading was greater in peri- compared with prepubertal boys.

10.4.272 History of amenorrhoea compromises some of the exercise-induced benefits in cortical and trabecular bone in the peripheral and axial skeleton: A study in retired elite gymnasts
Ducher G, Eser P, Hill B, Bass S
Bone 2009;45:760-7

24 retired artistic gymnasts, aged 17-36 years training for at least 15 h/week at the peak of their career and had been retired for 3-18 years, were recruited. Former gymnasts who reported history of amenorrhoea (AME, n=12: either primary or secondary amenorrhoea) were compared with former gymnasts (NO-AME, n=12) and controls (C, n=26) who did not report history of amenorrhoea. Menarcheal age was delayed in AME when compared to NO-AME (16.4±0.5 years vs. 13.3±0.4 years, $p<0.001$). No differences were detected between AME and C for height-adjusted spinal BMC, aBMD and BMAD, TrD and BSI at the distal radius and tibia, CoA at the proximal radius, whereas these parameters were greater in NO-AME than C ($p<0.05$-0.005). AME had lower TrD and BSI at the distal radius, and lower spinal BMAD than NO-AME ($p<0.05$) but they had greater ToA at the distal radius ($p<0.05$). Greater spinal BMC, aBMD and BMAD as well as trabecular volumetric density and bone strength in the peripheral skeleton were found in former gymnasts without a history of menstrual dysfunction but not in those who reported either primary or secondary amenorrhoea.

10.4.273 Influence of exercise mode and osteogenic index on bone biomarker responses during short-term physical training
Lester ME, Urso ML, Evans RK, Pierce JR, Spiering BA, Maresh CM, Hatfield DL, Kraemer WJ, Nindl BC
Bone 2009;45:768-76

In 56 women (20.3±1.8 years) after 8 weeks of training biomarkers of bone formation (BAP and osteocalcin) increased in the Resistance and Combined groups ($p<0.05$), while biomarkers of bone resorption (TRAP and DPD) decreased and increased, respectively, after training ($p<0.05$) in all groups. Small changes in volumetric and areal BMD ($p<0.05$) were observed in the distal tibia in the Aerobic and Combined groups, respectively. Mean weekly osteogenic indexes were 16.0±1.9, 20.6±2.2, and 36.9±5.2 for the Resistance, Aerobic, and Combined groups, respectively. The calculated osteogenic potential of our programs did not correlate with the observed changes in biomarkers of bone turnover. The results demonstrate that eight week physical training program that incorporates a resistance component by inactive young women results in alterations in biomarkers of bone remodeling indicative of increased formation without alterations in markers of resorption.

10.4.274 Physical exercise improves properties of bone and its collagen network in growing and maturing mice
Isaksson H, Tolvanen V, Finnila MA, Iivarinen J, Tuukkanen J, Seppanen K, Arokoski JP, Brama PA, Jurvelin JS, Helminen HJ
Calcif Tissue Int 2009;85:247-56

Half of the mice (total n=168) had access to running wheels, while half were kept sedentary. After 6 months, the exercising mice had 10% lower body weight than the sedentary group. There was no difference in the amount of collagen or collagen crosslinks, while tensile testing had higher breaking force and stiffness of the collagen network in runners after 4 months but not after 6 months. The BMD and cross-sectional area were higher in the running group after 6 months. Runners also showed higher breaking force and stiffness of the diaphysis and the femoral neck at 2 and 6 months. The significant modulation of mechanical properties of the collagen network without any change in collagen content indicates that physical exercise improves properties of the collagen network in maturing bone.

10.4.275 Does exercise modify the effects of zoledronic acid on bone mass, microarchitecture, biomechanics, and turnover in ovariectomized rats?
Lespessailles E, Jaffre C, Beaupied H, Nanyan P, Dolleans E, Benhamou CL, Courteix D
Calcif Tissue Int 2009;85:146-57

At 6 months of age, 60 female Wistar rats were OVX or sham operated (SH) and divided into five groups: SH, OVX, OVX-E, OVX-Z, and OVX-ZE. OVX rats were treated with a single i.v. injection of Z (20 μg/kg) or vehicle and submitted or not to treadmill exercise (15 m/min, 60 min/day, 5 days/week) for 12 weeks. After 12 weeks, bone volume fraction decreased in OVX rats, whereas bone turnover rate, trabecular spacing, and structure model index increased compared with those in the SH group ($P<0.05$). Zoledronic acid prevented the ovariectomy-induced trabecular bone loss and its subsequent trabecular microarchitectural deterioration. Treadmill exercise running was shown to preserve the bone strength and to induce bone turnover changes in favor of bone formation. However, the combined effects of zoledronic acid and running exercise applied simultaneously did not produce any synergetic or additive effects.

10.4.276 Constrained tibial vibration does not produce an anabolic bone response in adult mice
Christiansen BA, Kotiya AA, Silva MJ
Bone 2009;45:750-9

10.4.277 New suggestions for the mechanical control of bone remodeling
Dunlop JW, Hartmann MA, Brechet YJ, Fratzl P, Weinkamer R
Calcif Tissue Int 2009;85:45-54

10.4.278 Promiscuous and depolarization-induced immediate-early response genes are induced by mechanical strain of osteoblasts
Ott CE, Bauer S, Manke T, Ahrens S, Rodelsperger C, Grunhagen J, Kornak U, Duda G, Mundlos S, Robinson PN
J Bone Miner Res 2009;24:1247-62

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Summaries and Critical Analyses of the Current Literature
editor E. Seeman

Volume 10, Issue 4, 2009

Men

10.4.279 Assessment of determinants for osteoporosis in elderly men

Scholtissen S, Guillemin F, Bruyere O, Collette J, Dousset B, Kemmer C, Culot S, Cremer D, Dejardin H, Hubermont G, Lefebvre D, Pascal-Vigneron V, Weryha G, Reginster JY
Osteoporos Int 2009;20:1157-66

1004 men aged 60 years and older were recruited. In the multiple regression analysis, only age, BMI, CTX-1, and family history of osteoporosis and/or fracture were able to predict the femoral neck T-score. With the lumbar spine T-score, only age, BMI, and CTX-1 were retained. The best algorithm was based on age, BMI, family history, and CTX-1. A cut-off point of 0.25 yielded a sensibility of 78%, a specificity of 59% with an area under the curve of 0.73 in the development and validation cohorts. Ageing, a lower BMI, higher CTX-1, family history, and prior fracture were associated with T-score.

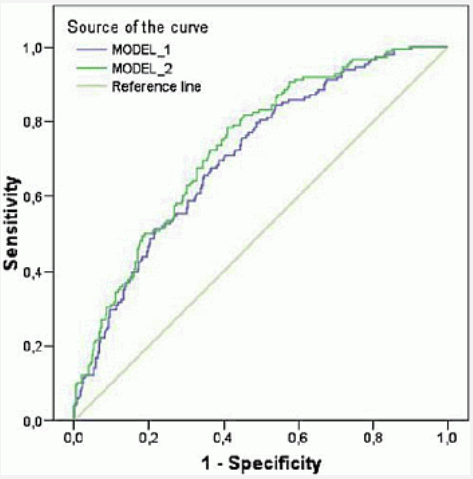

Fig. 10.4.279 Receiver operating characteristic areas under the curves of models I and II for identifying subjects with osteoporosis in the French cohort. Reproduced from Osteoporos Int 2009;20:1157-66 with permission from Springer.

10.4.280 Loss of hip BMD in older men: The Osteoporotic Fractures in Men (MrOS) Study

Cawthon PM, Ewing SK, McCulloch CE, Ensrud KE, Cauley JA, Cummings SR, Orwoll ES
J Bone Miner Res 2009;24:1728-35

4720 community-dwelling men ≥65 yr followed over 4.6 yr had FN BMD loss of 0.013 g/cm^2 (-1.72%). Bone loss accelerated with age. FN BMD in men 85 yr of age (0.021 g/cm^2) was 2.5 times greater than for men 65 yr of age (0.008 g/cm^2); such bone loss in 85-yr-old men may be sufficient to increase the risk of hip fracture by 25% (HR per 0.021 g/cm^2 cross-sectional decrease in FN BMD: 1.25; 95% CI: 1.18-1.31) over 4.6 yr. Men with lower BMD at baseline lost the most BMD over follow-up.

10.4.281 Increased bone resorption is associated with higher mortality in community-dwelling men ≥50 years of age: The MINOS study

Szulc P, Maurice C, Marchand F, Delmas PD
J Bone Miner Res 2009;24:1116-24

In 781 men ≥50 yr of age followed for 10 yr, men who died had lower BMD and higher BTM levels. In multivariate models, mortality was higher in men with low BMD (lowest quartile) at the total hip, whole body, and ultradistal radius (HR=1.49-1.70, p<0.05). After exclusion of the first 3 yr, higher levels (4th quartile) of free and total deoxypyridinoline and urinary and serum type I collagen C-telopeptide predicted mortality (HR=1.58-2.44, p<0.05-0.001).

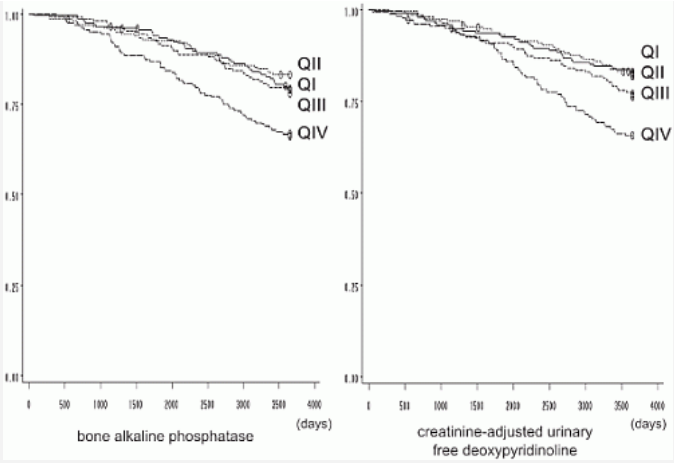

Fig. 10.4.281 Survival of men according to baseline levels of biochemical BTMs. Survival of men from the MINOS cohort during the 10 yr of follow-up according to the quartiles (QI, lowest; QII; QIII; QIV, highest) of the levels of biochemical BTMs presented with Kaplan-Meier curves: (left) BALP and (right) creatinine-adjusted urinary free DPD. Reproduced from J Bone Miner Res 2009;24:1116-24 with permission of the American Society of Bone and Mineral Research.

10.4.282 Natural history and correlates of hip BMD loss with aging in men of African ancestry: The Tobago Bone Health Study

Sheu Y, Cauley JA, Wheeler VW, Patrick AL, Bunker CH, Kammerer CM, Zmuda JM

J Bone Miner Res 2009;24:1290-8

Among 1478 Afro-Caribbean men ≥40 yr of age, femoral neck BMD declined by 0.29±0.81%/yr in the total sample (p<0.0001). The rate of decline in BMD at the femoral neck was -0.38±0.77%/yr among men 40-44 yr of age, decelerated to -0.15±0.81%/yr among men 50-54 yr of age, and then accelerated to -0.52±0.90%/yr among those 75+ yr of age (all p<0.003). Men who lost ≥5% of their body weight during follow-up had greater BMD loss than those who remained weight stable or gained weight (p<0.0001). Men of African ancestry experience substantial BMD loss with advancing age that seems to be comparable to the rate of loss among white men in other studies.

10.4.283 Low body mass index and declining sex steroids explain most age-related bone loss in Brazilian men

Lopes RF, Ferreira SA, Coeli CM, Farias ML

Osteoporos Int 2009;20:1175-82

In 104 men, aged 50-93 years old, increases in SHBG and ICTP and decreases in femoral neck BMD, FTI, FEI, BioT, and $BioE_2$ were observed with each additional decade of age. Femoral neck BMD was inversely correlated with ICTP, and both were associated with SHBG, FTI, BioT, FEI, and BioE. There was a direct and graded association between age and osteoporosis prevalence rate (OP PR; p=0.028). Compared to participants less than 70 years old, the crude OP PR of those 80 years and older was 3.2 (95% CI=1.4-7.3). Adjusting sequentially for BMI and bioavailable sex hormones attenuated the association between age and osteoporosis prevalence by 55% and 77%, respectively. Low BMI and declining sex steroids explain most of the association between aging, increased bone turnover, and osteoporosis in men.

10.4.284 Bone histomorphometry in male idiopathic osteoporosis

Pernow Y, Hauge EM, Linder K, Dahl E, Saaf M

Calcif Tissue Int 2009;84:430-8

51 eugonadal men with idiopathic osteoporosis median age 54 (range 29-73) years. 82% of the patients had a fracture history, and 57% had vertebral fractures. Bone volume, trabecular thickness, wall thickness, and osteoid thickness were reduced in compared with healthy men. Erosion depth was similar, as were the bone remodeling parameters such as bone formation rate, mineral apposition rate, and activation frequency. In the osteoporotic men, osteoid thickness was correlated to BMD at the lumbar spine (R^2=0.19, P<0.01); together with wall thickness, the two parameters could explain 27% of the variation in lumbar spine BMD. The osteoid thickness correlated with body weight (R^2=0.24, P<0.001) and BMI (R^2=0.14, P<0.01), as well as to serum estradiol levels (R^2=0.14, P<0.01) and to the ratio IGF-1 to IGFBP-1 (R^2=0.12, P<0.01).

10.4.285 Effects of lean and fat mass on BMD and arterial stiffness in elderly men

Benetos A, Zervoudaki A, Kearney-Schwartz A, Perret-Guillaume C, Pascal-Vigneron V, Lacolley P, Labat C, Weryha G

Osteoporos Int 2009;20:1385-91

In 169 French males over 60 years old. Aortic stiffness was assessed by carotid/femoral pulse wave velocity (PWV) lean mass was positively correlated with the three T-scores accounting for 11.6%, 26.6%, and 12.2% of the variability in the lumbar spine L1-L4, femoral neck, and total body BMD T-scores, respectively. Fat mass had no effect on BMD. However, fat mass was positively correlated with aortic PWV, accounting for 9.8% of its variability. Lean mass was not a determinant of PWV. Hypertension, diabetes, and dyslipidemia were associated with higher PWV but had no effect on BMD. In males from a general population over 60 years of age, bone and arterial aging are differently influenced by lean and fat mass.

10.4.286 Relation between fibroblast growth factor-23, body weight and BMD in elderly men

Marsell R, Mirza MA, Mallmin H, Karlsson M, Mellstrom D, Orwoll E, Ohlsson C, Jonsson KB, Ljunggren O, Larsson TE

Osteoporos Int 2009;20:1167-73

FGF23 is a hormonal factor produced in bone and regulates serum levels of phosphate (Pi) and vitamin D. FGF23 over-expression is associated with skeletal abnormalities, including rickets/osteomalacia. In 3014 Swedish men aged 69-80 years, there was a weak correlation between FGF23 and BMD in femoral neck (r=0.04, p<0.05), femoral trochanter (r=0.05, p=0.004), total hip (r=0.06, p=0.0015) and lumbar spine (r=0.07, p=0.0004). The correlations remained when adjusting for biochemical covariates

(Pi, calcium, PTH, 25(OH)D and renal function). However, the association became insignificant in all regions when adjusting for established confounding variables including age, height, weight and smoking. Further analysis confirmed a significant correlation between FGF23 and body weight (r=0.13, p<0.0001). The weak correlation between FGF23 and BMD in elderly male subjects is mainly due to an association between FGF23 and body weight.

10.4.287 Effects of hPTH(1-34) infusion on circulating serum phosphate, 1,25-dihydroxyvitamin D, and FGF23 levels in healthy men

Burnett-Bowie SA, Henao MP, Dere ME, Lee H, Leder BZ
J Bone Miner Res 2009;24:1681-5

FGF23 promotes phosphaturia and suppresses 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. PTH also promotes phosphaturia, but stimulates $1,25(OH)_2D$. 20 healthy men were infused with human PTH(1-34) [hPTH(1-34)] at 44 ng/kg/h for 24 h. Compared with baseline, FGF23, $1,25(OH)_2D$, ionized calcium (iCa), and serum N-telopeptide (NTX) increased over the 18-h hPTH(1-34) infusion (p<0.0001), whereas serum phosphate (PO_4) transiently increased. FGF23 increased from 35±10 pg/ml at baseline to 53 ±20 pg/ml at 18 h (p=0.0002); $1,25(OH)_2D$ increased from 36±16 pg/ml at baseline to 80±33 pg/ml at 18 h (p<0.0001); iCa increased from 1.23±0.03 mM at baseline to 1.46±0.05 mM at hour 18 (p<0.0001); and NTX increased from 17±4 nM BCE at baseline to 28±8 nM BCE at peak (p<0.0001). PO_4 was 3.3±0.6 mg/dl at baseline, transiently rose to 3.7±0.4 mg/dl at hour 6 (p=0.016), and then returned to 3.4±0.5 mg/dl at hour 12 (p=0.651). hPTH(1-34) infusion increases endogenous $1,25(OH)_2D$ and FGF23 within 18 h in healthy men. Whereas it is possible that the rise in PO_4 contributed to the observed increase in FGF23, the increase in $1,25(OH)_2D$ was more substantial and longer sustained than the change in serum phosphate.

10.4.288 Long-term follow-up of testicular cancer patients shows no predisposition to osteoporosis

Murugaesu N, Powles T, Bestwick J, Oliver RT, Shamash J
Osteoporos Int 2009;20:1627-30

This was a single-centre cross-sectional study, where BMD measurements were performed in male patients who were previously treated for testicular cancer. Neither orchidectomy alone nor orchidectomy and chemotherapy together predisposed to osteoporosis [p-value=0.4 (95%CI -0.1-0.8) and p-value=0.2 (95%CI -0.2-0.7), respectively]. Analysis also showed no evidence of an association between cases of osteopenia and length of follow-up (assessed by logistic regression).

10.4.289 Denosumab in men receiving androgen-deprivation therapy for prostate cancer

Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C
N Engl J Med 2009;361:745-55

In this double-blind, multicenter study, patients received denosumab 60 mg subcutaneously 6 months or placebo (734 patients in each group). At 24 months, Denosumab reduced new vertebral fractures at 36 months (1.5%, vs. 3.9% placebo) (RR, 0.38; 0.19 to 0.78;P=0.006). Spine BMD increased by 5.6% with denosumab and decreased 1.0% with placebo (P<0.001). Denosumab increased BMD at the total hip, femoral neck, and distal third of the radius.

10.4.290 Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma

Satoh T, Kimura M, Matsumoto K, Tabata K, Okusa H, Bessho H, Iwamura M, Ishiyama H, Hayakawa K, Baba S
Cancer 2009;115:3468-74

Androgen-deprivation therapy (ADT) decreases BMD and increases fracture risk in patients with prostate carcinoma. Forty men received zoledronic acid (4 mg intravenously on Day 1) or no infusion during ADT. At 6 months, mean (±standard error) BMD spine decreased 4.6%±1.0% in controls and increased 5.1%±1.2% in patients receiving zoledronic acid (P=0.0002). At 12 months, the change in BMD between the 2 groups was significantly different at the spine (P=0.0004), indicating that zoledronate preserved BMD. For u-NTX, bone turnover decreased in the zoledronate group (P<0.0001), but returned to pretreatment levels at 12 months in the zoledronate group. Bone loss begins at 6 months with ADT. A single infusion of zoledronic acid in patients receiving ADT reduces bone mineral loss and maintains BMD at least at 12 months during ADT.

10.4.291 Increased RANK ligand in bone marrow of orchiectomized rats and prevention of their bone loss by the RANK ligand inhibitor osteoprotegerin

Li X, Ominsky MS, Stolina M, Warmington KS, Geng Z, Niu QT, Asuncion FJ, Tan HL, Grisanti M, Dwyer D, Adamu S, Ke HZ, Simonet WS, Kostenuik PJ
Bone 2009;45:669-76

Orchiectomized (ORX) rats had serum testosterone decline by >95% with no changes in serum RANKL. In contrast, RANKL in bone marrow plasma and bone marrow cell extracts was increased (by approximately 100%) 1 and 2 weeks after ORX. Regression analyses of ORX and sham controls revealed an inverse correlation between testosterone and RANKL levels measured in marrow cell extracts (R=–0.58), while marrow plasma RANKL correlated positively with marrow plasma TRACP-5b, an osteoclast marker (R=0.63). The effects of RANKL inhibition were then studied by treating ORX rats for 6 weeks with OPG-Fc (10 mg/kg, twice/week SC) or with PBS, immediately after surgery. Sham controls were treated with PBS. Vehicle-treated ORX rats showed deficits in BMD of the femur/tibia and lower trabecular bone volume in the distal femur (p<0.05 vs. sham). OPG-Fc treatment increased femur/tibia BMD and trabecular bone volume to levels that exceeded values for ORX or sham controls. OPG-Fc reduced trabecular osteoclast surfaces in ORX rats by 99%, and OPG-Fc also prevented ORX-related increases in endocortical eroded surface and ORX-related reductions in periosteal bone formation rate. µCT of lumbar vertebrae from OPG-Fc-treated ORX rats demonstrated greater cortical and trabecular bone volume and density vs. ORX-vehicle controls. In summary, ORX rats exhibited increased RANKL protein in bone marrow plasma and in bone marrow cells, with no changes in serum RANKL.

10.4.292 Orchiectomy upregulates free soluble RANKL in bone marrow of aged rats

Proell V, Xu H, Schuler C, Weber K, Hofbauer LC, Erben RG
Bone 2009;45:677-81

The osteoprotegerin (OPG)/receptor activator of NFκB ligand (RANKL) axis upregulates bone turnover following sex steroid deficiency. Thirty-three 9-month-old male Fischer-344 rats were ORX or sham-operated (SHAM). Vehicle-treated SHAM and vehicle- or testosterone undecanoate (T, 6 mg/kg s.c. once weekly)-treated ORX rats (n=8-9 each) were killed 2 months after surgery. Vehicle-treated ORX rats showed lower seminal vesicle weight, loss of proximal tibial trabecular BMD, and reduced cortical thickness at the tibial shaft relative to SHAM. Bone loss in vehicle-treated ORX rats was associated with enhanced bone turnover. T restored seminal vesicle weight to SHAM levels, and protected against post-ORX bone loss by suppressing bone turnover. Free sRANKL in marrow supernatants from the proximal femur were about 3-fold higher in vehicle-treated ORX relative to SHAM rats, and returned to SHAM control levels in T-treated ORX rats. mRNA abundance of matrix metalloproteinase-14 (MMP-14) in marrow was 4-fold higher in vehicle-treated ORX rats relative to SHAM rats. T suppressed MMP-14 mRNA expression to SHAM control levels. Orchiectomy increases free sRANKL in marrow of aged rats. In addition, increased shedding of membrane-bound RANKL by MMP-14 may be a pivotal mechanism resulting in augmented free sRANKL in the marrow after androgen withdrawal.

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J Bone Miner Res 2009;24:975-9

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Bone 2009;45:154-7

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10.4.303 Regulation of osteogenesis-angiogenesis coupling by HIFs and VEGF
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10.4.304 CXCL12/CXCR4 axis in tissue targeting and bone destruction in cancer and multiple myeloma
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J Bone Miner Res 2009;24:1147-9

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10.4.305 Is bone quality associated with collagen age?
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Am J Med Sci 2009;338:34-9

10.4.310 Vitamin D deficiency and risk for cardiovascular disease
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10.4.311 Clinical value of monitoring BMD in patients treated with bisphosphonates for osteoporosis
Watts NB, Lewiecki EM, Bonnick SL, Laster AJ, Binkley N, Blank RD, Geusens PP, Miller PD, Petak SM, Recker RR, Saag KG, Schousboe J, Siris ES, Bilezikian JP
J Bone Miner Res 2009;24:1643-6

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Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e1-8

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Blake GM, Compston JE, Fogelman I
J Bone Miner Res 2009;24:1354-7

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Osteoporos Int 2009;20:1101-6

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Campaign Description

Campaign Vision

The IOF Invest in Your Bones campaign vision is of a world without osteoporotic fractures through increasing awareness and understanding of osteoporosis. The emphasis is also on improving quality of life and on the healthcare budget. In addition, the Invest in Your Bones campaign aims to sensitise health professionals, including general practitioners, radiologists and orthopaedic surgeons.

About the Campaign

In 2002, IOF inaugurated the first phase of the Invest in Your Bones Campaign. The campaign, now in its fourth phase (beginning in 2008), supports projects aimed at improving access to, and reimbursement of, diagnosis and proven therapies in individuals at high risk of fragility fracture. It has a geographic focus on France, Germany, Italy, Spain and the UK.

The campaign also helps the IOF to support the 'Call for Action' at the EU, through various policy and lobbying activities, including support to the European Parliament Osteoporosis Interest Group and EU Osteoporosis Consultation Panel.

Other key ongoing projects supported by the campaign include the Osteoporosis Education Program to Improve the Recognition and Reporting of Vertebral Fractures by Radiologists; an initiative involving orthopaedic surgeons aimed at optimizing the care of fragility fracture patients; the development of health economics studies in osteoporosis; and support to the development of new guidelines for assessing fracture risk in individuals.