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

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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 9, Issue 1, 2008

Best of 2007

- Introduction
- Paper of the year
- Therapeutics

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- Campaign vision
- About the campaign

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Volume 8, Issue 4 was the last print issue of *Progress in Osteoporosis*. I started this service 14 years ago, in October 1993, based on an idea from Pierre Delmas, the President of International Osteoporosis Foundation (IOF), a colleague and my dearest friend for 27 years. The journal was called *Advances in Osteoporosis* and was supported by a grant from MSD until 1999. The journal known as *Advances in Osteoporosis* did not end because advancement in the field ended, the name had to change because of a copyright issue. The journal continued as *Progress in Osteoporosis* during the last 8 years but now this ends but not because progress in the field has ceased. But the times they are indeed changing.

Just as we no longer write on tablets of stone or paint images of our daily lives on cave walls, we are coming to the end of the world of paper, apart from paper tigers who roam the corridors in search of place. Ends are beginnings and we live in a world that is more virtual than palpable and perhaps more dangerously fast as the position of an electron is never quite known.

Progress in Osteoporosis is not disappearing, we are not at the end of Progress but its letters are leaving paper to be beamed and reassemble as electrons appearing at your will with the touch of a button. This is the way of things, the world literature is instantaneously accessible in a park on a Sunday afternoon, in an airport terminal, in the bathtub, on your terrace, or during a boring meeting where you can pretend to take notes. The journal will provide you with information but you have to turn it into knowledge and turn knowledge into understanding.

The purpose of the web based journal is no different to its paper mate. All the important work in the field of osteoporosis will be served to you on a platter but the summary should not be cited. The purpose of the abstracts is not to be comprehensive but rather to provide the main message, and when appropriate I will highlight the work in the Overview. These summaries should only be used to direct your interest to the original work. They are not peer reviewed and some may contain errors of omission or commission. So please, refer to the original work. The inferences I make are my own, they do not necessarily reflect the opinion of the IOF. The second purpose is to include, when possible, the main graphical presentations from papers so that the reader has this available to make slides.

I thank Springer, in particular Christiane Notarmarco, the publisher in the UK for the hard work, their support, patience and willingness to please over the years. I have enjoyed working with Christiane and hope to continue to do so in the future. I thank GlaxoSmithKline and Roche for their financial support for paper edition of *Progress in Osteoporosis* that now ends, especially for their sensitivity to the essential requirement of complete editorial freedom at all times. I thank IOF for making all this possible in the last 14 years and now for their continuing trust in me to lead this new initiative. I look forward to this project with great excitement, optimism and energy.

None of this would have been possible or would have occurred without the fire and volcanic energy and determination of Pierre Delmas and I thank him for his initiative in 1993 and his commitment to ensuring the journal continues through a grant from the IOF Invest In Your Bones Campaign, for which I also thank for its goodwill and support of the field.

The journal now continues as a self-publishing part of IOF under the leadership of Fina Liu, the managing scientific editor. I have worked with Fina for some time now and her quiet efficiency, energy, speed and commitment to the production of *Osteoporosis International* is well known to all of the editorial staff in Europe who have worked with her; and it is a pleasure and privilege to be able to now work closely with Fina to make this venture a great success. I will do my best to fulfil the responsibility that comes with this task. Welcome to Volume 9, Issue 1, beginning with summaries of the best of the best from 2007.

Ego Seeman
Editor
March 5, 2008

Progress in
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The fine things we shall write if we have talent enough, are within us, dimly, like the remembrance of a tune which charms us though we cannot recall its outline, or hum it, nor even sketch its metrical form, say if there are pauses in it or runs of rapid notes.

Those who are haunted by this confused remembrance of truths they have never known are the men who are gifted; but if they never go beyond saying that they can hear a ravishing tune, they convey nothing to others, they are without talent.

Talent is like a kind of memory, which in the end enables them to call back this confused music, to hear it distinctly, to write it down, to reproduce it, to sing it.

There comes a time in life when talent, like memory, fails, and the muscle in the mind which brings inward memories before one like memories of the outer world, loses its power.

Sometimes, from lack of exercise or because of a too ready self-approval, this time of life extends over a whole lifetime, and no one, not your own self even, will ever know the tune that beset you with its intangible delightful rhythm.

Marcel Proust
On Art and Literature
Carroll and Graf publishers NY
Ontra Saint-beuve p 276

Paper of the year (2007)

Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. **Cell 2007;130:456-69**

Mice deficient in the osteoblast specific protein kinase OST-PTP have hyperinsulinemia, hypoglycemia and increased sensitivity to insulin. Bone regulates pancreatic ß-cells and insulin target tissues. Osteocalcin (-/-) mice have an opposite phenotype. Removing one osteocalcin allele corrects the OST-PTP phenotype. Administration of osteocalcin improves glucose tolerance in vivo. Uncarboxylated osteocalcin is a hormone that regulates energy metabolism. How this is achieved, whether direct or otherwise awaits more research from the genius of Gerard Karsenty.

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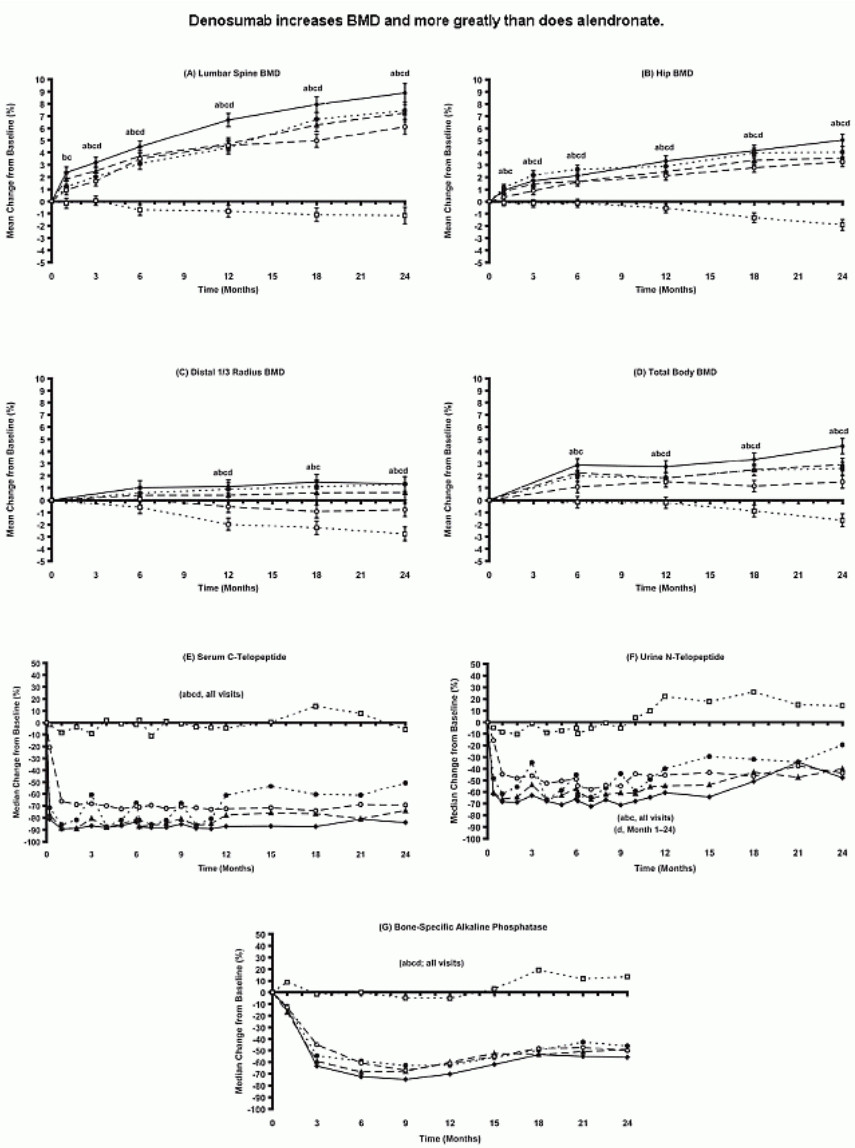
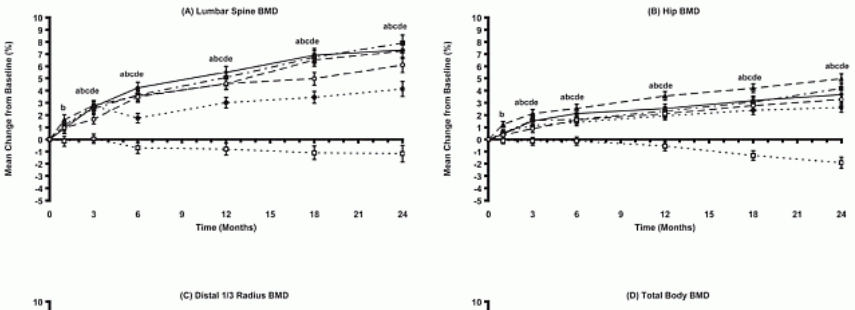
Therapeutics

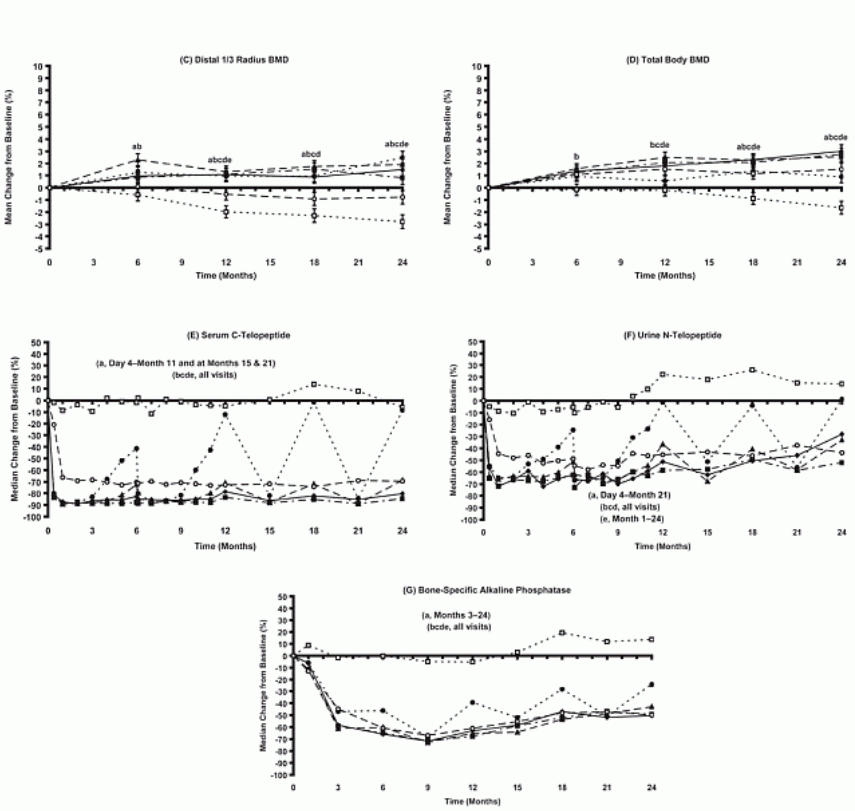
Denosumab – a different approach to remodeling suppression

Several important advances in therapeutics were published in 2007. **Lewiecki et al** reported that Denosumab, a monoclonal antibody to RANKL, reduced bone remodeling and increased BMD in women with postmenopausal osteoporosis (**J Bone Miner Res 2007;22:1832-41**). Is this anti-resorptive agent different to others? Yes, it certainly is – in several respects. First, the drug reversibly reduces remodeling so that it is possible to regulate the degree of suppression of remodeling in an individual by altering the dose and frequency of administration. Whether this is important is not clear, but prolonged suppression of bone remodeling may have deleterious effects on bone because remodeling is important in damage removal and repair.



Comparison of percentage change in BMD and laboratory parameters with denosumab 3-mo regimens, alendronate, and placebo (□, placebo; ●, denosumab 6 mg; ▲, denosumab 14 mg; ♦, denosumab 30 mg; ○, alendronate 70 mg weekly). Between-group differences at $p < 0.05$ were observed based on ANCOVA model adjusting for treatment group, geographical location, and baseline value as follows: [a]denosumab 6 mg vs. placebo; [b]denosumab 14 mg vs. placebo; [c]denosumab 30 mg vs. placebo; [d]alendronate vs. placebo. Error bars denote SE. Reproduced from J Bone Miner Res 2007;22:1832-41 with permission of the American Society for Bone and Mineral Research.





Comparison of percentage change in BMD and laboratory parameters with denosumab 6-mo regimens, alendronate, and placebo (□, placebo; •, denosumab 14 mg; ▲, denosumab 60 mg; ♦, denosumab 100 mg; ■, denosumab 210 mg; ○, alendronate 70 mg weekly). Between-group differences at $p < 0.05$ were observed based on ANCOVA model adjusting for treatment group, geographical location, and baseline value as follows: [a]denosumab 14 mg vs. placebo; [b]denosumab 60 mg vs. placebo; [c]denosumab 100 mg vs. placebo; [d]denosumab 210 mg vs. placebo; [e]alendronate vs. placebo. Error bars denote SE. Reproduced from J Bone Miner Res 2007;22:1832-41 with permission of the American Society for Bone and Mineral Research.

The drug appears to increase BMD at cortical sites while other anti-resorptive do less so, or not at all. This may not be a trivial difference. It is difficult to transcend the era we grow up in, with its historical context and 'facts'. We have grown up in the era of trabecular bone and vertebral fractures as the flagships of osteoporosis. Osteoporosis was hardly thought of before Albright noted fractures in postmenopausal women in around 1941.

After that, research launched forwards at a breathtaking pace as a few investigators took up the struggle about 30 years later to focus on trabecular bone because it is the vertebral body that fractures and this structure contains substantial amounts of trabecular bone. Trabecular bone has a large surface to volume ratio. As remodeling requires a surface to occur upon, trabecular bone is 'turned over' more rapidly than cortical bone and is lost more rapidly as each remodeling event executed by the cells of the basic multicellular unit (BMU) remove more bone than they put back. Trabecular bone loss was found to proceed more rapidly than cortical bone loss and deficits in BMD in women with vertebral fractures were greater at the spine and appendicular sites and so, osteoporosis, bone fragility, trabecular bone, vertebral fractures became the fashionable talk of the town and remain so to this day.

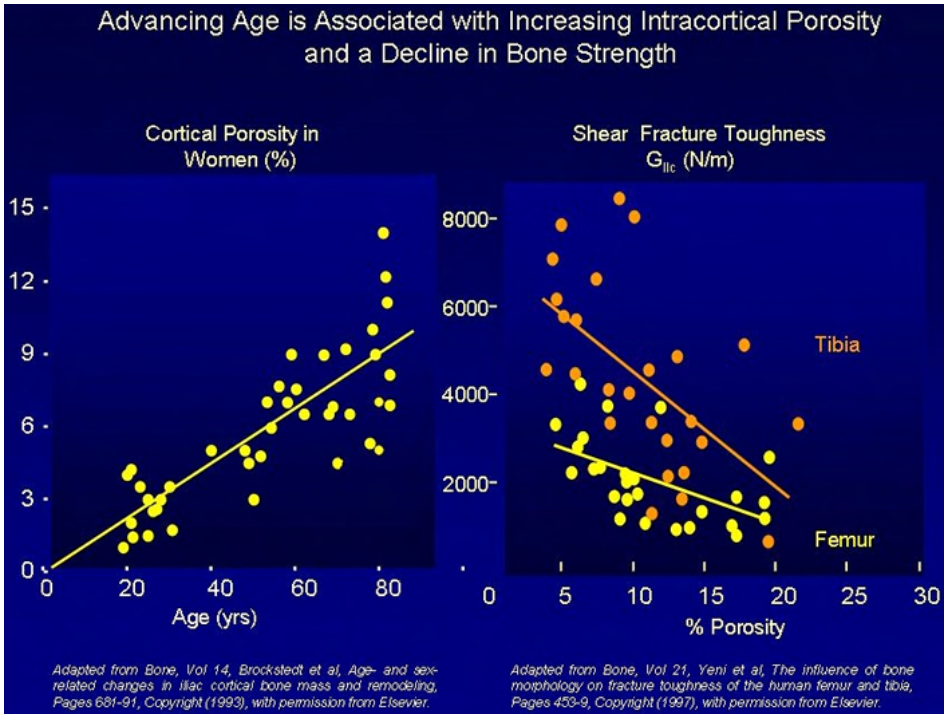
The times, they are a chang'n

Trabecular bone loss is important. Trabecular thinning reduces bone strength and loss of connectivity reduces it even more. But about 80% of the skeleton is cortical, only 20% is trabecular, and 80% of all fractures in the community are non-vertebral, not vertebral. So, have we been looking in the wrong place? I think so.

An important determinant of cortical strength – its resistance to crack propagation – is the osteonal density. The greater the number of osteons, the greater the resistance to crack propagation in interstitial bone between the osteons because cracks must navigate around the osteons with their lamellar structure and the cement line delineating each osteon.

With increased remodeling and a negative BMU balance, cortical porosity increases and is seem in cross section as pores – voids – but in fact these are the enlarged haversian canals in longitudinal section, often intersecting and replacing the mineralized bone with islands of nothing – fluid or marrow filled void space – the 'porosis' of osteoporosis.

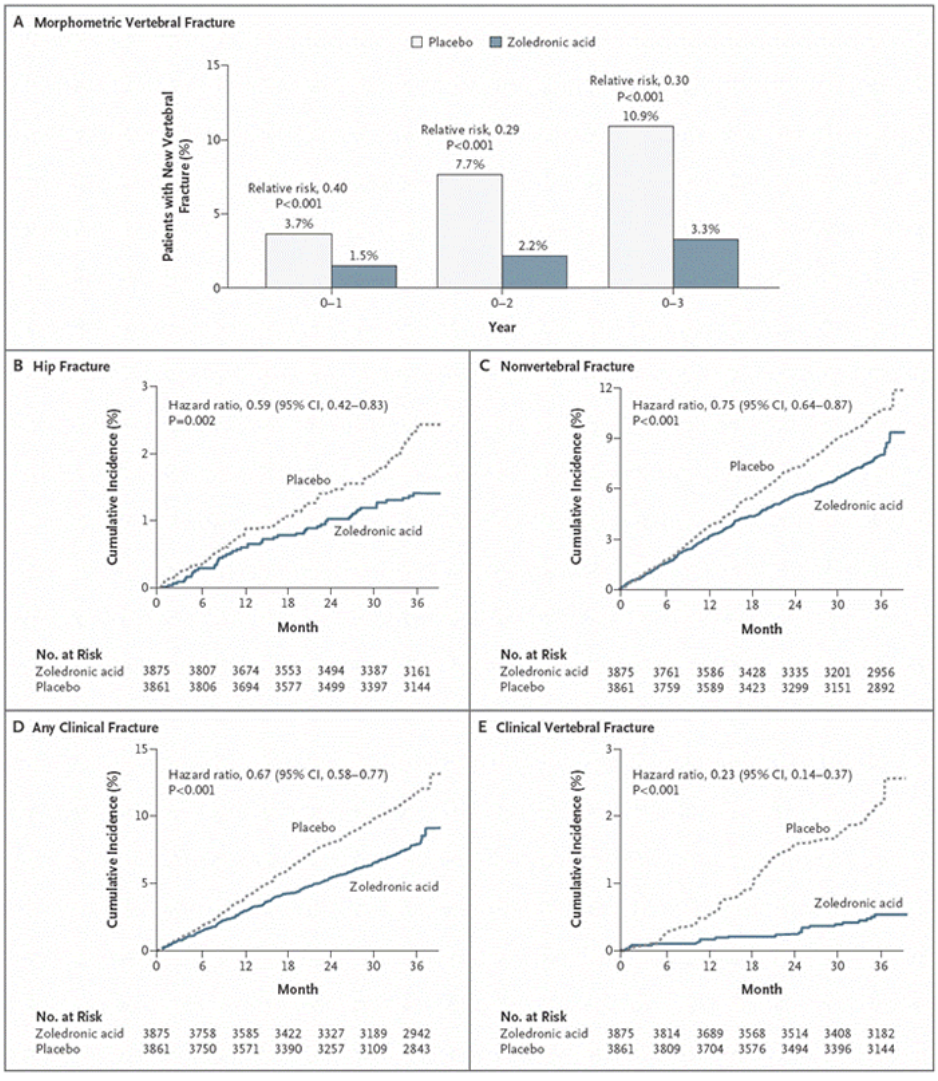
Concurrently, high remodeling on the endocortical surface thins the cortex and increases surface area of the endocortical surface as resorption tunnels burrow into the bone beneath the endocortical envelope the cortex so it starts to look like in intestinal villous projections. The combined effects of intracortical and endocortical remodelling trabecularize the cortex which is nolonger 'compact' bone, it is Swiss cheese.



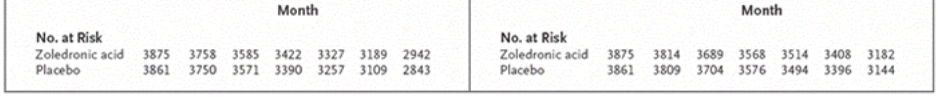
The notion that bone has a 'cortex' in old age is something of a delusion, there is no cortical 'thickness', there is just a porous structure. Cracks can move like the tip of the Titanic through the frozen waters of the Atlantic ocean with little resistance. With structural decay of such severity, how can drugs reverse fragility? It is little wonder that the reduction in non-vertebral fractures is only around 20%, much less than the 50% reduction found with vertebral fractures. Neither of these measures of anti-fracture efficacy are particularly satisfactory are they. So, back to denosumab – will this drug reduce non-vertebral fractures more greatly than currently reported using other agents – we will know soon.

One of the best designed and executed trials in the field was reported by **Black et al** who studied the effects of zolendronic acid in a double-blind, placebo-controlled trial of 3889 patients assigned to 5 mg annually and 3876 assigned to placebo (**N Engl J Med 2007;356:1809-22**). At 3 years, treatment reduced the risk of morphometric vertebral fracture by 70%, hip fracture by 41%, non-vertebral fractures by 25%, clinical and clinical vertebral fractures by 33% and 77%, respectively. The results are impressive and the appeal with this drug is the need for only once a year treatment. This is user friendly, provided that patients are not lost to follow-up. There needs to be a way of ensuring follow-up occurs; not too great a challenge.

Zolendronic Acid and Fracture Risk Reduction



Black et al, Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis, N Engl J Med 2007;356:1809-22



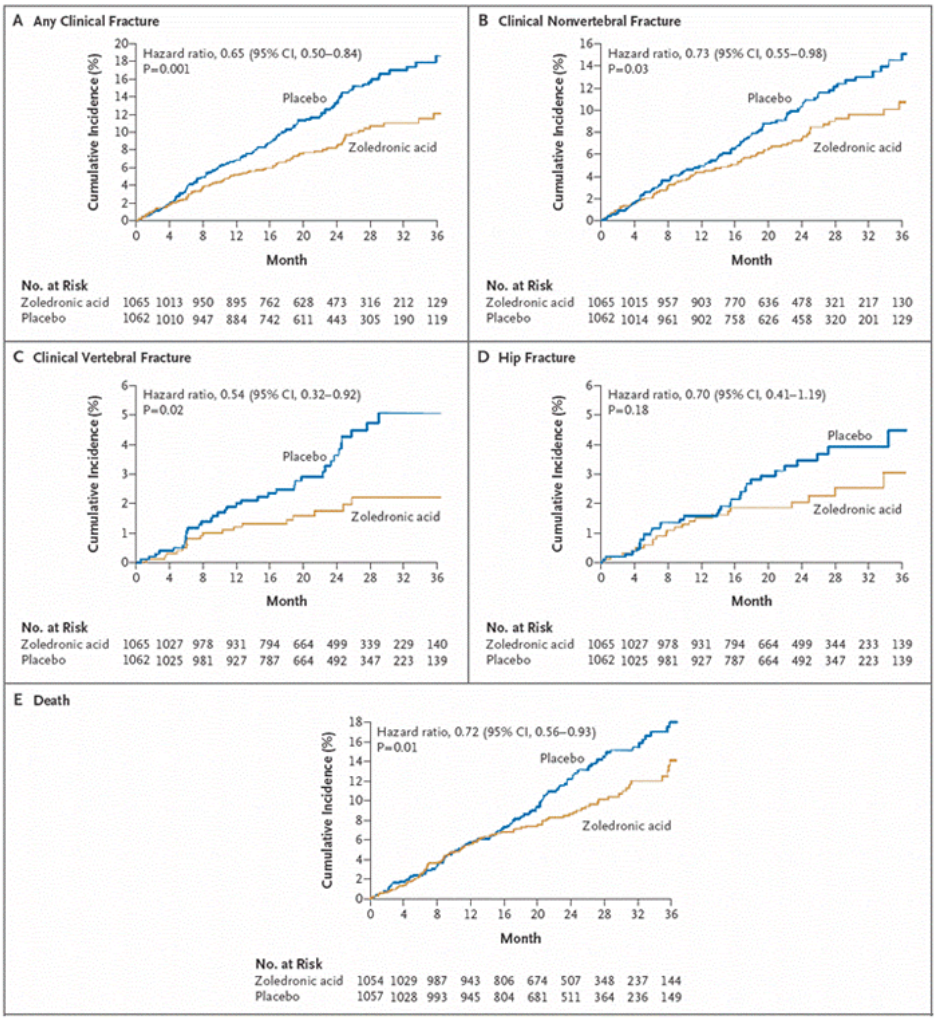
Black et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.

Atrial fibrillation (AF) occurred more frequently in the treated group (in 50 vs. 20 patients) but this has not been reported in other large trials using this agent. **Karam et al** re-analyzed the incidence of AF, cerebrovascular accidents and cardiovascular death recorded in randomized controlled trials with risedronate. Including more than 15,000 patients in total, no increase in AF were found with risedronate, but rather a decrease of cerebrovascular accidents. **N Engl J Med 2007;357:712-3; author reply 714-5**

Non-vertebral and hip fracture risk reduction were each assessed by pooling strata 1 and 2 (taking other anti-osteoporosis therapy as well). It would be of interest to see the results analyzed in each stratum. It is not clear whether the non-vertebral fracture risk reduction included hip fractures; if so, a separate analysis of non-hip non-vertebral fractures would be of interest. Another question is whether long-term suppression of remodeling may produce deleterious effects on the skeleton. The question of osteonecrosis of the jaw is best left for dentists to exaggerate.

Lyles et al report the results of the HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. Annual injections of zoledronate vs. placebo on fracture prevention in patients within 3 months after a hip fracture. Significant reduction of clinical vertebral and non-vertebral fractures was demonstrated, not hip fractures. This study shows a reduction of overall mortality in patients treated with a bisphosphonate, but whether the reduction in mortality is due to treatment is not clear. **N Engl J Med 2007;357:1799-809**

Zolendronic Acid and Fracture Rates After Hip Fractures

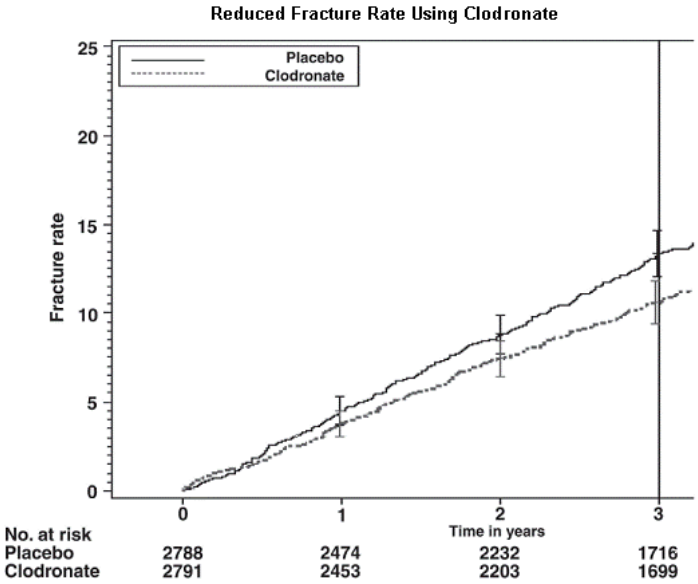


Lyles et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799-809.

Amanat et al report that in rats, the distribution of zoledronic acid at the fracture repair site (callus) is shown, together with an increase in strength after a single injection. **J Bone Miner Res 2007;22:867-76**

Clodronate reduces the incidence of fractures in a community

McCloskey et al report that of 5579 women ≥75 years of age recruited to a randomized, double-blind, controlled trial of 800 mg oral clodronate (Bonefos) or matching placebo daily over 3 years, 114 had a hip fracture: 56 (2.0%) women in the clodronate group and 58 (2.1%) women in placebo. Clodronate decreased the incidence of any clinical fracture by 20% (9.5% vs. 12.1% placebo). The incidence of osteoporosis-associated non-hip fractures was also decreased by 29% (5.2% vs. 7.4%). **J Bone Miner Res 2007;22:135-41**



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Vitamin D and calcium – elixirs of youth or fashion?

Love is a many splendid thing and it is in the air with vitamin D. Vitamin D seems to promise immortality, the solution to all ills with strong statements being made regarding benefits for many skeletal and non-skeletal illnesses. It reminds me of the faith expressed in the universal benefit of blood letting. This almost messianic approach is worrying particularly as it is often based on observational studies that are hypothesis generating rather than hypothesis testing. Many issues remain regarding the net health benefits and risk of sunlight exposure (**Moan et al, Proc Natl Acad Sci 2008;105:668-72**) and purported benefits of vitamin D.

Martins et al report that among 7186 male and 7902 female adults, mean 25(OH)D levels were lower in women, elderly persons, racial minorities, and participants with obesity, hypertension, and diabetes mellitus. The adjusted prevalence of hypertension (odds ratio [OR], 1.30), diabetes mellitus (1.98), obesity (2.29), and high serum triglyceride levels (1.47) was higher in the first than in the fourth quartile of serum 25(OH)D (P<0.001 for all). From these observations the authors infer that serum 25(OH) D levels are associated with cardiovascular disease risk factors in U.S. adults. **Arch Intern Med 2007;167:1159-65**

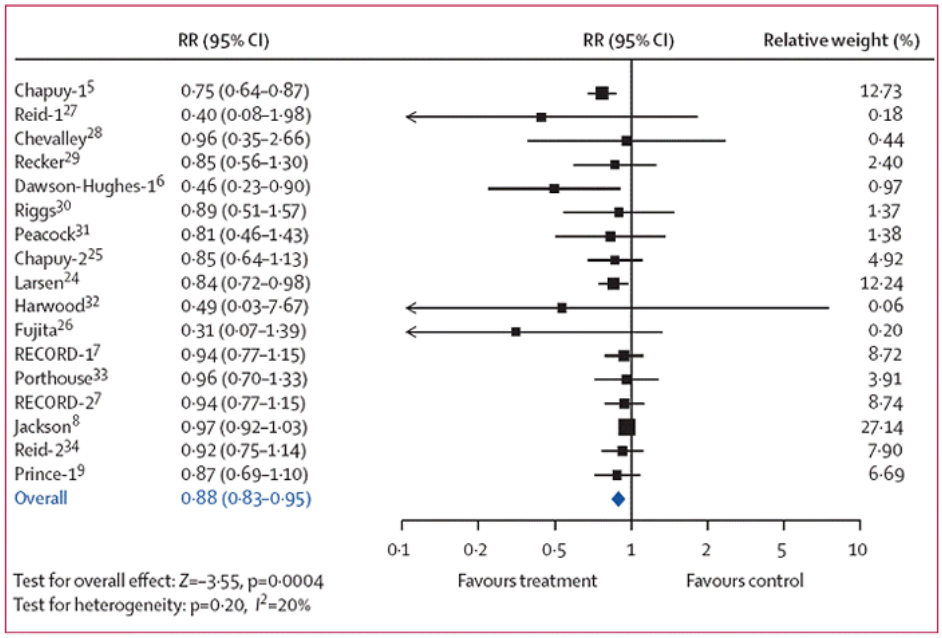
Lappe et al conducted a 4-year double-blind, randomized placebo-controlled trial of 1179 community-dwelling women randomly assigned to Ca, Ca+D or placebo. By intention-to-treat, cancer incidence was lower in the Ca+D than in controls. The unadjusted RR of incident cancer in the Ca+D and Ca-only groups were 0.40 and 0.53, respectively. When analysis was confined to cancers diagnosed after the first 12 months, RR for the Ca+D group was 0.23, both treatment and serum 25(OH)D were independent predictors of cancer risk. The authors infer that improving calcium and vitamin D nutritional status reduces all cancer risk in postmenopausal women. **Am J Clin Nutr 2007;85:1586-91**

Lin et al report that among 10,578 premenopausal and 20,909 postmenopausal women 45 years or older in the Women's Health Study, during 10 years, 276 premenopausal and 743 postmenopausal women had incident invasive breast cancer. Higher intakes of calcium and vitamin D were associated with a lower risk of breast cancer in premenopausal women; HR for highest to the lowest quintile of intake were 0.61 for calcium (P=0.04 for trend) and 0.65 for vitamin D intake (P=0.07 for trend). The inverse association with both nutrients was also present for large or poorly differentiated breast tumors among premenopausal women. By contrast, intakes of both nutrients were not inversely associated with the risk of breast cancer among postmenopausal women. **Arch Intern Med 2007;167:1050-9**

Autier et al report in 18 randomized controlled trials (n=57,311) 4777 deaths from any cause occurred during 5.7 years. The trial size-adjusted mean daily vitamin D dose was 528 IU. In nine trials, there was a 1.4- to 5.2-fold difference in serum 25(OH)D between the intervention and control groups. The relative risk for mortality from any cause was 0.93 (95% CI 0.87-0.99). Intake of ordinary doses of vitamin D was inferred to be associated with decreases in total mortality rates. **Arch Intern Med 2007;167:1730-7**

Tang et al report that in 29 randomized trials (n=63,897), 17 had fracture outcomes (n=52,625). Treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004) and in 23 trials (n=41,419), treatment was associated with a reduced bone loss of 0.54% (0.35-0.73; p<0.0001) at the hip and 1.19% (0.76-1.61%; p<0.0001) in the spine. Fracture risk reduction was greater (24%) in trials in which the compliance rate was high (p<0.0001). The treatment effect was better with calcium 1200 mg or more than less than 1200 mg (0.80 vs. 0.94; p=0.006), and with vitamin D doses of 800 IU or more than with doses less than 800 IU (0.84 vs. 0.87; p=0.03). Evidence supports the use of calcium, or calcium + vitamin D in the prevention of osteoporosis in people aged 50 years or older. **Lancet 2007;370:657-66**

Effect of Calcium and Calcium in Combination with Vitamin D on Fracture Risk



Reprinted from The Lancet, Vol. 370, Tang et al, Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis, Pages 657-66, Copyright (2007), with permission from Elsevier.

Lyons et al report a double blind 3-year randomized controlled trial in 2,624 women and 816 men in residential or homecare received four-monthly oral 100,000 IU vitamin D2 (ergocalciferol) or no treatment in 314 care homes or sheltered accommodation. In intent-to-treat, 205 (intervention) vs. 218 fractures in controls. HR=0.95 (95% CI 0.79-1.15) was not significant. **Osteoporos Int 2007;18: 811-818**

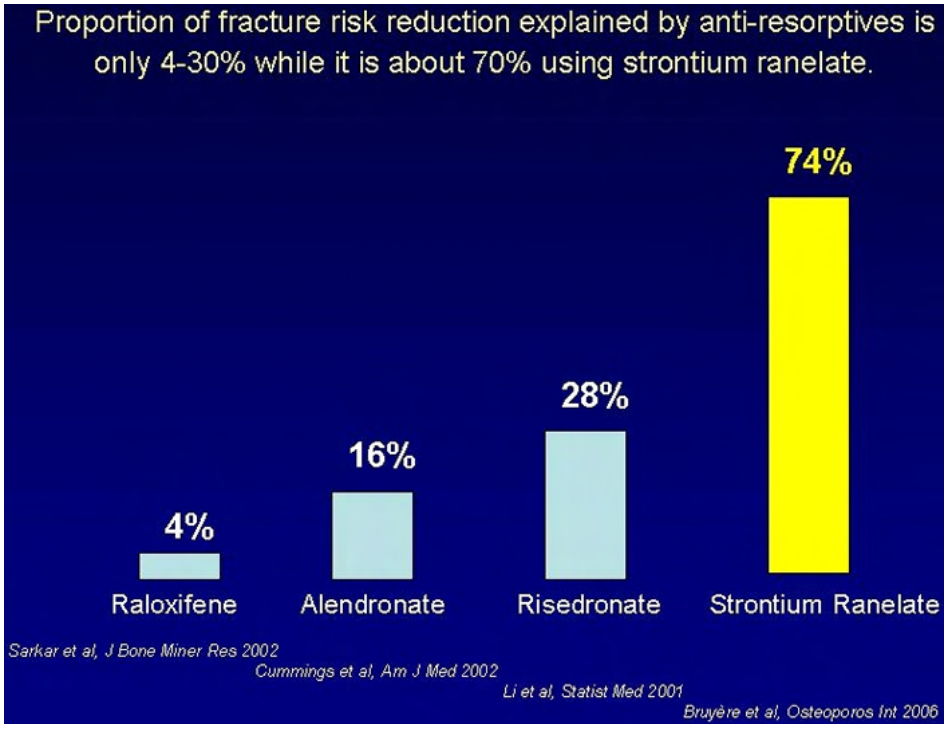
Nieves et al report the impact of calcium and vitamin D intake on BMD and fracture incidence was in 76,507 postmenopausal Caucasian women completing a dietary questionnaire including childhood, adult, and current consumption of dairy products. BMD was measured at the forearm, finger or heel. About 3 years later, 36,209 participants returned a questionnaire about new fractures. Higher lifetime calcium intake was associated with reduced odds of osteoporosis (peripheral BMD T-score ≤-2.5; OR=0.80; 95% CI 0.72,0.88), as was a higher current calcium (OR=0.75; 95% CI 0.68, 0.82) or vitamin D intake (OR=0.73; 95% CI 0.66, 0.81). Women reported 2,205 new fragility fractures. The 3-year risk of any fracture combined or separately was not associated with intake of calcium or vitamin D. **Osteoporos Int 2007;Nov 13[Epub ahead of print]**

Although published this year I can't resist including this study by **Reid et al (Osteoporos Int 2008; Feb 20[Epub ahead of print])** which reports that meta-analysis of the effect of calcium on hip fracture involving 5,500 suggest adverse trends in numbers of hip fractures (RR=1.50, 95% CI 1.06-2.12). Now that's interesting but is it right? The pendulum will always swing widely to the left or right when trials poorly designed and executed. All papers have an inference irrespective of the flaws such as including subjects replete in calcium, subjects poorly compliant with treatment, large numbers of drops, and other issues. Meta-analyses impress editors because they have large numbers but nothing can save a poorly executed study, certainly not more poorly executed studies. In another study from this group, vascular events appear to occur more commonly in patients randomized to calcium supplementation (**Bolland et al, BMJ 2008;336:262-6**). This will be reviewed in the next issue of Progress in Osteoporosis.

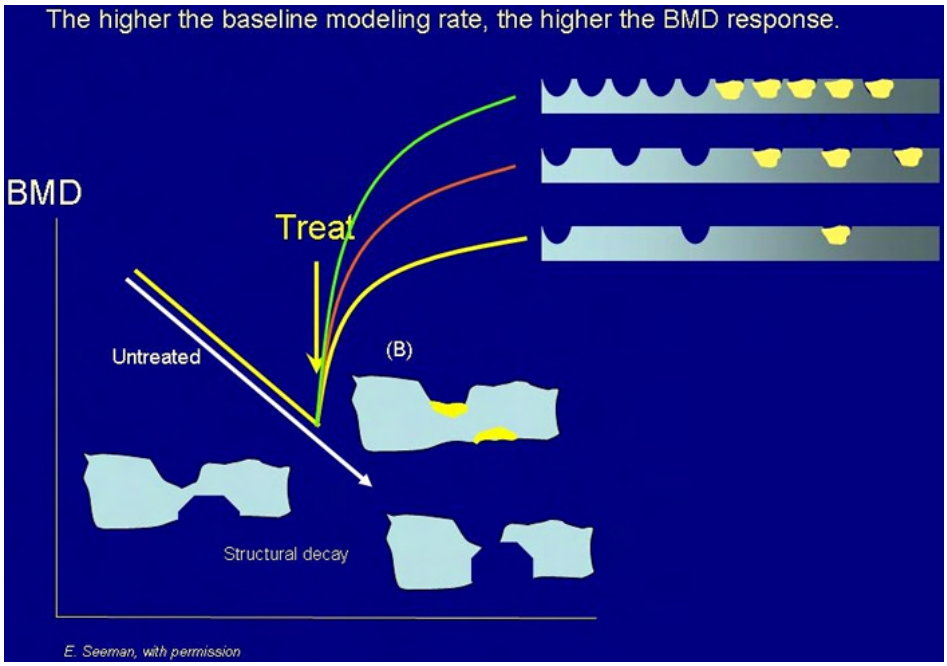
Strontium ranelate and BMD

Strontium ranelate is an interesting new drug reported convincingly to reduce the risk of vertebral and non-vertebral fractures by intention-to-treat analysis, and hip fractures in post hoc analyses. **Bruyere et al** report that in women receiving strontium ranelate, after 3 years, changes in femoral neck and total proximal femur BMD explained 76% and 74% of the reduction in vertebral fractures, respectively, but not non-vertebral fractures; and 3-year changes in spine BMD were not associated with vertebral fracture. **J Clin Endoc Metab 2007;92:3076-81**

This data differs from the predictive value of a change in BMD as a surrogate of anti-fracture efficacy for anti-resorptive agents; no more the 4-30% of the risk reduction is explained by the increase in BMD following treatment using anti-resorptives such as bisphosphonates, SERMS or estrogen.

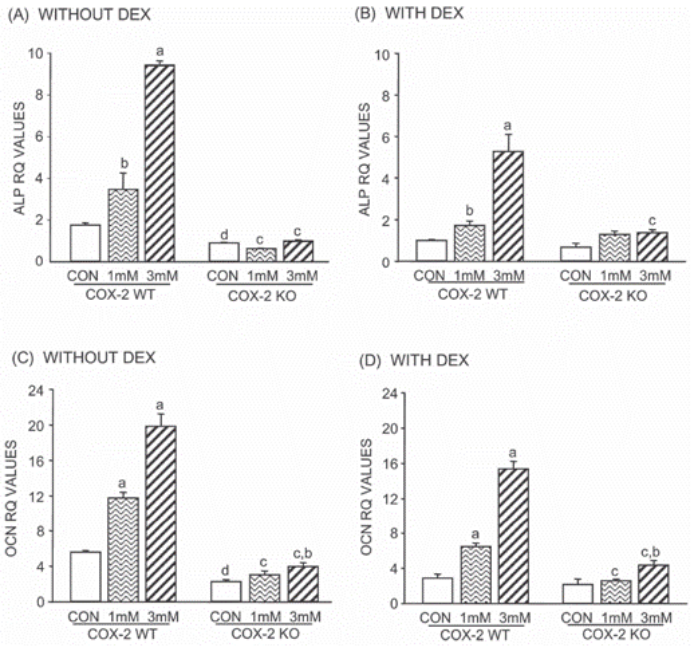


The reasons for the lack of predictive value with anti-resorptives is multifactorial but in large part relates to the dependence of the increase in BMD on the rate of remodeling prior to starting treatment. The greater the baseline remodeling, the greater the increase in BMD. Patients with high baseline remodeling have a greater increase in BMD than those with low baseline remodeling even though they are given the same drug and same dose of drug.



The incorporation of strontium into the hydroxyapatite may be a marker of compliance or may contribute to the anti-fracture efficacy. It remains uncertain as to whether patients who do not have a rise in BMD with strontium ranelate also have a fracture risk reduction so the sensitivity and specificity of the change in BMD in predicting fracture risk remains to be established.

The mechanism of action of this drug remains uncertain. One of the best studies published so far is that by **Choudhary et al (J Bone Miner Res 2007;22:1002-10)**. Marrow stromal cells from wild type and COX-2 knockout mice were cultured. In cells from wild type mice, strontium increased ALP activity, ALP and OCN mRNA expression, and mineralization. Strontium increased PGE (2) production. NS-398, a selective COX-2 inhibitor, blocked the strontium stimulation of PGE(2) and inhibited stimulation of ALP activity. In cells from COX-2 knockout mice, the stimulation of ALP and OCN mRNA expression and mineralization were reduced. PGE(2) produced by the strontium ranelate induction of COX-2 expression plays a role in strontium ranelate-induced osteoblastic differentiation in mesenchymal stem cells in vitro.



Effect of COX-2 gene disruption on strontium ranelate (1 and 3 mM Sr+2)-induced markers of differentiation. (A) Realtime PCR for ALP mRNA expression at 14 days without DEX (10 nM) and (B) with DEX. (C) Real-time PCR for OCN mRNA expression at 21 days without DEX and (D) with DEX. Each bar is the mean ± SE of n=3 samples. Significant effect of strontium ranelate, $^{a}p < 0.01$; $^{b}p < 0.05$. Significant effect of genotype, $^{c}p < 0.01$; $^{d}p < 0.05$. Reproduced from J Bone Miner Res 2007;22:1002-10 with permission of the American Society for Bone and Mineral Research.

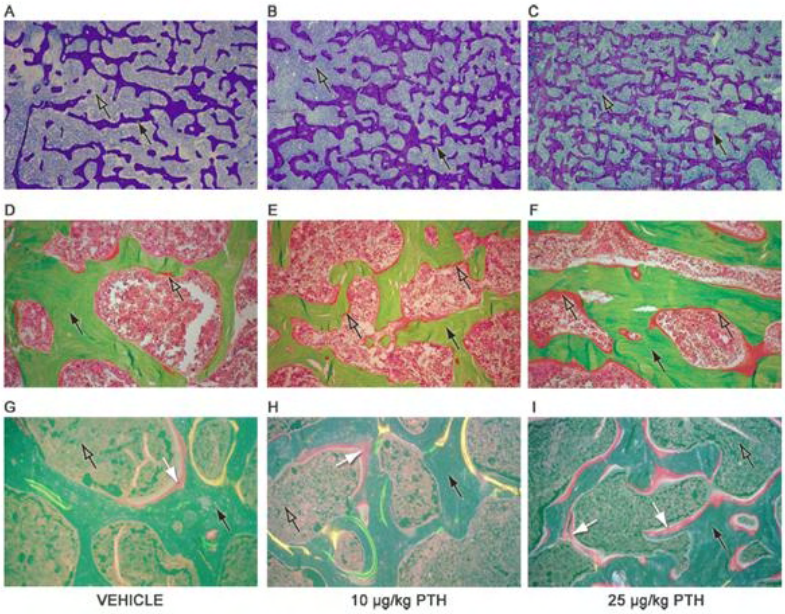
Anabolic therapy

The paper by **Linsday et al** is the first to report periosteal apposition in human subjects produced by PTH treatment, and the likelihood that the increased bone formation on the endocortical and trabecular surfaces has its origins within existing remodeling sites, not from quiescent surfaces (**J Bone Miner Res 2007;22:495-502**). One-month hPTH(1-34), 50 _g daily subcutaneously increased bone formation rate on the cancellous and endocortical surfaces and on the periosteal surface. On the cancellous and endocortical surfaces, the increased bone formation rate was primarily caused by stimulation of formation in remodeling units, with a modest amount of increased formation on quiescent surfaces. hPTH(1-34)-stimulated bone formation was associated with an increase in osteoblast apoptosis.

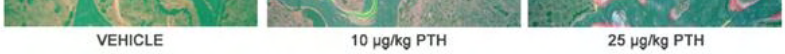
Iida-Klein et al examined the effects of cyclic PTH in mice. In the lumbar vertebrae, daily and cyclic PTH increased trabecular number, osteoclast and osteoblast perimeters, MAR and BFR, and periosteal MAR and BFR with no difference between the two groups. Both regimens increased vertebral cortical bone formation with the effects at the periosteum resulting in increases in cortical width. In the femur, the effects of cyclic PTH were less than those of daily PTH (**Bone 2007;40:391-8**). If this holds true in human subjects, then perhaps less frequent dosing might be efficacious and reduce the cost of this drug.

Kostenuik et al report that a long acting PTH-Fc fusion protein has anabolic effects on cortical and trabecular bone. PTH(1-34) was fused to the Fc fragment of human IgG1 to increase the half-life of PTH. PTH-Fc and PTH(1-34) had similar effects on PTH/PTHrP receptor activation, internalization, and signaling in vitro. PTH-Fc had a 33-fold longer mean residence time in the circulation compared with PTH(1-34). Subcutaneous PTH-Fc once or twice weekly increased bone volume, density, and strength in osteopenic ovariectomized mice and rats and produced hypercalcemia more than with high daily PTH(1-34). PTH-Fc also improved cortical bone volume and density under conditions where daily PTH(1-34) did not. Co-therapy with estrogen enhanced the ability of PTH-Fc to increase bone mass and strength in ovariectomized rats. **J Bone Miner Res 2007;22:1534-1547**

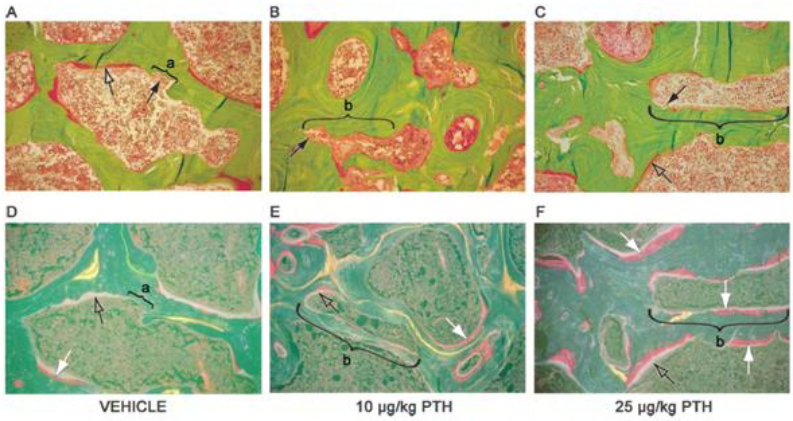
Fox et al report that 9 months after OVX of mature rhesus monkeys treated for 16 months with PTH(1-84) restored BMD to sham levels. PTH(1-84) increased trabecular bone volume (BV/TV) by increasing trabecular number, and dose-dependently increased bone formation rate (BFR). **J Bone Miner Res 2007;22:260-73**



Trabecular bone histology and bone formation at L3 of OVX rhesus monkeys treated daily with vehicle or PTH for 16 months. (A-C) Trabecular bone histology (trabecular bone, solid arrows;



Trabecular bone histology and bone formation at L3 of OVX rhesus monkeys treated daily with vehicle or PTH for 16 months. (A-C) Trabecular bone histology (trabecular bone, solid arrows; bone marrow, open arrows) in OVX monkeys receiving vehicle or PTH at 10 or 25 ug/kg/day, respectively. Note the increased trabecular bone volume with the 10 ug/kg dose and the markedly increased number of thinner trabeculae with the 25 ug/kg dose. (D-F) Bone surfaces covered with osteoid (trabecular bone, solid arrows; osteoid, open arrows) in the same groups of animals. Note increased osteoid surface but no increase in osteoid thickness in PTH-treated animals. (G-I) Fluorochrome labels depicting new bone mineralization (trabecular bone, solid arrows; bone marrow, open arrows; xylenol orange labels, white arrows) in the same groups of animals. Calcein (green), oxytetracycline (yellow), and xylenol orange (red) were given 16 months, 10 months, and 2 weeks, respectively, before death. Note the increased bone formation in PTH-treated animals and, in particular, the virtual absence of calcein and oxytetracycline labels in animals given the 25 ug/kg dose. Reproduced from J Bone Miner Res 2007;22:260-73 with permission of the American Society for Bone and Mineral Research.



Intratrabecular tunneling as a mechanism responsible for increased trabecular number at L3 of OVX rhesus monkeys treated daily with vehicle or PTH for 16 months. The images show (A-C) Goldner's-stained sections and (D-F) unstained sections viewed under UV light. Shown is (a) active trabecular remodeling and (b) intratrabecular tunneling both created by osteoclasts (solid arrows) and followed by bone-forming osteoblasts. Osteoid (open arrows) and xylenol orange labels (white arrows) show actively forming and mineralizing surfaces, respectively. Intratrabecular tunneling was observed in OVX monkeys receiving vehicle or PTH at 10 g/kg, but occurred at a much greater frequency with the 25 g/kg dose of PTH. Reproduced from J Bone Miner Res 2007;22:260-73 with permission of the American Society for Bone and Mineral Research.

Greenspan et al report the results of the effects of PTH(1-84) on fractures during 18 months in 2532 postmenopausal women. Vertebral fracture rates declined but the magnitude of the risk reduction depended on how the analysis was performed. A high incidence of hypercalciuria, hypercalcemia and nausea occurred, and many patients discontinued the trial prematurely. **Ann Intern Med 2007;146:326-39**

Turner et al studied hind limb unloaded male rats treated with recombinant human PTH(1-34). Unloading resulted in a decrease in cancellous bone volume caused by a 83% decrease in bone formation. All doses increased bone formation. The increases in bone formation were accompanied by increases in mRNA levels for type I collagen, osteocalcin, and osteonectin. PTH resulted in increases in mineral apposition rate and double-labeled perimeter. **J Bone Miner Res 2007;22:64-71**

Statins stimulate bone formation via BMP2 (**Mundy et al, Science 1999;286:1946-9**). The real question is do these agents reduce fractures. This is not known. **Bone et al** report the results of a multicenter controlled trial in postmenopausal women with mildly elevated cholesterol levels but without osteoporosis. No effects were found on either BMD nor on biochemical markers of bone turnover. **J Clin Endocrinol Metab 2007;92:4671-7**

Fluoride

Is fluoride is back? **Vestergaard et al** report the results of a meta-analysis which suggests that a daily dose of ≤20 mg fluoride equivalents was associated with a reduction in vertebral (OR=0.3, 95% CI 0.1-0.9) and non-vertebral (OR=0.5, 95% CI 0.3-0.8) fracture risk. A daily dose >20 mg fluoride had no benefit in risk reduction. More studies are needed but the question is also whether peripheral fracture rates increase with lower doses. **Osteoporos Int 2008;19:257-68**

Reid et al report that addition of monofluorophosphate to estrogen therapy in postmenopausal osteoporosis in a randomized controlled trial involving 80 women with osteoporosis. Women taking estrogen were randomized to monofluorophosphate (fluoride 20 mg/day) or placebo over 4 years. There were large increases in spine BMD. Hyperosteoidosis was present in biopsies from 5 of 7 subjects, with osteomalacia in 2 of 7. The hazards ratio for vertebral fractures was 0.20 (95% CI 0.05-1.30) and the incidence rate ratio was 0.12 (95% CI 0.06-0.23, P<0.01). The hazards ratio for non-vertebral fractures was 3.3 (0.8-12.0) (**J Clin Endocrinol Metab 2007;92:2446-52**). Is fluoride back – I don't think so.

Combined therapies – does one plus one equal less than 2?

Know what we don't is what an expert is and that is why the expert should be the most humble of all. We have no studies comparing one anti-resorptive with another, two vs. one anti-resorptive, an anti-resorptive vs. PTH, or PTH vs. PTH plus an anti-resorptive given before, during or after PTH using anti-fracture efficacy as an endpoint. Although some our learned colleagues give two anti-resorptives, choose one over another, substitute one for another, or choose PTH over an anti-resorptive, these decisions have no scientific basis. When comparisons are made, the surprise came that alendronate with PTH was not better than PTH alone at least in terms of BMD change. Even if two was better than one in increasing BMD, this is not proof of greater anti-fracture efficacy of two drugs over another.

The bisphosphonates may blunt the anabolic effect of PTH because the latter may partly depend on resorptive activity in bone. However, not all bisphosphonates are created equal. **Yao et al** treated mature rats with risedronate, PTH or both. Bone gains were similar with and without pretreatment with risedronate compared to the PTH alone. Risedronate prior to PTH produced a lower percentage increase in proximal tibial BMD during the first 8 weeks of PTH, and had lower active forming surface and formation rates after PTH 12 weeks as compared to the PTH alone. Withdrawal did not blunt the stimulatory effect of PTH on osteoblast activity. Risedronate slows the anabolic response to PTH, a withdrawal period prior to PTH allows osteoblastic activity

to respond normally to PTH. It's a pity there was no group treated with other bisphosphonates, **Bone 2007;41:813-9**

Washimi et al report that PTH and calcitonin preserves trabecular microarchitecture better than single-drug therapy in OVX rats. BV/TV, Tb.N, fractal D and N.Nd/TV were greater in the E+PTH than with PTH. Trabecular separation (Tb.Sp) was lower in the E+PTH5 and E+PTH10 than respective PTH5 and PTH10. E+PTH had higher strength than the PTH, however, the three-point bending of the diaphysis of femur in the E+PTH10 and E+PTH20 groups tended to be lower than PTH10 and PTH20. **Bone 2007;41:786-93**

Samadfam et al report alendronate and osteoprotegerin (OPG) influence the anabolic activity of PTH(1-34) in 4-month old oophorectomized mice. Mice treated with alendronate, OPG, PTH, PTH plus alendronate or PTH plus OPG, were compared. Alendronate and OPG suppressed turnover, more with OPG. Increases in spine and femoral BMD and in trabecular bone volume were similar with OPG and alendronate, but mechanical indices of femoral strength improved only with OPG. PTH with each produced additive increases in BMD in the femur and supra-additive increases in the spine. Neither impeded the PTH-induced increase in bone volume or the increase in mechanical strength of the femur. **J Bone Miner Res 2007;22:55-63**

Fuchs et al report that 7-month old virgin female rats were assigned to ALN or treadmill running or both. After 14 weeks, exercise and ALN had additive benefits on whole body and proximal femur BMC, cross sectional area of the L4 vertebrae, and mechanical properties of the midshaft femur. In comparison, for total and midshaft femur BMC, L4 vertebrae BMC, and midshaft femur cortical thickness and area, there were significant exercise and ALN interactions indicating that the two interventions worked in synergy. ALN reduced medullary canal area suggesting it reduced endocortical bone resorption, whereas exercise augmented periosteal perimeter. **Bone 2007;41:290-6**

Why repeat BMD?

Why repeat it if it does not tell us how will and won't fracture based on the result? Even in untreated subjects, a second measurement is closely correlated to the first, so closely in fact that it may not give further fracture prediction over that determined by the first measurement which tells us about the position of an individual's BMD in the population distribution achieved during growth.

Variability in rates of bone loss (1 SD=~1% of the mean) are an order of magnitude less than variability in peak bone density (1 SD=~10% of the mean) so the position of an individual's BMD in young adulthood is the most important determinant of the position during the subsequent 10-20 years, more so probably than the rate of bone loss.

Hillier et al studied 4124 women, during 5 years following a repeat BMD measurement done ~8 years after the initial measurement. Fracture risk was no better predicted by the repeat measurement. Areas under the receiver operating curves revealed no differences in discriminating fractures with initial BMD, repeat BMD, or initial BMD plus change in BMD. **Arch Intern Med 2007;167:155-60**

Damage and remodeling suppression

Yao et al report that estrogen deficiency lowered the degree of mineralization while tissue mineral density was maintained with single intravenous bisphosphonates in aged estrogen-deficient rats and predicted bone strength. Bisphosphonates were more effective than raloxifene in preventing the loss of mineralization, trabecular bone volume and bone compression strength. **Bone 2007;41:804-12**

Allen and Burr report that bisphosphonate-associated increases in microdamage occur early. After 3 years, alendronate resulted in similar vertebral microdamage as one year. One-year old female beagles were treated with vehicle, alendronate for 3 years. Microdamage accumulation (crack surface density) was not higher at 3 years but increased (100%; $p<0.05$) with the higher dose of ALN. When adjusted for areal BMD, ALN-treated animals had lower energy absorption (-20%). Toughness, was ~30% lower for ALN. Toughness was lower in animals treated for 3 years with ALN1.0 (-18%) than for one year. Although 3 years of ALN resulted in higher microcrack density compared with control dogs, the amount of microdamage was not higher than animals treated for 1 year. Because toughness continued to decline over 3 years at the higher ALN dose, decreases in toughness are probably not dependent on damage accumulation. **J Bone Miner Res 2007;22:1759-65**

Stepan et al report that 38 women with osteoporosis received ALN (10 mg/day or 70 mg/week for 63.6 months) while 28 were untreated. Cr.Dn was elevated in ALN patients. In ALN patients, lower femoral neck BMD (Cr.S.Dn, r=-0.58, P=0.003; Cr.Dn, r=-0.54, P=0.005) and increased age (Cr.S.Dn, r=0.43, P=0.03; Cr.Dn, r=0.43, P=0.03) were associated with microdamage. Femoral neck BMD was the only independent predictor for Cr.Dn and Cr.S.Dn. Microdamage accumulation may occur in patients with low BMD treated with ALN. **Bone 2007;41:378-85**

Chapurlat et al examined transiliac bone biopsies in 50 postmenopausal osteoporotic women (mean age=68 years) who received BP (3 on intravenous pamidronate, 37 on oral alendronate, and 10 on oral risedronate) for at least 3 years (mean=6.5 years), compared with results in 12 cadavers, cancellous bone microcrack frequency was low (mean, 0.13/mm2) and did not differ from controls (0.05/mm2). 54% of cases and 58% of the controls had no microcracks. There was no association between microcrack frequency and the duration of BP and between age and the number of microcracks. No relationship between microcrack density and activation frequency was found. Among postmenopausal osteoporotic women on long-term BPs, microcrack frequency in the iliac bone is low, despite a reduction in turnover. **J Bone Miner Res 2007;22:1502-9**

Osteonecrosis of the jaw

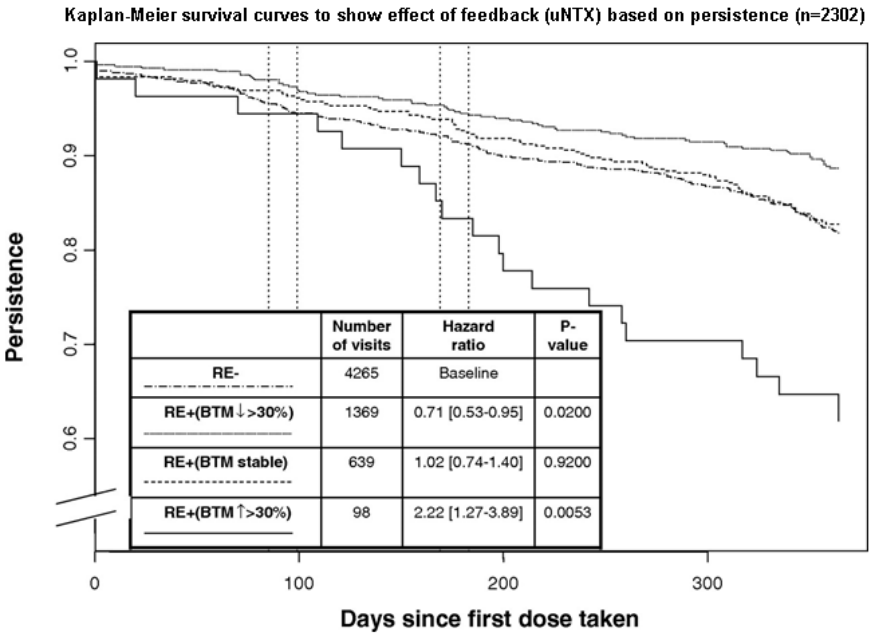
The association between osteonecrosis of the jaw and bisphosphonate therapy remains controversial. **Choi et al** report that pamidronate reduced bone healing in a model of bone defects using rabbit calvaria. Radiopacity was lower in pamidronate groups than controls. Bone formation was lower in the pamidronate groups than control after 2 weeks. Newly formed bone at 1 week underwent avascular necrosis after 2 weeks with pamidronate. Avascular necrosis was not observed until 8 weeks in both topically applied pamidronate groups. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:321-8**

Compliance and adherence with therapy

Compliance and adherence with therapy is poor in the bone field where 50% of patients given a prescription for an anti-osteoporosis therapy are not taking it within 12 months and many of these individuals stopped at 3 months. The reasons for poor compliance and adherence are not known but fracture rates are higher in individuals who fail to comply with treatment. Mortality is also higher in persons who fail to comply with placebo suggesting there is something about the poor complier making them more liable to morbidity and mortality – not just the absence of the effect of the drug they are failing to adhere to!

Delmas et al assessed the impact of physician reinforcement using bone turnover markers (BTMs) on persistence with risedronate in 2382 postmenopausal women (**J Clin Endocrinol Metab 2007;92:1296-304**). A good BTM response was associated

with improvement in persistence but when reinforcement was based on a stable or poor BTM response, persistence was unchanged or lower, respectively. Reinforcement was associated with a lower incidence of new vertebral fractures (OR=0.4; 95% CI 0.2-1.0). This is an interesting study with a strange result. When markers were bad or unchanged, advice did not help improve compliance. This is consistent with the notion that poor compliers have some feature in their nature that results in poor compliance and adverse health outcomes. Perhaps some of us can't be helped.



Delmas et al., J Clin Endrocrin Metab, Effect of Monitoring Bone Turnover Markers on Persistence with Risedronate Treatment of Postmenopausal Osteoporosis, volume 92, issue 4, April 2007, and page 1296-1304. Copyright 2007, The Endocrine Society.

Briesacher et al report a retrospective cohort study used 2000-2004 pharmacy and medical claims data from 45 large U. S. employers. Of 17,988 new users of bisphosphonate therapy, after 1 to 3 years of follow-up, 30.6% to 42.9% achieve compliance of 80%-100%, 17.4%-23.0% moderate compliance (79%-40%), and 33.8%-52.0% had low compliance (0%-39%). Benefits with better compliance of at least 60% were found but not below. Multivariate models of health care costs showed significant total costs savings of $859 to $366 per year with high to moderate compliance levels. However, individuals achieving less than 40% compliance had no decrease in inpatient or outpatient costs. **Bone 2007;41:882-7**

Failure to treat those in need

Gehlbach et al report data from NHANES for 1999–2000 and 2001–2002 combined. Of more than 15 million U.S. women, about 40% had one risk factor in addition to age; 20% had two or more. More than 5 million women were in the highest category; 26% of these will have a non-vertebral fracture and 10% will have a vertebral fracture in the next 5 years. Anti-resorptives are being taken by less than 50% of women in most risk categories; only 17% of older women with a prior fracture and 13% in the highest category of risk. **Osteoporos Int 2007;18:805-10**

Burden of disease

Burge et al report the burden of fragility fractures in the U.S. was >2 million fractures, costing about $17 billion in 2005. Total costs including prevalent fractures are >$19 billion. Men account for 29% of fractures and 25% of costs. Total incident fractures by site were vertebral (27%) and hip (14%) with the remaining ~50% being wrist (19%), pelvic (7%), and other (33%). Total costs by fracture type were vertebral (6%), hip (72%), wrist (3%), pelvic (5%), and other (14%). By 2025, annual fractures and costs are projected to rise by almost 50%. Fracture prevention should address all skeletal sites. **J Bone Miner Res 2007;22:465-75**

HRT, cancer and death

Rossouw et al report the results of a secondary analysis of the Women's Health Initiative (WHI) trials of hormone therapy in which 10,739 women who had undergone a hysterectomy and 16,608 postmenopausal women who had not. In this post hoc analysis the authors report increased risk for CHD in only those 20 or more years postmenopausal with some suggestion of a protective effect in younger women while the risk of stroke did not vary by age or time since menopause. The authors do not make inferences one way or another, which is a good thing. **JAMA 2007;297:1465-77**

Osteocytes

This will be the century of the osteocyte. **Tan et al** report that osteocytes were stimulated with pulsating fluid flow (PFF, 0.70±0.30 Pa) at 5 Hz. Osteocytes produced conditioned medium that inhibited osteoclast formation. For osteoblast PFF-conditioned medium, such effect was also observed. PFF-treated osteocytes produced conditioned medium that resulted in a decreased bone resorption. The NO synthase inhibitor NG-nitro-l-arginine methyl ester attenuated the inhibitory effects on osteoclast formation and resorption. **Bone 2007;41:745-51**

Murshid et al report that three-dimensionally cultured osteoblasts have a morphology that resembles osteocytes, Actin, fimbrin, alpha-actinin, myosin, and tropomyosin all appeared in the processes of both cell types, but fimbrin and myosin showed differences in their distribution patterns between cell types. Microtubules were essential for the integrity and formation of MC3T3-E1 cell processes, but osteocyte processes were dependent on actin. Differences in the cytoskeleton of the processes of 3D-cultured osteoblasts and of osteocyte dendrites suggest that osteoblast processes may have a different role than the osteocyte dendritic network. **J Bone Miner Metab 2007;25:151-8**

Huber et al report that in 24 juvenile female rats, the percentage of apoptotic osteocytes increased with OVX in the radius and ulna. Treatment with 17ß-estradiol or LY 117018 prevented these increases similarly. **Calcif Tissue Int 2007;81:139-44**

Aguirre et al report that mechanical stimulation promotes osteocyte and osteoblast survival by activating the extracellular signal regulated kinases ERKs. Estrogens have similar effects and adaptation to mechanical forces is defective in mice lacking the estrogen receptor (ER)a or the ERb. ERKs are not activated by stretching in osteocytic and osteoblastic cells in which both ERa and ERb have been knocked out. This is reversed partially by transfection of either one of the two ERs and fully by transfection of both. The ER antagonist ICI 182,780 abrogates ERK activation and the anti-apoptotic effect of mechanical stimulation. ERs participate in the transduction of mechanical forces into pro-survival signaling in bone cells, albeit in a ligand-independent manner. **J Biol Chem 2007;282:25501-8**

T**atsumi et al** report that when osteocytes are modified by targeting diphtheria toxin receptors to them, using the DMP-1 promoter, and then ablated, there is loss of trabecular and cortical bone and increased cortical porosity. The synthetic and mineralizing function of osteoblasts is impaired. Bone is no longer lost in response to tail suspension, suggesting that osteocytes play a role in mechanotransduction. **Cell Metab 2007;5:464-75**

Tissue strains which are usually under 0.1% caused by locomotion are too small to initiate signaling in osteocytes. To reconcile the proposed function of osteocytes in mechanotransduction, amplification mechanisms may exist that are sufficient to initiate adaptation. **Wang et al** report that a cell level strain amplification system is achieved by integrins that attach osteocyte processes to the canalicular wall. Tensile forces on the integrins are <15 pN. Axial strains caused by sliding of actin microfilaments about the fixed integrin attachment are an order of magnitude larger than radial strains and two orders of magnitude greater than whole tissue strains, and are large enough to open stretch-activated cation channels. **Proc Natl Acad Sci 2007;104:15941-6**

Follet et al report that fatigue loading induces microdamage and causes osteocyte apoptosis. The mechanism of action of bisphosphonates in reducing fracture risk remains incompletely understood. The authors demonstrate that risedronate or alendronate suppressed osteocyte apoptosis induced by fatigue loading of the ulna in rats and do so equally effectively and within 3 days. **Bone 2007;40:1172-7**

Exercise

There is good evidence that structural benefits result from exercise during growth. An important remaining issue is whether these benefits are sustained into adulthood when exercise is ceased and a sedentary life is followed. **Warden et al** addressed this issue in exercising 5-week old rats detrained for 92 weeks after 7 weeks of exercise. Exercise induced consistent bone quantity and structural adaptation. Bone quantity differences did not persist with detraining, whereas difference in structure was maintained. After detraining, exercised ulnas had 23.7% greater ultimate force but lower post-yield displacement indicating increased brittleness due to greater mineralization. Fatigue life was 10-fold greater in exercised ulnas. **J Bone Miner Res 2007;22:251-9**

Armstrong et al report that the Wnt-LRP5 signaling pathway mediates the skeletal response to loading. Estrogens participate in the maintenance of the osteoblastic response to mechanical stimuli. In the presence of a SERM or in the absence of estrogen receptor (ER)_, activation of the _-catenin pathway in osteoblasts by shear strain is reduced. In vivo expression of genes related to the Wnt-LRP5 pathway were reduced in the loaded tibia of ER_ KO mice so loss of estrogen may lead to a lower Wnt-LRP5 response to mechanical stimulation, which in turn might contribute to the negative bone mineral balance after menopause. **J Biol Chem 2007;282:20715-27**

Genetics

Makovey et al studied 177 monozygotic [MZ] and 185 dizygotic [DZ] pairs), 45-82 yr of age. The mean annual _BMD was -0.37% (SD) per year at the spine, -0.27% at the total hip, -0.77% at the total forearm, -0.36 % at the femoral neck, and -0.16 % at the whole body. Intraclass correlation coefficients were higher in MZ than in DZ twins except at the hip sites and heritability for _BMD were 0.38, 0.49, and 0.44 for the lumbar spine, total forearm, and whole body, respectively. The genetic effect on _BMD at all hip sites was not significant. Genetic effects on bone loss with aging are less pronounced than on peak bone mass, they still account for ~40% of the between-individual variation in bone loss in peri- and postmenopausal women. **J Bone Miner Res 2007;22:1773-80**

Bone formation

Holmes et al report stem cell antigen 1 (Sca-1)-null mice undergo normal bone development but have decreased bone mass due to an age-dependent, cell-autonomous osteoclast deficiency in vitro. From 7 months of age, reduced femoral BMD was observed with reduced mesenchymal progenitor frequency, and decreased in vitro osteogenic and adipogenic differentiation potential. Sca-1-deficient mice exhibited reduced whole body BMD. Although no differences in spinal BMD were observed, Sca-1(-/-) vertebrae exhibited decreased bone formation, with a maximal difference at 7 months of age, inferior trabecular microarchitecture, and a greater degree of mineralization. Sca-1-null bones exhibited reduced energy to failure from 5 months onward. **J Bone Miner Res 2007;22:1373-86**

Bone resorption

Henriksen et al measured age-isomerized _CTX and the non-isomerized _CTX fragment ratio. By measurement of TRACP activity, CTX release, number of TRACP positive cells and pit area/pit number. _CTX / _CTX ratio is 3:1 in young compared to aged bones, and _ and _CTX are released by osteoclasts during resorption. Osteoclastogenesis was augmented on aged compared to young bones, and the difference was enhanced under low serum conditions. Mature osteoclasts resorb more on aged than on young bone, despite unchanged adhesion and morphology. **Osteoporos Int 2007;18:751-9**

Risk factors

Kanis et al report 9 population-based studies in which BMD and clinical risk factors (CRFs) were documented. CRFs alone predicted hip fracture with a gradient of risk (GR) of 2.1/SD at 50 years and decreased with age. BMD alone provided a higher GR (3.7/SD), and was improved combined with CRFs (4.2/SD). For other osteoporotic fractures, the GRs were lower than for hip fracture. The GR with CRFs alone was 1.4/SD at the age of 50 years, similar to that provided by BMD and was not increased by the combination. The performance characteristics of clinical risk factors with and without BMD were validated in 11 population-based cohorts. **Osteoporos Int 2007;18:1033-46**

Sievänen et al examined the proximal femur anatomy of medieval and contemporary adults. Within ~1000 years, the femoral axis length was longer with neck circumference being unchanged. In hip fracture cases femoral axis length was further lengthened but the circumference was smaller so the estimated fall-induced stress can be ~1.5-fold today in the modern, relatively

slender phenotype. **J Bone Miner Res 2007;22:537-43**

Ardeshirpour et al report that weaning triggers a decrease in RANKL expression, osteoclast apoptosis and rapid recovery of bone mass after lactation in mice. During lactation large amounts of calcium are incorporated into bone. Calcium is delivered to the newborn at the expense of bone loss that is completely reversible after weaning. Within three days after weaning in mice there is a fall in RANKL, a wave of osteoclast apoptosis, and a fall in urinary CTX, with preservation of bone formation and rapid subsequent recovery of bone mass. **Endocrinology 2007;148:3875-86**

Yang et al report that proton pump inhibitors (PPIs) induce hypochlorhydria and reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. In 13,556 hip fracture cases and 135,386 controls, the adjusted odds ratio (AOR) for hip fracture with more than one year of PPI was 1.44 (1.30-1.59), and 2.65 (1.80-3.90) for long-term high-dose usage, with the strength of the association increasing with years of use. **JAMA 2006;296:2947-53**

Fracture risk increases in women taking the PPAR-_ activators rosiglitazone or pioglitazone, drugs that redirect mesenchymal cells from the osteoblast to the adipocyte lineage _ expression. **Wan et al** that osteoclasts are involved as well, with mild osteopetrosis in mice in which PPAR-_ was removed from hematopoietic cells with Tie2/cre. **Nat Med 2007;13:1496-503**

Cost

Borgström et al report the total annual fracture cost in Sweden was estimated at MSEK 5639, about 3.2% of the total healthcare costs. Community care accounted for 66% followed by medical care costs (31%), informal care (2%) and indirect costs (1%). The total annual societal burden of osteoporosis in Sweden was estimated at MSEK 15183 and is projected to increase to MSEK 26301 in 2050. **Bone 2007;40:1602-9**

Men

Leder et al report that in 1,029 men (age 30-79) compared to Black men, OC levels were 17.6% and 20.5% higher in Hispanic (p=0.02) and White men (p<0.01), respectively. Adjusted mean CTx were 14.3% higher in White than Black men (p=0.04). OC declined by 0.4%/yr from age 30-65 years, and increased thereafter by 2.1%/yr. Bone turnover markers are lower in Black men compared to White and Hispanic men. **J Clin Endocrinol Metab 2007;92:3453-7**

Androgen deficiency is difficult to define. **Araujo et al** report that in 1,475 Black, Hispanic, and White Boston men between the ages of 30-79 years, 24% had total testosterone <300 ng/dL and 11% had free testosterone <5 ng/dL. Prevalence of symptoms were: low libido (12%), erectile dysfunction (16%), osteoporosis/fracture (1%), and two or more non-specific symptoms (20%). About 50% of men with low testosterone were asymptomatic. Prevalence of symptomatic androgen deficiency was 5.6%. **J Clin Endocrinol Metab 2007;92:4241-7**

Bone loss begins shortly after completion of growth. **Nordstrom et al** report that between 17 and 25 years, peak BMD of healthy males was achieved at 19 years of age at the proximal femur, followed by losses of 25% of peak BMD by the age of 50. **J Clin Endocrinol Metab 2007;92:1902-8**

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Humpty Dumpty: When I use a word, it means just what I choose it to mean - neither more nor less.
Alice: The question is, whether you can make words mean so many different things.
Humpty Dumpty: The question is: which is to be master - that's all.

From Alice In Wonderland
Lewis Carroll

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

Invest in Your Bones Campaign

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 (thinking skull) [before restoration]. Vatican, Sistine Chapel.

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DO be born with a good intellect
DO NOT have more mind than matter
DO develop an inquisitive mind

DO be ambitious
DO NOT be too ambitious

DO have originality
DO NOT jump at the first problem
DO obtain money

DO look from all points of view
DO NOT be a lone wolf

DO measure something
DO NOT be secretive

DO arrange your data in chart form
DO NOT be fooled by figures

DO develop a theory
DO NOT be a slave to your theory
DO NOT be too disturbed to produce papers

DO some unadulterated thinking
DO NOT wake up in an executive job

Fuller Albright
J Clin Invest 1944;23:921-6

Overview

Calcium, vitamin D, both – yes – no – maybe

There is little convincing evidence that calcium reduces vertebral and nonvertebral fractures because there have been no replicated and credible trials (randomized, double-blind, placebo-controlled, large samples, prolonged follow up, few dropouts) demonstrating a reduction in vertebral or nonvertebral fractures in children, women or men. Nevertheless, the believers keep believing data if it suits their opinion and criticize the data if it does not. This is dangerous, particularly when it comes from a respected authority or prestigious journal.

Surrogate endpoints of fracture are used and inferences such as rise in BMD are made even though a change in BMD is a poor predictor of fracture risk reduction. **Lambert et al** report a randomized trial of calcium (792 mg/d) with follow up 2 years

after supplement withdrawal in 96 girls with low calcium intakes (mean: 636 mg/d). Compared with the controls, the supplemented group showed greater gains in BMD. Resorption markers and parathyroid hormone were lower. After 42 months, gains in BMD and differences in bone resorption markers were no longer evident. Calcium effects are short-lived because remodelling is suppressed and then reversed on supplement withdrawal. The question is whether the structural effects produced by remodelling suppression might reduce fracture risk while treatment continues. **Am J Clin Nutr 2008;87:455-62**

Zhu et al report that among 120 community-dwelling women aged 70-80 years given calcium 1200 mg/d, calcium with 1000 IU/d vitamin D2 or double placebo in a randomised controlled double-blind trial, hip BMD was preserved in treated groups and not in controls during 5 years. When split by the median, benefits were seen in those with baseline 25OHD levels below the median (68 nmol/L). At year one, Ca and CaD groups had lower alkaline phosphatase and lower urinary DPD/Cr ratio. At 5 years, this suppression was maintained in the CaD group. CaD reduced PTH at 3 and 5 years in those with baseline PTH above the median. A lot of subgroup analyses were undertaken. The authors infer that addition of vitamin D to calcium has long term beneficial effects on BMD, but does that mean calcium alone does not? **J Clin Endocrinol Metab 2008;93:743-9**

Prince et al report that, in a 1-year double-blind, randomized trial of 302 community-dwelling ambulant women aged 70-90 years with a serum 25-hydroxyvitamin <24.0 ng/mL and a history of falling, ergocalciferol at 1000 IU/d reduced the risk of having at least 1 fall after adjustment for height (OR, 0.61; 95% CI, 0.37-0.99). Ergocalciferol reduced the risk of a first fall in winter and spring, but not in summer and autumn, and reduced the risk of having one but not multiple falls. There were no data concerning fractures reported (**Arch Intern Med 2008;168:103-8**). **Richy et al** report that in 14 trials including 21,268 subjects, vitamin D analogs provided a lower risk for falling than native vitamin D: RR = 0.79 (0.64-0.96) vs. 0.94 (0.87-1.01) (intergroup difference P= 0.049). **Calcif Tissue Int 2008;82:102-07**

van Schoor et al studied 1311 community-dwelling older men and women. During 6 years, 115 persons (8.5%) had one or more osteoporotic fractures. serum 25(OH)D cut point of 12 ng/ml gave the best discrimination between persons with and without fractures. The lowest percentage of fractures (5.6%) was found above 30 ng/ml. After adjustment for age, serum 25(OH)D below or equal to 12 ng/ml was associated with an increased fracture risk in the youngest (HR = 3.1; 95% CI: 1.4-6.9), not the oldest age group (HR = 1.3; 95% CI: 0.7-2.2). Cut points of 25(OH)D (<10 ng/ml, 10-19.9 ng/ml, 20-29.9 ng/ml, ≥30 ng/ml) were not associated with fractures. **Bone 2008;42:260-6**

Looker and Mussolino studied 1917 men and women over 65 yr of age. There were 156 incident hip fractures. Serum 25(OH)D exceeding 60 nM was related to hip fracture risk. For example, the multivariate-adjusted RR was 0.64 (0.46-0.89) among individuals with serum 25(OH)D >62.5 nM compared with those with values below this level. The multivariate-adjusted RRs for the second, third, and fourth vs. the first quartile were 0.50 (0.25-1.00), 0.41 (0.24-0.70), and 0.50 (0.29-0.86), respectively. Serum 25(OH)D was related to a lower hip fracture risk. **J Bone Miner Res 2008;23:143-50**

It's not calcium in milk anyway – angiogenin

Morita et al report that a factor responsible for inhibiting osteoclast-mediated bone resorption is present in the basic protein fraction of bovine milk (milk basic protein, MBP). The purified bovine angiogenin inhibited the pit forming activity of both unfractionated bone cells and purified osteoclasts in a dose-dependent manner, and the inhibitory activity was suppressed by anti-bovine angiogenin antibody. The inhibitory activity was confirmed in mice in vitro and in vivo. Treatment of osteoclasts with bovine angiogenin resulted in an impairment of the formation F-actin ring and a reduction in the mRNA levels of TRAP and cathepsin K. **Bone 2008;42:380**

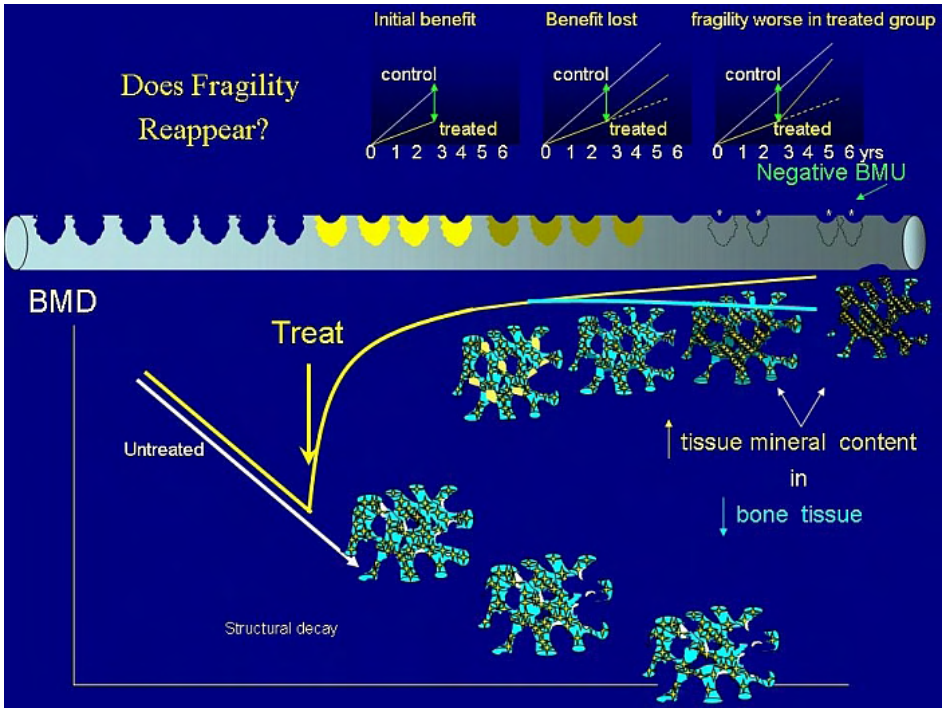
Risedronate and reduced osteoclastogenesis

Bisphosphonates reduce bone resorption by inducing osteoclast apoptosis. **D'Amelio et al** examined the influence of risedronate on the formation of osteoclast precursors and cytokine production. In 25 patients treated with risedronate 5 mg/d, there was a reduction in the number and degree of differentiation of osteoclast precursors, osteoclast formation, vitality and activity, in the level of RANKL and TNF in cultures and of TNF and OPG in serum, and no changes in the group treated with calcium and vitamin D. **J Bone Miner Res 2008;23:373-9**

Sustained fracture risk reduction and antiresorptives

Few anti-fracture efficacy trials extend longer than 3 years with retention of at least the majority of the cohort was originally allocated to treatment or placebo. Lack of controls has obvious implications; nothing can be said about fracture rates without controls – have they decreased during treatment, remained unchanged or increased ……. relative to controls. We certainly don't mean relative to pre-treatment fracture rates in the same cohort because no study has ever been done to measure fracture rates for say 1-3 years before treatment, then compared fracture rate during treatment in year 1, 2, and 3 with the pretreatment period.

As shown in the figure, when an antiresorptive is given, the resorptive cavities excavated and present before treatment go to completion with the bone formation phase of the remodelling cycle. As the bone tissue deposited mineralizes, BMD rises. This increase is unopposed by the birth of the same numbers of new remodelling units because the antiresorptive has reduced this birth rate. Fracture rates continue in control and treated subjects, but less frequently in treated subjects. The precise morphological basis for the reduced progression of bone fragility is uncertain because it has not been studied.



As time goes by, steady state is achieved and the rise in BMD continues slowly, but the morphological basis for the rise changes. Now the increase in BMD is the result of secondary mineralization (crystal enlargement) of the newly deposited bone that has undergone primary mineralization. Concurrently there is continued secondary mineralization of the existing bone tissue which has not been recently remodelled. The total bone tissue may be decreasing as remodelling with the negative BMU balance continues to remove bone from bone slowly (because remodelling is suppressed during treatment). So bone tissue density increases in a tissue that is decreasing. The net effect is a rise in BMD as the densitometer does not 'see' tissue mass decreasing.

What is in question is whether the fracture risk reduction seen in many studies within the first 12-36 months is sustained. In most clinical trials there is a dropout rate of about 10% per year, so after 5 years half the sample is lost. Has randomization been violated? It is very difficult to determine whether the Kaplan-Myer curves continue to diverge, which means the risk reduction is maintained. If they become parallel, this suggests fracture incidence is the same in the treated and control group; and if the lines converge, this suggests the fracture rates are higher under treatment than without treatment.

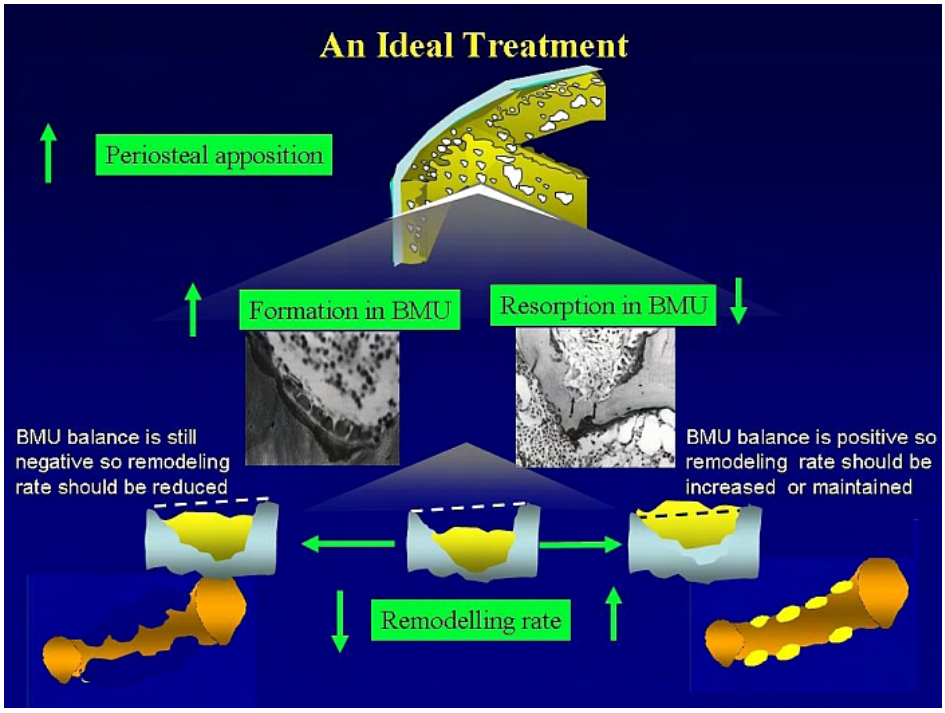
Loss of subjects in a trial potentially violates randomization. Randomization ensures that known *and unknown* covariates influencing fracture (independent of the drug) are equally present in treatment and placebo arm of the trial. Is this potential important? Of course it is. Say healthy people in the placebo arm drop out, the fracture rate will be higher and exaggerate the benefit of the drug. If sicker people drop out of the placebo arm, then fracture rates will be lower and the benefit of the drug will be obscured. A range of scenarios result when dropouts occur in the treatment arm. Is this corrected by bringing the last measurement point forwards or doing other analyses? If the design and execution of a trial are flawed, nothing can save it, nothing can give it credibility, not even statistics.

Watts et al report that patients who received risedronate 5 mg daily (N=398) or placebo (N=361) during the VERT-NA study stopped therapy after 3 years but continued taking vitamin D and calcium for one year. In the year off treatment, BMD decreased but remained higher than baseline and placebo at the spine and hip. Urinary NTX and BSAP decreased with treatment, were not different from placebo after 1 year off treatment. The incidence of new morphometric vertebral fractures was 46% lower in the former risedronate than former placebo (RR 0.54, 0.34, 0.86). **Osteoporos Int 2008;19:365-72**

Ensrud et al studied 10,101 postmenopausal women ≥55 yr of age with coronary heart disease. Women received 60 mg raloxifene or placebo daily for a median of 5.6 yr. No risk reduction for nonvertebral fractures was observed but women treated with raloxifene had a lower risk of clinical vertebral fractures (64 vs. 97 events; HR, 0.65, 0.47-0.89) (**J Bone Miner Res 2008;23:112-20**). This is probably one of the longest follow up studies reported and provides compelling data regarding the anti-vertebral fracture efficacy of this drug and the lack of it for nonvertebral fractures.

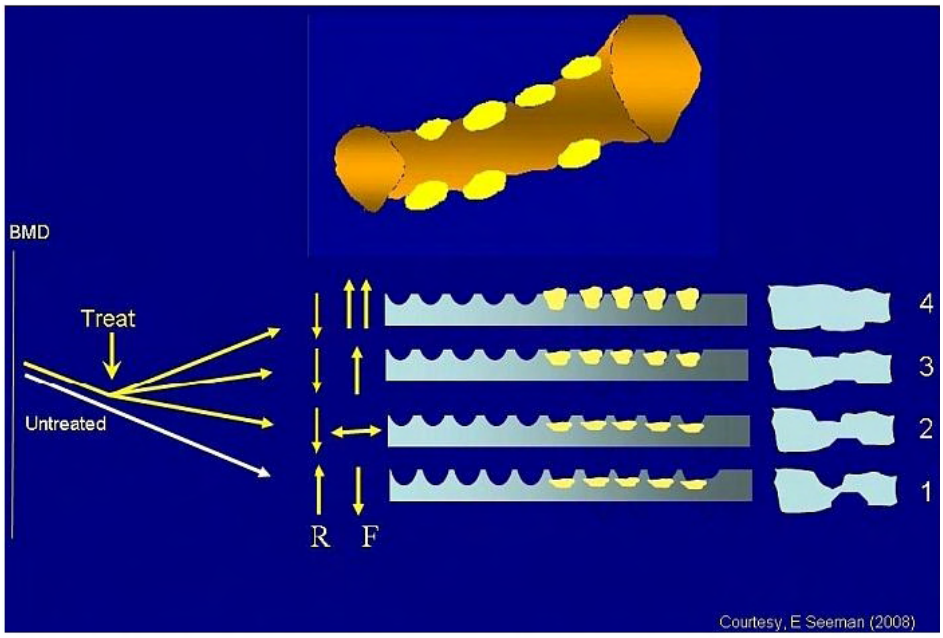
Strontium ranelate under the microscope

As illustrated in the figure, ideally a drug should increase periosteal apposition, reduce the volume of bone resorbed by each BMU and increase the volume of bone formed by each BMU so that the net effect is a positive bone balance. If the bone balance is positive, it is of interest to make bone remodelling rapid so that each remodelling event deposits bone on bone to help reconstruct the skeleton. If bone balance is not restored by the BMU, then the drug should also slow remodelling because each remodelling event robs bone of bone. If there is a positive balance produced by the BMU, then it is of interest for the drug to increase the rate of remodelling or at least maintain it.



Arlot et al report that in 141 transiliac bone biopsies from 133 postmenopausal osteoporotic women, 49 biopsies after 1-5 yr of 2 g/d strontium ranelate and 92 biopsies at baseline or after 1-5 yr of placebo, strontium ranelate was associated with 9% higher mineral apposition rate in cancellous bone. Osteoblast surfaces were 38% higher and 3D analysis of 3-yr biopsies suggested 18% higher cortical thickness and 14% higher trabecular number with a 22% lower structure model index and 16% lower trabecular separation with no change in cortical porosity. **J Bone Miner Res 2008;23:215-22**

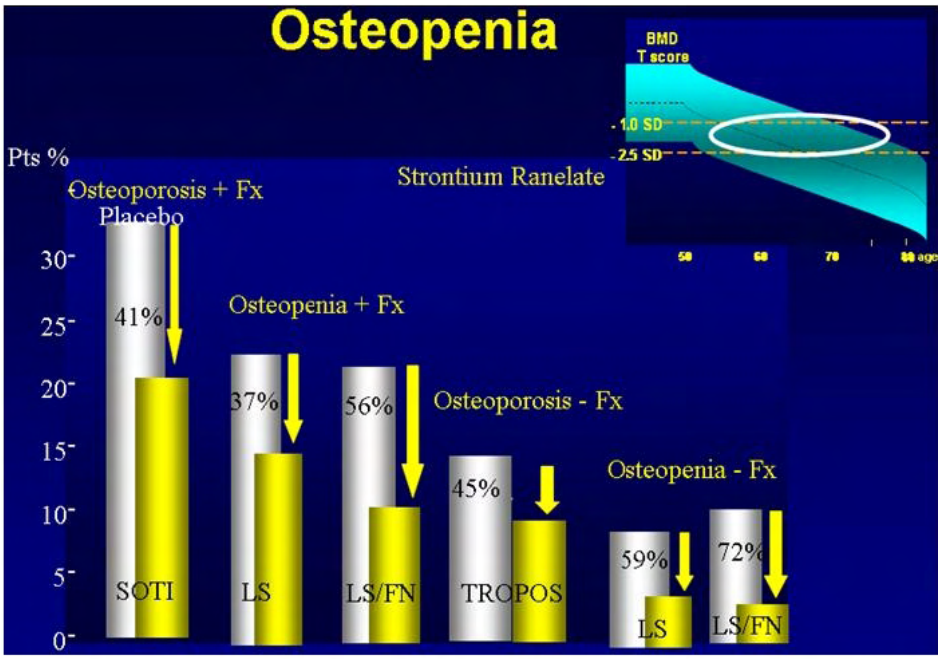
These are encouraging results but they are cross-sectional, so 'change', 'increased' or 'decreased' should be 'difference', 'higher' or 'lower', respectively. Activation frequency, the measure of the birth rate of new remodelling units did not change in this study – it decreases with antiresorptive agents and increases with PTH. The importance of the remodelling rate depends on what the net effect of the volumes of bone resorbed and deposited by each BMU during the life cycle as described above.



(1) Bone loss occurs because volume of bone resorbed exceeds the volume of bone formed by each basic multicellular unit (BMU), so structure decays. (2) If a drug reduces the volume of bone resorbed without affecting the volume of bone deposited, there will be less structural decay than in (1). (3) If volume of bone resorbed is reducec and the volume formed is increased, each remodelling event may not produce any bone loss. (4) If the drug reduces the volume of bone resorbed and increases the volume of bone formed, the positive balance makes it best to keep remodelling high to reconstruct the skeleton. No drug has been shown to do this yet.

Bonnelye et al studied primary mouse osteoblasts and osteoclasts derived from calvaria and spleen cells. Strontium ranelate continuously or during proliferation or differentiation phases stimulated osteoblast formation. After 22 days of continuous treatment, expression of the osteoblast markers ALP, BSP and OCN increased, and was combined with an increase in bone nodule numbers. The number of mature osteoclasts decreased after treatment. Osteoclast resorbing activity was also reduced, with strontium ranelate being associated with a disruption of the osteoclast actin-containing sealing zone. **Bone 2008;42:129-38**

Seeman et al report that data was pooled from the Spinal Osteoporosis Therapeutic Intervention study (SOTI; n=1649) and the TReatment Of Peripheral OSteoporosis (TROPOS; n=5091) to evaluate the antivertebral fracture efficacy of strontium ranelate in women with lumbar spine (LS) osteopenia with any BMD value at the femoral neck (FN; N=1166) and in 265 women with osteopenia at both sites (intention-to-treat analysis). The women were randomized to strontium ranelate 2 g/d orally or placebo for 3 yr. In women with LS osteopenia, treatment reduced the risk of vertebral fracture by 41%. In women with osteopenia at both sites, treatment reduced the risk of fracture by 52%. **J Bone Miner Res 2008;23:433-8**



Placebo fracture rates (white bars) are highest in women with osteoporosis and a fracture and are higher in women with osteopenia plus a fracture than in women with osteoporosis without a fracture. In all groups, strontium ranelate reduced fracture risk relative to placebo. *Adapted from J Eone Miner Res 2008;23:433-8 with permission of the American Society for Bone and Mineral Research.*

Osteonecrosis and bisphosphonates

Etminan et al report that for each case of osteonecrosis, 10 controls were randomly selected. The initial cohort consisted of 87,837 subjects. In the primary analysis, the adjusted RR for AON among bisphosphonate users was 2.87 (1.71-5.05). The adjusted RR for alendronate, etidronate, and risedronate were 2.87 (1.46-5.67), 2.43 (1.05-5.62), and 3.34 (1.04-10.67), respectively. There were no differences in RR for AON among current users and past users of bisphosphonates. **J Rheumatol 2008 [Epub ahead of print]**

Anabolic therapy – are we there yet?

Mukherjee et al report that Bortezomib (Bzb), a proteasome inhibitor used in multiple myeloma, induces MSCs to undergo osteoblastic differentiation, in part, by modulating transcription factor Runx-2 in mice. Mice implanted with MSCs showed increased ectopic ossicle and bone formation when recipients received low doses of Bzb. Bone formation increased and bone loss was rescued in a mouse model of osteoporosis. Tissue-resident adult stem cells in vivo can be pharmacologically modified to promote a regenerative function in adult animals. **J Clin Invest 2008;118:491-504**

Boonen et al report that 245 women with osteoporosis had 2 years teriparatide and were stratified to alendronate (n=107), risedronate (n=59), etidronate (n=30), non-bisphosphonate (n=49). Increases in bone formation markers occurred in all groups after 1 month teriparatide. Spine BMD increased while a transient decrease in hip BMD reversed. BMD change was similar in all prior antiresorptives. Duration of prior antiresorptive and lag time between stopping prior therapy and starting teriparatide did not affect the BMD response. Teriparatide induces positive effects on BMD and markers of bone formation in postmenopausal women with osteoporosis, regardless of prior exposure to antiresorptives. **Clin Endocrinol Metab 2008;93:852-60**

Adami et al report that following a year teriparatide 20 µg/day, women with osteoporosis were assigned to raloxifene 60 mg/day or placebo for a year, then a year of raloxifene. The raloxifene and placebo groups showed a decrease in spine (LS) BMD in year 2 (-1.0%, P=0.004; and -4.0%, P<0.001, respectively); the decrease was less with raloxifene. Open-label raloxifene reversed the LS BMD decrease with a placebo, resulting in similar decreases at 2 years: -2.6% (raloxifene-raloxifene) and -2.7% (placebo-placebo). At study end, LS and femoral neck (FN) BMD were higher than pre-teriparatide, with no differences between the raloxifene-raloxifene and placebo-raloxifene groups, respectively (LS: 6.1% vs. 5.1%; FN: 3.4% vs. 3.0%). Sequential raloxifene prevented rapid bone loss at the LS and increased FN BMD, whether raloxifene was started immediately or after a one-year delay following teriparatide. **Osteoporos Int 2008;19:87-94**

Fluoride won't go away – should it ?

Vestergaard et al report the results of a meta-analysis including 25 studies. Spine BMD increased 7.9% and hip BMD by 2.1%. Overall, there was no effect on the risk of vertebral or nonvertebral fracture. Daily dose of ≤20 mg fluoride (152 mg monofluorophosphate/44 mg sodium fluoride) were associated with a reduction in vertebral (OR=0.3, 0.1-0.9) and nonvertebral (OR=0.5, 0.3-0.8) fracture risk. With a daily dose >20 mg fluoride equivalents, there was no reduction in vertebral or nonvertebral fracture risk (**Osteoporos Int 2008;19:257-68**). It's a shame to discard a drug like fluoride which has an anabolic effect but, at least in the way it is used, is producing poor quality bone. Low dose fluoride may well be worth studying alone or in combination with an antiresorptive but who will fund this sort of study ?

Cost-effectiveness

Kanis et al report alendronate 70 mg weekly for 5 years was cost-effective for the primary fracture prevention in women with osteoporosis irrespective of age as was treatment of women with a prior fracture irrespective of BMD. NICE guidelines are misguided. **Bone 2008;42:4-15**

Lekander et al reported the cost-effectiveness of 50 year old women. Hormone therapy (HT) compared to no treatment was cost-effective for most subgroups of hysterectomised women; whereas for women with an intact uterus without a previous fracture, HT was dominated by no treatment. Fracture risks were the single most important determinant of the cost-effectiveness. **Bone 2008;42:294-306**

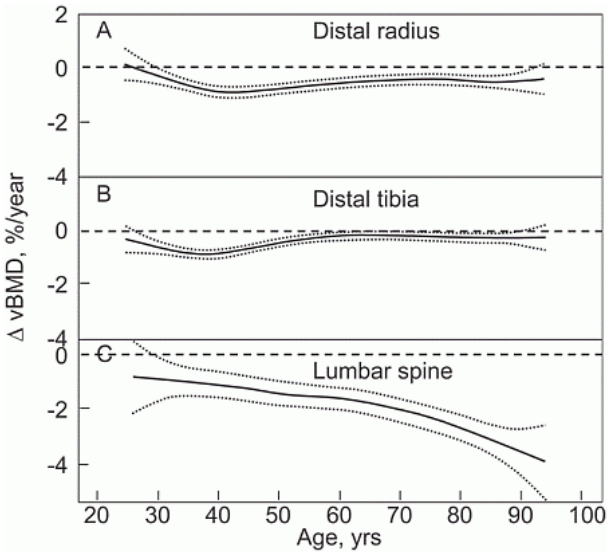
Compliance with therapy

Sinsky et al assessed how patient and provider compliance with osteoporosis guidelines varies when efficacy is presented as relative risk (35% RRR) vs. absolute risk reduction (1% ARR). Compliance fell when the expression of treatment benefit was switched from RRR to ARR for both patients (86% vs. 57% compliance; P<0.001) and physicians (97% vs. 56% compliance; P<0.001). Increasing drug copayment from 0% to 10% of total drug cost decreased patient compliance with CPGs from 80% to 57% (P<0.001) but did not impact physician compliance. **J Gen Intern Med 2008;23:164-8**

Bone loss before menopause

When I asked the late Harold Frost when ageing began he replied, “at birth”. It is likely that bone loss begins shortly after completion of growth. There are several studies suggesting this and a recent study from Larry Riggs sheds some interesting insights into this process. The authors studied an age- and sex-stratified sample (n=553) by QCT for up to 3 years. Substantial cortical bone loss began in middle life in women but began mainly after age 75 in men. Trabecular bone loss began in young adult women and men at all skeletal sites and continued with acceleration during perimenopause. Women experienced 37% and men experienced 42% of their total lifetime trabecular bone loss before age 50 compared with 6% and 15%, respectively, for cortical bone. Median rates of change in trabecular bone (%/yr) were -0.40, -0.24, and -1.61 in young adult women and -0.38, -0.40, and -0.84 in young adult men at the DR, DT, and LS, respectively (all p<0.001). **J Bone Miner Res 2008;23:205-14**

The question is, what are the effects on bone strength? If remodelling is slow and the loss of bone is due more to reduced bone formation than increased rate of remodelling or increased volume of bone resorbed in each remodelling unit, then the same loss of bone produces less loss of strength when bone loss proceeds, producing thinning of trabeculae rather than loss of connectivity. In addition, as periosteal apposition continues, any loss of bone from the endocortical surface may be offset by the independent and continued gain of bone on the periosteal surface. The authors reported little change in cortical bone, but they did not report marrow cavity size, which would be of interest.



Reproduced from J Bone Miner Res 2008;23:205-14 with permission of the American Society for Bone and Mineral Research.

Ursus arctos horribilis and remodelling balance

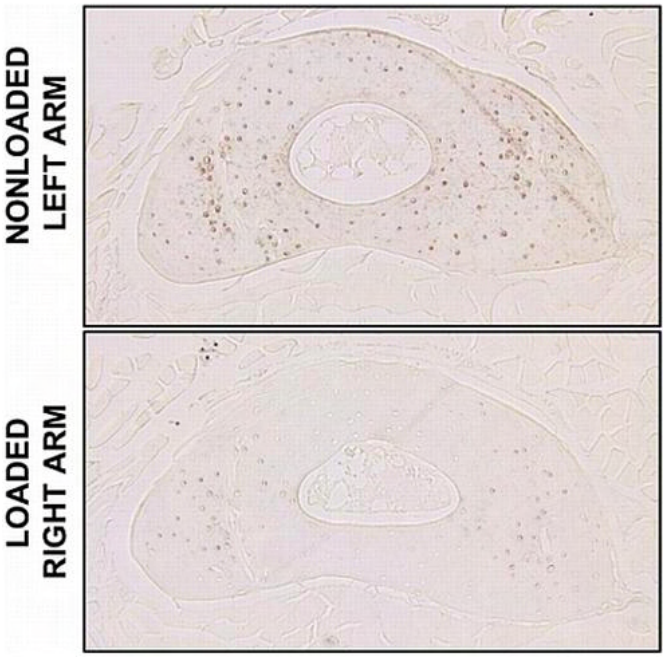
McGee et al report cortical bone turnover during hibernation is balanced, bone formation and resorption replace the same volume of bone removed by each BMU in grizzly bear femurs, which avoids bone loss. Hibernating grizzly bear femurs were less porous and more mineralized and did not have changes in cortical bone geometry or mechanical properties. Activation frequency was 75% lower but mineral apposition rate was unchanged, so turnover decreases but osteons continue to refill at normal rates. Grizzly bears prevent bone loss during disuse by decreasing bone turnover and maintaining balanced formation and resorption, which preserves bone structure and strength. **Bone 2008;42:396-404**

Osteocytes – damage prevention and removal

This osteocytic-canalicular system functions in damage *prevention* by orchestrating adaptive remodelling, and damage *removal* by orchestrating reparative remodelling. Osteocytes detect strain and initiate modelling and remodelling to adapt bone’s material properties and structural design to offset the strain that will otherwise damage bone. Adaptation can be viewed as a damage-prevention mechanism. The change in bone size, shape and mass distribution during growth achieved by modelling and remodelling is successful adaptation; it is damage prevention by pre-emptive modification of structural strength in response to increasing stresses imposed by growth.

Microdamage, when it accumulates, compromises bone strength and must be removed. The second important function of the osteocyte is the detection of damage and initiation of focal remodelling to remove and replace damage with new bone. The osteocyte is pivotal in detecting damage and initiating remodelling and in adapting bone structure to its loading circumstances. Sclerostin, the protein product of the Sost gene, inhibits bone formation and is found nearly exclusively in osteocytes, the cell type that has is implicated in sensing and initiating mechanical signalling. Osteocytes control mechanotransduction by adjusting sclerostin (Wnt inhibitory) signal output to modulate Wnt signalling in the effector cells.

Robling et al report that Sost transcripts and sclerostin protein levels were reduced by ulnar loading. Portions of the ulnar cortex receiving a greater strain stimulus were associated with a greater reduction in Sost staining intensity and sclerostin-positive osteocytes than were lower-strain portions of the tissue. Hindlimb unloading yielded an increase in Sost expression in the tibia. Modulation of sclerostin levels allows osteocytes to coordinate regional and local osteogenesis in response to increased mechanical stimulation, perhaps via releasing the local inhibition of Wnt/Lrp5 signalling. **J Biol Chem 2008;283:5866-75**



Immunolabelling for sclerostin, which can be visualized by the brown staining. Copyright 2008 by Alex Robling (courtesy of C. Turner).

The purpose of modelling and remodelling during adulthood is to maintain bone strength achieved during growth but in accordance with the prevailing loading circumstances. Part of the notion of maintaining strength is the detection and removal of damaged bone. The osteocyte plays a pivotal role in bone modelling and remodelling by sacrificing itself. Microcracks sever osteocyte processes in their canaliculi, producing osteocyte apoptosis. Osteocyte apoptosis is likely to be one of the first events signalling the need for remodelling.

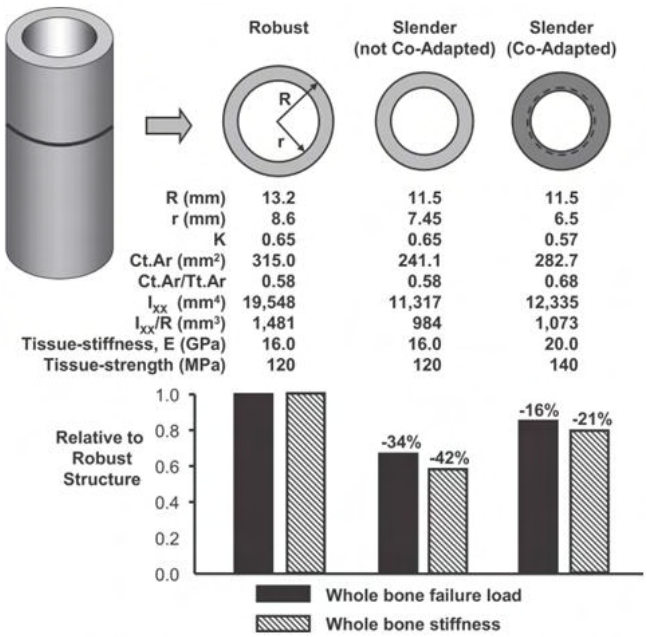
In vivo, osteocyte apoptosis occurs within 3 days of immobilization and is followed within 2 weeks by osteoclastogenesis. In vitro, death of the osteocyte-like MLO-Y4 cells induced by scratching results in the formation of TRACP positive (osteoclast-like) cells along the scratching path.

You et al report that osteocytes cocultured with osteoclast precursors support osteoclast formation and activation. Mechanical stimulation of MLO-Y4 osteocyte-like cells decreases their ability to facilitate osteoclastogenesis, suggesting soluble factors are released by mechanically stimulated MLO-Y4 cells that inhibit osteoclastogenesis. Soluble RANKL and OPG were released by MLO-Y4 cells and the expressions of both are mechanically regulated. Mechanical loading decreases the osteocyte's potential to induce osteoclast formation by direct cell-cell contact. **Bone 2008;42:172-79**

Adaptation

Bone's material composition and structural design determine its strength. These two components interact and adapt to ensure whole bone strength is appropriate to the loading requirements. Changes in one trait can result in adaptive changes in another so the whole bone strength is maintained. There are many examples of this, but one of the best known is the MOV13 mouse model. The mutant produces abnormal collagen and the material abnormality is compensated for by greater periosteal apposition, which offsets the loss of strength (Bonadio et al. J Clin Invest 1993; 92:1697-1705).

Tommasini et al measured slenderness (area/length) and tissue level mechanical properties from tibias from 14 female (22-46 yr old) and 17 male (17-46 yr old) donors. Ash content correlated negatively with slenderness and marrow area indicating that slender bones were constructed of tissue with higher mineralization. Slender tibias were compensated by higher mineralization and a greater area fraction of bone suggesting that bone adapts by varying the relative amount of cortical bone within the diaphysis and by varying matrix composition. **J Bone Miner Res 2008;23:236-46**



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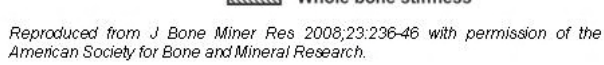

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Bone loss determines structure determines bone loss

Bone remodelling is surface based so that higher remodelling on trabecular bone than cortical bone is partly the result of trabecular bone being fashioned with more surface than cortical bone – it has a higher surface to volume ratio. As remodelling events in adulthood usually remove bone from bone (because the volume of bone removed during the resorptive phase of a remodelling event is greater than the volume of bone deposited), there is a change in structure that accompanies this loss of bone.

Net loss of bone occurs on bone surfaces, so trabeculae thin; and when vigorous enough remodelling causes perforation, so the surface disappears and remodelling intensity on the trabecular surface decreases or stops. In cortical bone, remodelling produces intracortical porosity which increases the amount of surface within cortical bone, making it look like trabecular bone so that the intensity of remodelling in the intracortical compartment increases. So this is a self defeating process, this change in structure within cortical bone – trabecularizing it increases bone remodelling, increases bone loss and structural decay – hence the title.

Squire et al report that 21 days of unloading produces greater trabecular bone loss in the distal femur and proximal tibia in the metaphyses than in the epiphyses and 2-fold greater in females than in males. Disuse-induced changes were also greater in trabecular than in cortical bone. Bone loss was inversely related to baseline bone volume fraction (R2 = 0.51 for females and 0.43 for males) and directly related to baseline bone surface to volume ratio (R2 = 0.69 for females and 0.60 for males). Trabecular bone loss correlated osteoclast surface to bone surface ratios. Baseline bone morphology modulates bone loss; anatomical regions with high surface-to-volume ratios, and high levels of osteoblastic and osteoclastic activity are particularly susceptible to disuse. **Bone 2008;42:341-9**

Time to see architecture not shadows

Boutroy et al report that in 33 postmenopausal women with a prior wrist fracture, areal and volumetric densities, cortical thickness, trabecular number, and mechanical parameters were associated with wrist fracture. Five independent components explained 86.2% of the total variability of bone characteristics. The first component included FE-estimated failure load, areal and volumetric BMD, and cortical thickness, explaining 51% of the variance with an OR for wrist fracture = 2.49. The second component included trabecular architecture, explaining 12% of the variance, with an OR=1.82. The third component included the proportion of the load carried by cortical vs. trabecular bone, assessed by FEA, explaining 9% of the variance, and had an OR=1.61. Thus, the proportion of load carried by cortical vs. trabecular bone seems to be associated with wrist fracture independently of BMD and microarchitecture. **J Bone Miner Res 2008;23:392-9**

Cortical thickness is the net result of periosteal apposition and endocortical resorption, the absolute and relative movement of these surfaces during growth and ageing determine the total bone cross-sectional size, its external shape and the distance the cortical mass is placed from the neutral or long axis of the long bone. This 3D structural organisation determines bone strength. Bone strength cannot be understood using bone densitometry.

Lauretani et al report that 345 men and 464 women, 21 to 102 years of age, had tibial QCT measured during 6-yr. Periosteal apposition was higher in younger than in older men; whereas in women, the rate of apposition was homogenous across age groups. The age-related medullary expansion was higher in women than men. In women, not men, endocortical resorption was not matched by periosteal apposition caused loss of cortical bone. Endocortical resorption causes bone loss in older women despite periosteal apposition. **J Bone Miner Res 2008;23:400-8**

Marshall et al report dimensions and vBMD in the femoral neck and shaft obtained using QCT in 3,305 men >65 yr of age in the Osteoporotic Fractures in Men (MrOS) study. All groups had similar femoral neck integral (total) volume. Blacks and Asians had 6% greater mean cortical volume as a percent of integral volume, integral vBMD was 6-10% greater, and trabecular vBMD was 33-36% greater than Whites. Shaft cross-sectional area was similar in Blacks and Whites, but smaller among Asians than Whites. Mean shaft cortical area was greater among Blacks but similar among Asians and Whites, resulting in mean cortical thickness being 5% greater among Black and Asian men. Blacks also had greater mean cortical vBMD in both the femoral neck and shaft. Blacks and Asians have features in the proximal femur that may confer advantages for bone strength. **J Bone Miner Res 2008;23:121-30**

Collagen crosslinking – the good, bad and ugly

Material of bone is composed of collagen containing crystals of calcium hydroxyapatite-like mineral. The mineral confers stiffness, the collagen confers toughness or the ability to absorb energy by deforming without cracking. If the collagen molecules are crosslinked with advanced gylcation products (AGEs) they lose their ability to deform, and so they cannot absorb energy which is, therefore, dissipated in the worst of all possible ways by causing failure of the material – cracking.

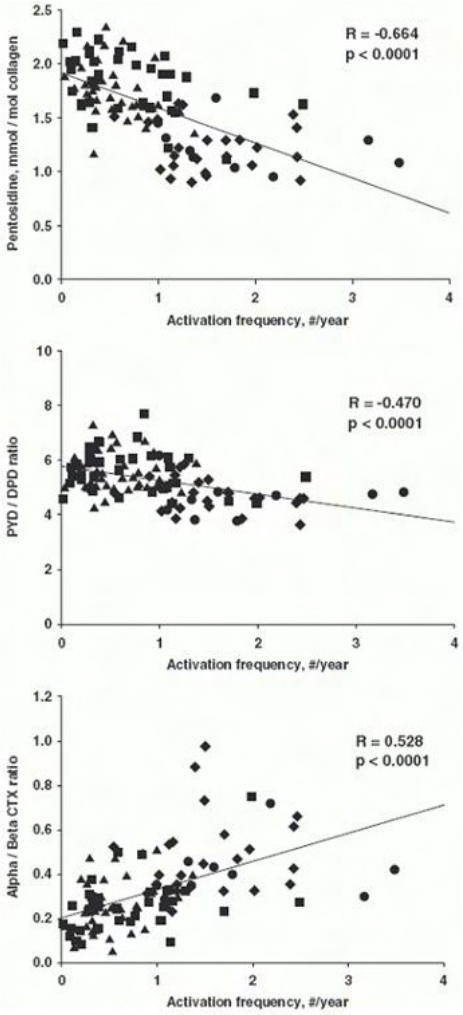
Yamamoto et al report that increased bone pentosidine is associated with its plasma levels and bone fragility in type 2 diabetics with and without VFs. Although BMD did not differ, pentosidine was higher in women with VFs than in those without VFs (0.0440±0.0136 vs. 0.0321±0.0118 μg/ml, p<0.001) (**J Clin Endocrinol Metab 2008;92:1013-9**). **Shiraki et al** report that in 432 Japanese elderly women followed for 5.2 years, 97 incident vertebral fractures occurred in 72 subjects. Urinary pentosidine was a predictor of vertebral fracture (hazard ratio, 1.33; 95% CI, 1.01-1.76, P=0.04). **J Bone Miner Metab 2008;26:93-100**

Viguet-Carrin et al report an in vitro model of young bovine cortical bone specimens incubated in a sugar (ribose - an inducer of AGEs). Pentosidine concentration increased in specimens incubated with ribose, an effect inhibited by AMG. **Bone 2008;42:139-49**

Byrjalsen et al report that collagen maturation measured as the ratio between ααCTX and ββCTX showed that bisphosphonate induced a collagen profile consistent with an older matrix with a 52% (alendronate) and 38% (ibandronate) reduction in the ratio between the two CTX isoforms vs. 3% and 15% with HRT or raloxifene, respectively. Antiresorptives had different effects on the endogenous profile of bone collagen maturation. **Osteoporos Int 2008;19:339-48**

Allen et al report neither alendronate nor risedronate altered the strength-density relationship compared to control. The energy absorption-density relationship was altered by alendronate, resulting in lower energy absorption capacity at a given aBMD compared to both controls (-22%) and risedronate (-14%). After adjusting for increased aBMD, vertebrae from animals treated with bisphosphonates had similar strength as those from untreated animals. Conversely, when adjusted for increased aBMD, alendronate reduced the energy required for vertebral fracture. **Osteoporos Int 2008;19:95-9**

Allen et al treated female beagles for 1 year with vehicle, risedronate, alendronate or raloxifene. Vertebral trabecular bone collagen isomerization (α/βCTX), enzymatic (PYD and DPD), and non-enzymatic (pentosidine) crosslinks. Bisphosphonates increased pentosidine (+34 to 58%) and PYD/DPD (+14 to 26%), and decreased α/βCTX (-29 to 56%), raloxifene did not. Bone turnover correlated to pentosidine (R = -0.664), α/βCTX (R=0.59), and PYD/DPD (R = -0.47). **Osteoporos Int 2008;19:329-37**



Relationship between bone turnover and collagen crosslinking and isomerization. Significant linear relationships existed between the rate of vertebral bone turnover (activation frequency) and pentosidine (a), enzymatic crosslink ratio (b), and collagen isomerization (c). Vehicle (●), risedronate (■), alendronate (▲), raloxifene (♦). *Reproduced from Osteoporos Int 2008; 19:329-37 with permission from Springer.*

Morbidity and mortality

Vestergaard et al report 169,145 hip fractures in Denmark between 1977 and 2001. Compared to 524,010 controls, the cases had twice the prevalence of comorbidity (HR=2.26, 95% CI: 2.24-2.27). Adjustments for confounders changed little the excess mortality risk. The mortality after hip fracture was divided into an excess mortality of 19% within the first year following the fracture (relative survival = 0.81 compared to controls), and an excess mortality of 1.8% per year (relative survival 0.982) for every additional year following the fracture. The major causes of the excess mortality were due to fracture event complications (70.8% within the first 30 days). **Osteoporos Int 2007;18:1583-93**

'... My intention is not to prove that I was right but to find out whether I was right. "Abandon hope all ye who enter – an observation." Before assuming these phenomena are spots, which would suit us, let us first set about proving they are not fried fish. We crawl by inches. What we find today we will wipe from the blackboard tomorrow and reject it unless it shows up again the day after tomorrow. And if we find anything which would suit us, that thing we will eye with particular distrust. In fact, we will approach this observing of the sun with the implacable determination to prove that the earth stands still, and only if hopelessly defeated in this pious undertaking can we allow ourselves to wonder if we may not have been right all the time: the earth revolves. Take the cloth off the telescope and turn it on the sun.'

Bertoldt Brecht
From Galileo

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 9, Issue 2, 2008

Epidemiology

9.2.1 Epidemiology of hip fracture in the elderly in Spain
Alvarez-Nebreda ML, Jimenez AB, Rodriguez P, Serra JA
Bone 2008;42:278-85

9.2.2 Epidemiology of osteoporosis related fractures in Hungary from the nationwide health insurance database, 1999-2003
Pentek M, Horvath C, Boncz I, Falusi Z, Toth E, Sebestyen A, Majer I, Brodszky V, Gulacsi L
Osteoporos Int 2008;19:243-9

Volume 9, Issue 2, 2008

Morbidity/Mortality

9.2.3 Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications
Vestergaard P, Rejnmark L, Mosekilde L
Osteoporos Int 2007;18:1583-93

All subjects with a hip fracture in Denmark between 1977 and 2001. 169,145 fracture cases were compared to 524,010 controls. The cases had higher prevalence of co-morbidity than the controls. The mortality rate was twice as high in fracture cases (HR=2.26, 95% CI: 2.24-2.27). Adjustments for confounders changed the excess mortality risk little. The mortality after the hip fracture was divided into two categories: an excess mortality of 19% within the first year following the fracture (relative survival = 0.81 compared to controls), and an excess mortality of 1.8% per year (relative survival 0.982) for every additional year following the fracture. The major causes of the excess mortality were due to complications to the fracture event (70.8% within the first 30 days). Patients with a hip fracture have a excess mortality risk linked to the fracture event, not to pre-existing co-morbidity.

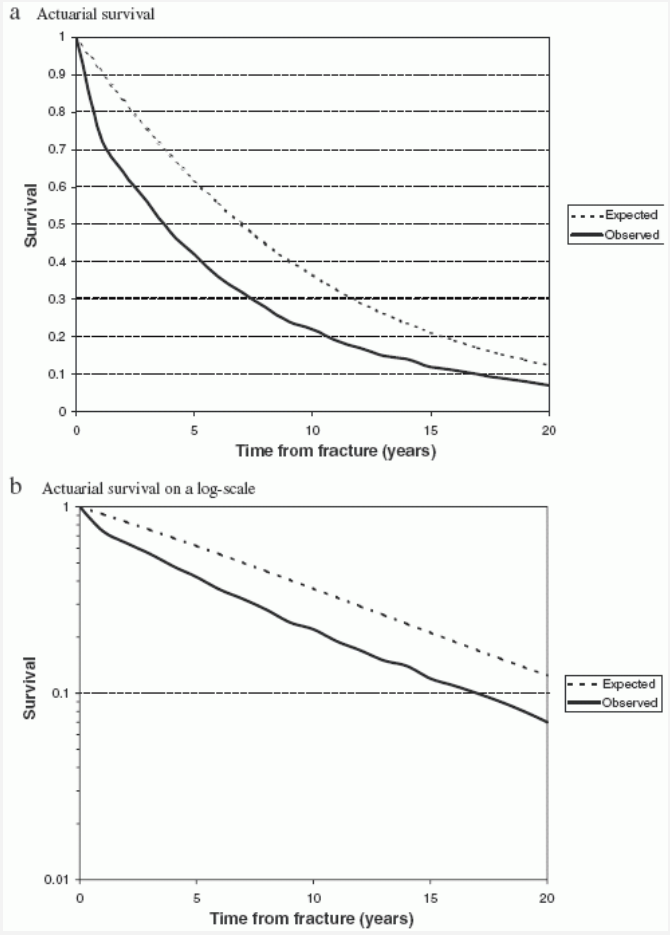


Fig. 9.2.3 Observed and expected long-term survival among patients with a hip fracture. a) Actuarial survival. Footnote: The expected survival was based on an age- and gender matched selection of the general population. b) Actuarial survival on a log-scale. Reproduced from Osteoporos Int 2007; 18:1583-93 wih permission from Springer.

9.2.4 Survival and functional outcome according to hip fracture type: A one-year prospective cohort study in elderly women with an intertrochanteric or femoral neck fracture
Haentjens P, Autier P, Barette M, Venken K, Vanderschueren D, Boonen S
Bone 2007;41:958-64

In a one-year prospective cohort study of 170 women enrolled, 86 (51%) had an intertrochanteric and 84 (49%) a femoral neck fracture. At discharge, intertrochanteric hip fracture patients had a higher mortality (p=0.006) and were more impaired (p=0.005). One year later, mortality was still higher after intertrochanteric fracture (relative risk 2.5: 1.3-5.1), but functional outcome among surviving patients was similar by group. Intertrochanteric fractures are associated with increased mortality. Functional outcome differs by fracture type at hospital discharge, but these differences do not persist.

Volume 9, Issue 2, 2008

Financial Cost

9.2.5 The cost-effectiveness of alendronate in the management of osteoporosis
Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, Selby P, Compston J
Bone 2008;42:4-15

Cost-effectiveness of alendronate 70 mg weekly for 5 years in postmenopausal women with clinical risk factors for fracture was computed using the incremental cost-effectiveness ratio (ICER) in Markov methodology. Using a threshold of 30,000 and 20,000 GBP per quality of life-year (QALY) gained, alendronate was cost-effective for the primary prevention of fracture in women with osteoporosis irrespective of age as was treatment of women with a prior fragility fracture irrespective of BMD. Cost-effective scenarios were also found in women with risk factors for fracture with a BMD above the threshold for osteoporosis.

9.2.6 Direct costs of osteoporosis and hip fracture: An analysis for the Mexican healthcare system
Clark P, Carlos F, Barrera C, Guzman J, Maetzel A, Lavielle P, Ramirez E, Robinson V, Rodriguez-Cabrera R, Tamayo J, Tugwell P
Osteoporos Int 2008;19:269-76

The total direct costs for OP and hip fracture were estimated for 2006 based on the projected annual incidence of hip fractures in Mexico. A total of 22,233 hip fracture cases were estimated for 2006 with a total cost to the healthcare system of US$97,058,159 for the acute treatment alone ($4,365.50 per case).

9.2.7 Economic implications of osteoporosis-related femoral fractures in Saudi Arabian society
Bubshait D, Sadat-Ali M
Calcif Tissue Int 2007;81:455-8

This is a retrospective study of all patients admitted to the orthopaedic department of the King Fahd Hospital of the University, Al Khobar between January 2001 and December 2006. There were 63 patients admitted to the hospital with osteoporosis-related fractures and 43 sustained proximal femoral fractures. The cost of management of these patients from admission to discharge was analyzed. A verbal survey was carried with all the hospitals in the eastern province to establish the prevalence of osteoporosis-related femoral fractures for a 12-month period. There were 23 male and 20 female patients with average age of 72.11 years and the hospital stay was for 760 days. The cost of managing these patients was SR2.09 million (US$557,333.00) at the rate of SR48,712 (US$12,989.90) per patient. The survey of all hospitals in the eastern province of Saudi Arabia showed that 984 proximal femoral fractures occurred in a population of 164,121. The estimated cost was SR48 million (US$12.78 million) annually. On a national basis, with a population of 1,461,401 Saudis aged 50 years or more, 8,768 would suffer femoral fractures yearly at a cost of SR4.27 billion (US$1.14 billion).

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

Volume 9, Issue 2, 2008

Genetics

9.2.8 A whole genome linkage scan for QTLs underlying peak BMD
Zhang F, Xiao P, Yang F, Shen H, Xiong DH, Deng HY, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Deng HW
Osteoporos Int 2008;19:303-10

A whole genome linkage scan (WGLS) for peak BMD using 2,200 Caucasians from 207 pedigrees, aged 20-50 years were genotyped with 410 microsatellite markers. The most impressing region is 12p12 for hip PBMD (LOD=2.79) in the total sample. Epistatic interaction analyses found a epistatic interaction between 12p12 and 22q13 (p=0.0021) for hip PBMD. Additionally, we detected suggestive linkage evidence at 15q26 (LOD=2.93), 2p13 (LOD=2.64), and Xq27 (LOD=2.64). Sex-specific analyses suggested the presence of sex-specific QTLs for PBMD variation.

9.2.9 Sex-specific association of the glucocorticoid receptor gene with extreme BMD
Peng YM, Lei SF, Guo Y, Xiong DH, Yan H, Wang L, Guo YF, Deng HW
J Bone Miner Res 2008;23:247-52

The glucocorticoid (GC) receptor (GR) gene is an important candidate for BMD regulation in GC-induced osteoporosis (GIO). However, no study has explored the genetic effects of the GR gene on BMD variation in the Chinese population. Our sample consisted of 800 unrelated subjects (400 women and 400 men) with extreme age-adjusted hip BMD Z-scores selected from a population composed of 1988 normal adult Chinese Han. Four single nucleotide polymorphisms (SNPs) in the GR gene were genotyped. Both single SNP and haplotype association analyses were conducted. SNP rs1866388 (p(c)=0.028) was associated with extreme BMD only in men. In both sexes, haplotypes involving rs1866388 and rs2918419 were found to have different frequency distributions in extremely low and high BMD groups (p(p)=0.024, 0.001, and 0.002 in women and 0.002, 0.003, and 0.003 in men for window sizes of two, three, and four SNPs, respectively). Most shared haplotypes showed opposite effects between women and men. For the first time, our study suggested the possible role of the GR gene on BMD regulation and sex specificity in the association of GR with extreme BMD in the Chinese.

9.2.10 Family-based association study of ROR2 polymorphisms with an array of radiographic hand bone strength phenotypes
Ermakov S, Malkin I, Keter M, Kobyliansky E, Livshits G
Osteoporos Int 2007;18:1683-92

Bone size and BMD are major determinants of bone strength. This study tested the hypothesis of association of radiographic hand bone length (BL) and BMD with polymorphisms in ROR2 gene that is important in skeletal development. Nineteen ROR2 SNPs were genotyped in 705 individuals, belonging to 212 nuclear families. The four tagging SNPs (tSNPs) and the pairwise haplotypes between adjacent tSNPs were tested for association with series of hand BL and BMD measurements, adjusted for covariates, using family-based association tests. We observed associations with BL and BMD mean values for all 18 studied hand bones (p=0.0080, 0.0030), mean BL and BMD for proximal phalanges (p=0.0218, 0.0060) and metacarpal bones (p=0.0014, 0.0004). The region of the first through the second ROR2 introns is most likely to contain the functional polymorphism/s responsible for the observed associations.

9.2.11 Bone microstructure and its associated genetic variability in 12 inbred mouse strains: µCT study and in silico genome scan
Sabsovich I, Clark JD, Liao G, Peltz G, Lindsey DP, Jacobs CR, Yao W, Guo T-Z, Kingery WS
Bone 2008;42:439-51

This study examined the genetic variation of cortical and trabecular bone microarchitecture across 12 strains of 4-month old inbred male mice. Skeletal microarchitecture varied in a compartment- and site-specific fashion across strains. Genome mapping identified 13 chromosomal intervals associated with skeletal traits and 5 of these intervals were novel. Trabecular microarchitecture in different bone sites correlated across strains and most of the chromosomal intervals associated with these trabecular traits were shared between skeletal sites. Conversely, no chromosomal intervals were shared between the trabecular and cortical bone compartments in the femur, even though there was a strong correlation for these different bone compartments across strains, suggesting site-specific regulation by environmental or intrinsic factors.

9.2.12 Epistatic effects contribute to variation in BMD in Fischer 344 x Lewis F2 rats
Koller DL, Liu L, Alam I, Sun Q, Econs MJ, Foroud T, Turner CH
J Bone Miner Res 2008;23:41-7

The variation in risk factors including BMD is caused largely by genetic differences. We have reported quantitative trait locus (QTL) results for BMD from a genome screen of 595 female F(2) progeny of Fischer 344 and Lewis rats. Microsatellite marker data from a 20 cM genome screen was analyzed along with weight-adjusted BMD (DXA and pQCT) phenotypic data using the R/qtl software package. Genotype and phenotype data were permuted to determine a genome-wide significance threshold. Novel loci on chromosomes 12 and 15 showed a epistatic effect on total BMD at the femoral midshaft by pQCT (LOD=5.4). A QTL on chromosome 7 was found to interact with a novel locus on chromosome 20 to affect whole lumbar BMD by pQCT (LOD=6.2).

9.2.13 Genetic loci affecting bone structure and strength in inbred COP and DA rats
Sun Q, Alam I, Liu L, Koller DL, Carr LG, Econs MJ, Foroud T, Turner CH
Bone 2008;42:547-53

A sample of 828 (405 males and 423 females) COP x DA F2 progeny had extensive phenotyping for bone structure snd strength phenotypes. A whole-genome screen was conducted in the F2 rats, using microsatellite markers spaced at approximately 20 cM intervals. Significant QTL for femur structure and strength were identified on chromosome (Chr) 1 with a maximum LOD

score of 33.5; evidence of linkage was found in both the male and female rats. In addition, Chrs 6, 7, 10, 13, 15 and 18 were linked to femur midshaft structure. QTL linked to femur strength were identified on Chrs 5 and 10. For L5 vertebrae, Chrs 2, 16, and 18 harbored QTL for cortical structure and trabecular structure for L5 was linked to Chrs 1, 7, 12, and 18. One female-specific QTL for femur ultimate force was identified on Chr 5, and two male-specific QTL for L5 cortical area were found on Chrs 2 and 18.

9.2.14 The skeletal response to estrogen is impaired in female but not in male steroid receptor coactivator (SRC)-1 knockout mice

Modder UI, Sanyal A, Xu J, O'Malley BW, Spelsberg TC, Khosla S

Bone 2008;42:414-21

Steroid receptor coactivator (SRC)-1 mediates estrogen (E) effects on bone in female mice. Analysis of male and female mice showed a decrease in trabecular vBMD in SRC-1 KO mice in both genders. Following gnx and E (10 mg/kg/day), SRC-1 KO female mice have a defect in E action in trabecular, not cortical bone. The same dose of E to gnx'd male SRC-1 KO mice prevented trabecular bone loss. For example, in WT female mice, gnx followed by E maintained spine BMD as compared to gnx without E replacement - this effect of E was absent in SRC-1 KO female mice. By contrast, the same dose of E was equally effective in maintaining spine BMD in E-treated gnx'd male WT and male SRC-1 KO mice, respectively, as compared to gnx'd mice without E. E was effective in suppressing cancellous bone turnover in both gnx'd WT and SRC-1 KO male mice; however, in female mice, E only suppressed bone turnover in WT but not in SRC-1 KO mice. Loss of SRC-1 results in trabecular osteopenia in male and female mice, but in contrast to female mice, this is not due to any detectable resistance to E action in trabecular bone in male SRC-1 KO mice.

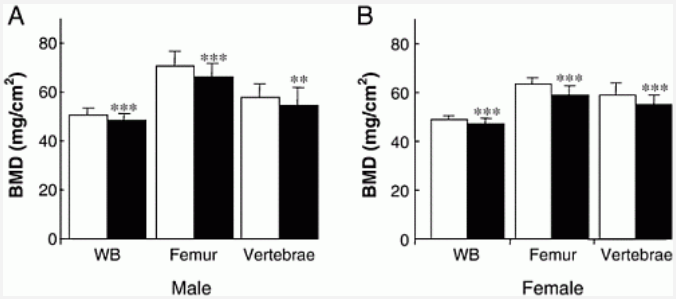


*Fig. 9.2.14a Osteopenia in SRC-1 KO mice. BMD measurements by DXA revealed a significant decrease of the whole body (WB), femur, and vertebral bone density of A) male WT (n=67, open bars) and male SRC-1 KO (n=56, solid bars) and B) female WT (n=66, open bars) and female SRC-1 KO (n=70, solid bars) mice. Bars represent means±SEM. The P-values for the comparison between the WT and SRC-1 KO mice are noted, **P<0.01 and ***P<0.001. Reproduced from Bone, 42:414-21, Copyright (2008), with permission from Elsevier.*

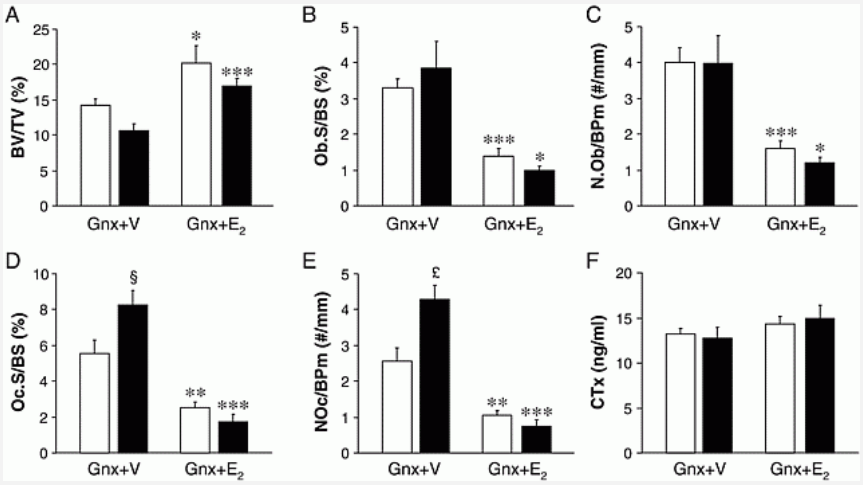


*Fig. 9.2.14b Bone histomorphometry data were determined at the lumbar vertebrae of male WT (n=8-10, open bars) and SRC-1 KO (n=7-11, solid bars) mice either gnx'd and treated with a slow release E2 pellet or vehicle for 60 days. (A) Trabecular bone volume expressed as percentage bone volume/tissue volume (BV/TV). (B) Percentage of osteoblast surface per bone surface (Ob. S/BS). (C) Number of osteoblast per bone parameter (N.Ob/BPm). (D) Percentage of osteoclast surface per bone surface (Oc.S/ BS). (E) Number of osteoclast per bone parameter (N.Oc/BPm). (F) C-terminal telopeptide of collagen type I cross links (CTx) was determined in serum of n=7 male WT and SRC-1 KO mice. *P<0.05, **P<0.01, and ***P<0.001 for direct comparison with the respective gnx+vehicle group. In addition the gnx+V, WT and SRC-1 KO mice were compared with each other. §P<0.01, and £P<0.001. Reproduced from Bone, 42:414-21, Copyright (2008), with permission from Elsevier.*

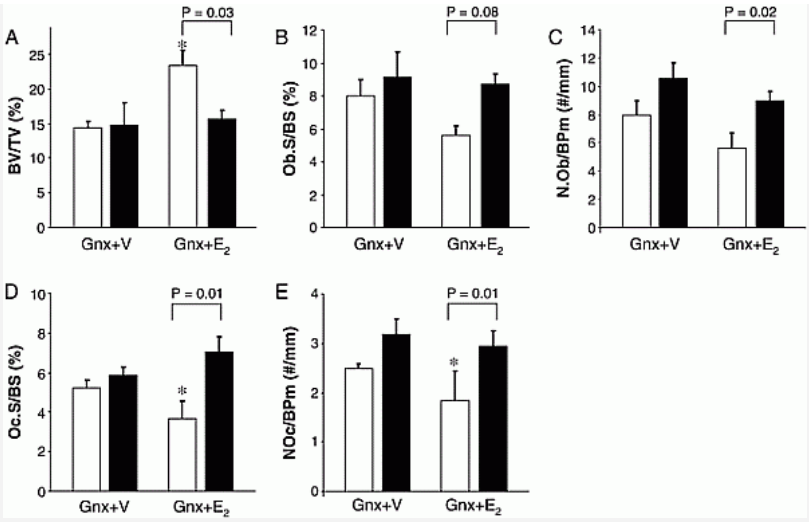


*Fig. 9.2.14c Bone histomorphometry data were determined at the lumbar vertebrae of female WT (n=5, open bars) and SRC-1 KO (n=3-6, solid bars) mice either gnx'd and treated with a slow release E2 pellet or vehicle for 60 days. (A) Trabecular bone volume expressed as percentage bone volume/tissue volume (BV/TV). (B) Percentage of osteoblast surface per bone surface (Ob. S/BS). (C) Number of osteoblast per bone parameter (N.Ob/BPm). (D) Percentage of osteoclast surface per bone surface (Oc.S/ BS). (E) Number of osteoclast per bone parameter (N.Oc/BPm). *P<0.05 for direct comparison with the respective gnx+vehicle group. WT and SRC-1 KO gnx+E groups were compared with each other; the P-values are noted in the figure. For the statistical analyses the post hoc Fisher's PLSD test was used. Reproduced from Bone, 42:414-21, Copyright (2008), with permission from Elsevier.*

9.2.15 The RIZ Pro704 insertion-deletion polymorphism, BMD and fracture risk: The Rotterdam study
Stolk L, van Meurs JBJ, Arp PP, Hofman A, Pols HAP, Uitterlinden AG
Bone 2008;42:286-93

9.2.16 The COMT val158met polymorphism is associated with prevalent fractures in Swedish men
Eriksson AL, Mellstrom D, Lorentzon M, Orwoll ES, Redlund-Johnell I, Grundberg E, Holmberg A, Ljunggren O, Karlsson MK, Ohlsson C
Bone 2008;42:107-12

9.2.17 Association between myostatin gene polymorphisms and peak BMD variation in Chinese nuclear families
Zhang ZL, He JW, Qin YJ, Hu YQ, Li M, Zhang H, Hu WW, Liu YJ, Gu JM
Osteoporos Int 2008;19:39-47

9.2.18 Three novel mutations of the PHEX gene in three Chinese families with X-linked dominant hypophosphatemic rickets
Xia W, Meng X, Jiang Y, Li M, Xing X, Pang L, Wang O, Pei Y, Yu LY, Sun Y, Hu Y, Zhou X
Calcif Tissue Int 2007;81:415-20

9.2.19 Polymorphisms and haplotypes of integrinalpha1 (ITGA1) are associated with BMD and fracture risk in postmenopausal Koreans
Lee HJ, Kim SY, Koh JM, Bok J, Kim KJ, Kim KS, Park MH, Shin HD, Park BL, Kim TH, Hong JM, Park EK, Kim DJ, Oh B, Kimm K, Kim GS, Lee JY
Bone 2007;41:979-86

9.2.20 Different gene expression patterns in the bone tissue of aging postmenopausal osteoporotic and non-osteoporotic women
Balla B, Kósa JP, Kiss J, Borsy A, Podani J, Takács I, Lazáry A, Nagy Z, Bácsi K, Speer G, Orosz L, Lakatos P
Calcif Tissue Int 2008;82:12-26

9.2.21 Bivariate whole genome linkage analyses for total body lean mass and BMD
Wang XL, Deng FY, Tan LJ, Deng HY, Liu YZ, Papasian CJ, Recker RR, Deng HW
J Bone Miner Res 2008;23:447-52

9.2.22 Clinical and cellular manifestations of OSTM1-related infantile osteopetrosis
Maranda B, Chabot G, Decarie JC, Pata M, Azeddine B, Moreau A, Vacher J
J Bone Miner Res 2008;23:296-300

9.2.23 A new heterozygous mutation (R714C) of the osteopetrosis gene, pleckstrin homolog domain containing family M (with run domain) member 1 (PLEKHM1), impairs vesicular acidification and increases TRACP secretion in osteoclasts
Del Fattore A, Fornari R, Van Wesenbeeck L, de Freitas F, Timmermans JP, Peruzzi B, Cappariello A, Rucci N, Spera G, Helfrich MH, Van Hul W, Migliaccio S, Teti A
J Bone Miner Res 2008;23:380-91

9.2.24 Development of craniofacial structures in transgenic mice with constitutively active PTH/PTHrP receptor
Tsutsui TW, Riminucci M, Holmbeck K, Bianco P, Robey PG
Bone 2008;42:321-31

9.2.25 Dysregulated BMP signaling and enhanced osteogenic differentiation of connective tissue progenitor cells from patients with fibrodysplasia ossificans progressiva
Billings PC, Fiori JL, Bentwood JL, O'Connell MP, Jiao X, Nussbaum B, Caron RJ, Shore EM, Kaplan FS
J Bone Miner Res 2008;23:305-13

9.2.26 A chemical mutagenesis screen to identify modifier genes that interact with growth hormone and TGFb signaling pathways
Mohan S, Baylink DJ, Srivastava AK
Bone 2008;42:388-95

9.2.27 Polymorphisms in the endothelial nitric oxide synthase gene and bone density/ultrasound and geometry in humans
Cho K, Demissie S, Dupuis J, Cupples LA, Kathiresan S, Beck TJ, Karasik D, Kiel DP
Bone 2008;42:53-60

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Measurement of Bone Mass

9.2.28 Calcifications in the abdominal aorta predict fractures in men: MINOS study
Szulc P, Kiel DP, Delmas PD
J Bone Miner Res 2008;23:95-102

In 781 men ≥50 yr of age during a 10-year follow-up, 66 men sustained incident clinical fractures. Calcifications in the abdominal aorta expressed as an aortic calcification score (ACS) were assessed by a semiquantitative method. ACS>2 was associated with a 2-fold increase in the mortality risk after adjustment. After adjustment men in the highest quartile of ACS (>6) had lower BMD of distal forearm, ultradistal radius, and whole body than men in the lower quartiles. Log-transformed ACS predicted fractures when adjusted for age, BMI, age by BMI interaction, prevalent fractures, BMD, and history of two or more falls (e.g., hip BMD; OR=1.44; p<0.02). ACS, BMD at all the skeletal sites, and history of two or more falls were independent predictors of fracture. Men with ACS>6 had a 2- to 3-fold increased risk of fracture after adjustment for confounding variables (OR=2.54-3.04; p<0.005-0.001 according to the site). This long-term prospective study showed that elevated ACS (>6) is a robust and independent risk factor for incident fracture in older men regardless of age, BMI, BMD, prevalent fractures, history of two or more falls, comorbidities, and medications.

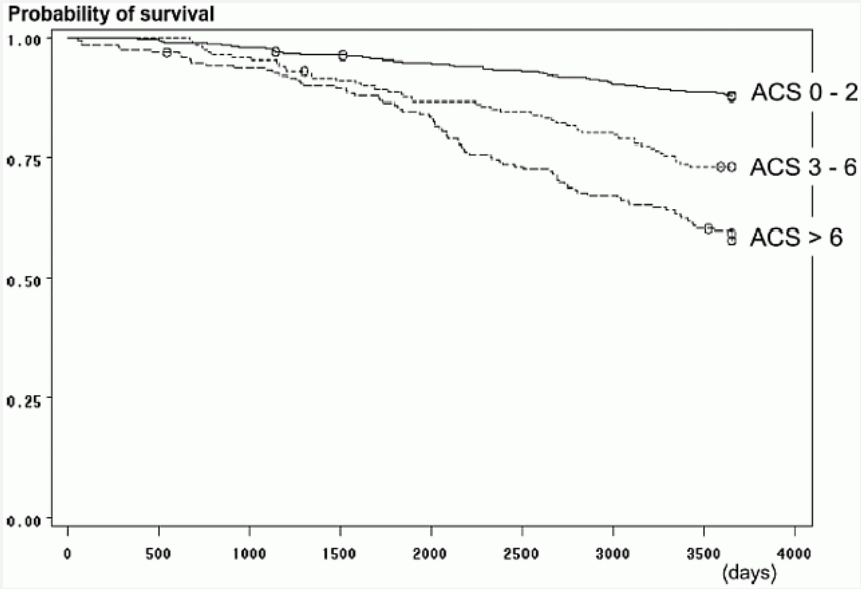

Fig. 9.2.28 Survival of men according to the baseline ACS. Survival of men from the MINOS cohort during the 10 yr of the follow-up according to the ACS at baseline: ACS in two first quartiles (0-2), third quartile (3-6), and fourth quartile (>6). Reproduced from J Bone Miner Res 2008;23:95-102 with permission of the American Society for Bone and Mineral Research.

9.2.29 Longitudinal changes in BMD and bone geometry in a population-based study
Lauretani F, Bandinelli S, Griswold ME, Maggio M, Semba R, Guralnik JM, Ferrucci L
J Bone Miner Res 2008;23:400-8

Three hundred forty-five men and 464 women 21-102 years of age from the InCHIANTI study had tibial QCT measured during 6-yr. Periosteal apposition occurred both in men and women. The annual rate of bone periosteal apposition was higher in younger than in older men, whereas in women, the rate of apposition was homogenous across age groups. The age-related medullary expansion, was higher in women compared with men. In women, but not in men, accelerated endocortical resorption not sufficiently balanced by periosteal apposition caused accelerated loss in cortical bone mass. The cross-sectional moment of inertia decreased progressively over the life span in both sexes. Endocortical resorption causes bone loss in older women despite periosteal apposition. Obtaining a balance between endocortical resorption and periosteal apposition should be the target for interventions aimed to decrease bone loss and prevent osteoporosis in older women.

9.2.30 Algorithm-based qualitative and semiquantitative identification of prevalent vertebral fracture: Agreement between different readers, imaging modalities, and diagnostic approaches
Ferrar L, Jiang G, Schousboe JT, DeBold CR, Eastell R
J Bone Miner Res 2008;23:417-24

The aims of this study were to (1) compare the prevalence of VFs; (2) compare the characteristics of women with and without VFs; (3) compare interobserver agreement; and (4) compare agreement between methods and imaging modalities for ABQ and SQ definitions of VFs. Spine radiographs and absorptiometry images for 203 elderly women were assessed using ABQ (readers ABQ-1 and ABQ-2). These readings were compared with SQ assessments (readers SQ-1 and SQ-2) of the same images performed in a previous study. The prevalence of VF was 15-18% (radiography) and 12-24% (VFA) for ABQ and SQ, respectively. Women with ABQ or SQ fractures were older and had lower BMD than those without fracture (p<0.01). Mild ABQ (but not SQ) VF was associated with low BMD. Kappa scores for interobserver agreement for radiography and VFA, respectively, were as follows: ABQ, kappa=0.74 (95% CI, 0.60, 0.87) and 0.65 (95% CI, 0.48, 0.81); SQ, kappa=0.53 (95% CI, 0.46, 0.60) and 0.51 (95% CI, 0.44, 0.58). For agreement between ABQ-1 and SQ-1, kappa=0.55 (95% CI, 0.39, 0.72) for radiography and 0.41 (95% CI, 0.25, 0.58 for VFA. The prevalence of radiographic VF identified by ABQ and SQ was similar, but on VFA was 50% higher for SQ. Mild ABQ VF was associated with low BMD. Interobserver agreement for radiographic diagnosis was significantly better for ABQ

than for SQ. Agreement between ABQ and SQ was moderate.

9.2.31 Comparison of densitometric and radiographic vertebral fracture assessment using the algorithm-based qualitative method in postmenopausal women at low and high risk of fracture
Ferrar L, Jiang G, Clowes JA, Peel NF, Eastell R
J Bone Miner Res 2008;23:103-11

Using densitometric vertebral fracture assessment (VFA), prevalent fractures are identified when vertebral height appears reduced by ≥20% does not discriminate osteoporotic vertebral fracture (VF) and nonosteoporotic deformity. Algorithm-based qualitative diagnosis (ABQ) focuses on vertebral endplate fracture to exclude these deformities but has not been applied in VFA. Postmenopausal women at low risk (LR; n=459) and high risk (HR; n=298) of VF were assessed using ABQ. The prevalence of VF was 11-29% (radiography) and 9-26% (VFA) in the LR and HR groups, respectively. Agreement between imaging modalities was good or very good (kappa=0.62-0.81 in the LR and HR populations). The sensitivity to detect women with VF by VFA was 71% and 84% in the LR and HR populations, respectively, and specificity was 97%. Fifty-two (77%) and 60 (61%) of vertebrae misclassified by VFA in the LR and HR populations were mild fractures and 37 (54%) and 62 (63%) were wedge fractures. One third of fractures missed by VFA were related to poor or unreadable image quality (n=27 and 28 vertebrae in the LR and HR populations, respectively). Vertebrae misclassified by VFA were primarily mild fractures or deformities, and two thirds of all fractures missed by VFA were related to poor or unreadable image quality.

9.2.32 Correlates of BMD in men of African ancestry: The Tobago Bone Health Study
Hill DD, Cauley JA, Sheu Y, Bunker CH, Patrick AL, Baker CE, Beckles GL, Wheeler VW, Zmuda JM
Osteoporos Int 2008;19:227-34

9.2.33 Effects of the sample size of reference population on determining BMD reference curve and peak BMD and diagnosing osteoporosis
Hou YL, Liao EY, Wu XP, Peng YQ, Zhang H, Dai RC, Luo XH, Cao XZ
Osteoporos Int 2008;19:71-8

9.2.34 Factors affecting short-term bone density precision assessment and the effect on patient monitoring
Leslie WD
J Bone Miner Res 2008;23:199-204

9.2.35 Measurements of mobile and bound water by nuclear magnetic resonance correlate with mechanical properties of bone
Nyman JS, Ni Q, Nicolella DP, Wang X
Bone 2008;42:193-9

9.2.36 In vivo 3D reconstruction of human vertebrae with the three-dimensional X-ray absorptiometry method
Kolta S, Quiligotti S, Ruyssen-Witrand A, Amido A, Mitton D, Bras AL, Skalli W, Roux C
Osteoporos Int 2008;19:185-92

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Bone Material

9.2.37 The associations between mineral crystallinity and the mechanical properties of human cortical bone
Yerramshetty JS, Akkus O
Bone 2008;42:476-82

Raman spectroscopy was used to provide information on the crystallinity of bone's mineral phase, a parameter which is an overall indicator of mineral crystal size and stoichiometric perfection. Raman scans and mechanical tests (monotonic and fatigue; n=64 each) were performed on the anterior, medial, lateral and posterior quadrant sections of 16 human cadaveric femurs (52 y.o.-85 y.o.). Crystallinity explained 6.7% to 48.3% of the variation in monotonic mechanical properties. Tissue-level strength and stiffness increased with increasing crystallinity while the ductility reduced. Crystallinity explained 11.3% to 63.5% of the variation in fatigue properties. Moduli of specimens with greater crystallinity degraded at a slower rate and, also, they had longer fatigue lives.

9.2.38 Variations of microstructure, mineral density and tissue elasticity in B6/C3H mice
Raum K, Hofmann T, Leguerney I, Saied A, Peyrin F, Vico L, Laugier P
Bone 2007;41:1017-24

200-MHz scanning acoustic microscopy (SAM) and synchrotron radiation microCT (SR-μCT) were used to assess microstructure, acoustic impedance Z and tissue degree of mineralization (DMB) in femora. Transverse femoral sections from B6 and C3H mice (5.5 months old) were explored. Mass density rho, elastic coefficient c(11) and Young's modulus E(1) were locally derived in the distal epiphysis, distal metaphysis for trabecular bone and mid-diaphysis. Structural parameter estimates from X-ray tomographic and acoustic images were almost identical. Both strains had the same bone diameter, but the C3H mice had greater cortical thickness and smaller cancellous diameter than B6. DMB and impedance values were between 1.13 and 1.33 g/cm3 and 5.8 and 7.8 Mrayl, respectively. All tissue parameters were lower in B6 than C3H. However, interstrain differences of DMB were much less (up to 3.8%) than differences of Z (up to 13.2%). SAM provides a quantitative estimate of elastic properties at the tissue level that cannot be captured by SR-μCT.

9.2.39 Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes
Yamamoto M, Yamaguchi T, Yamauchi M, Yano S, Sugimoto T
J Clin Endocrinol Metab 2008;93:1013-9

Increased bone pentosidine (PEN) is associated with its plasma levels and bone fragility. In Japanese type 2 diabetic patients (77 male over 50 years old and 76 postmenopausal female), with and without VFs revealed no differences in BMD or markers. PEN in women with VFs was higher than in those without VFs (0.0440±0.0136 vs. 0.0321±0.0118 microg/ml, p<0.001) independent of BMD (odds ratio=2.50, 1.09-5.73 per SD increase, p=0.0302 PEN levels, but not BMD, may be useful for assessing the risk of prevalent VFs in postmenopausal diabetic women.

9.2.40 Regional variations in mineralization and strain distributions in the cortex of the human mandibular condyle
Cioffi I, van Ruijven LJ, Renders GA, Farella M, Michelotti A, van Eijden TM
Bone 2007;41:1051-8

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Volume 9, Issue 2, 2008

Bone Structure

9.2.41 Structural determinants of vertebral fracture risk

Melton LJ, 3rd, Riggs BL, Keaveny TM, Achenbach SJ, Hoffmann PF, Camp JJ, Rouleau PA, Bouxsein ML, Amin S, Atkinson EJ, Robb RA, Khosla S

J Bone Miner Res 2007;22:1885-92

From an age-stratified sample 40 women with vertebral fracture (cases; mean age, 78.6±9.0 yr) were compared with 40 controls with no fracture (mean age, 70.9±6.8 yr). Spine loading (axial compressive force on L3) was similar in vertebral fracture cases and controls (e.g., for 90 degrees forward flexion, 2639 vs. 2706 N; age-adjusted p=0.173). However, fracture cases had inferior values for most bone density and structure variables. Bone strength measures were also reduced, and the factor-of-risk (phi) was 35-37% greater (worse) among women with a vertebral fracture. Relative risks for the strongest fracture predictor were bone density (total lumbar spine vBMD: OR per SD change, 2.2; 95% CI, 1.1-4.3), bone geometry (vertebral apparent cortical thickness: OR, 2.1; 95% CI, 1.1-4.1), bone microstructure (nonsignificant); bone strength ("cortical" [outer 2 mm] compressive strength: OR, 2.5; 95% CI, 1.3-4.8), and factor-of-risk (phi for 90 degrees forward flexion/overall vertebral compressive strength: OR, 3.2; 95% CI, 1.4-7.5). These variables correlated with spine aBMD (partial r, -0.32 to 0.75), but each was a stronger predictor of fracture in the logistic regression analyses.

9.2.42 Regional variation in vertebral bone morphology and its contribution to vertebral fracture strength

Hulme PA, Boyd SK, Ferguson SJ

Bone 2007;41:946-57

To quantify regional variations in architecture and vertebral strength soft tissue and posterior elements of 20 human functional spine units (FSU) were removed (T9 to L5, mean 74.45±4.25 years). Specimens were loaded in compression to failure. Vertebrae were not homogeneous. Posterior regions had greater bone volume, more connections, reduced trabecular separation and more platelike isotropic structures than anterior regions. Heterogeneity also exists between posterior superior and inferior regions (BV/TV: posterior superior 12.6±2.8%, inferior 14.6±3%; anterior superior 10.5±2.2%, inferior 10.7±2.4%). Of the two endplates that abutted a common disc, the cranial inferior endplate was thicker (0.44±0.15 mm) than the caudal superior endplate (0.37±0.13 mm). Correlations occurred between BV/TV, connective density and yield strength. Fracture risk prediction, using BV/TV multiplied by the cross sectional area of the endplate, can be improved through regional analysis of the underlying cancellous bone of the endplate of interest (R(2) 0.78) rather than analysis of the entire vertebra (R(2) 0.65) or BMD (R (2) 0.47). A negative linear relationship between disc health and vertebral strength (R(2) 0.70) was observed, perhaps due to a shift in loading from the weaker anterior to the stronger posterior region and cortical shell.

9.2.43 Trabecular structure quantified with the MRI-based virtual bone biopsy in postmenopausal women contributes to vertebral deformity burden independent of areal vertebral BMD

Ladinsky GA, Vasilic B, Popescu AM, Wald M, Zemel BS, Snyder PJ, Loh L, Song HK, Saha PK, Wright AC, Wehrli FW

J Bone Miner Res 2008;23:64-74

Postmenopausal women, 60-80 yr of age, were screened by DXA, and those with T-scores at either the hip or spine falling within the range of -2.5±1.0 were studied with the MRI-based virtual bone biopsy, along with heel broadband ultrasound absorption and pQCT of the tibia. The data from 98 subjects meeting the enrollment criteria. A spinal deformity index (SDI) was obtained from morphometric measurements in midline sagittal MR images of the thoracic and lumbar spine to evaluate associations between structure and deformity burden. A number of structural indices obtained at the distal radius were correlated with the SDI. Among these were the topological surface density (a measure of trabecular plates) and trabecular bone volume fraction, which were inversely correlated with SDI (p<0.0001). Combinations of two structural parameters accounted for up to 30% of the variation in SDI (p<0.0001) independent of spinal BMD, which was not correlated. pQCT trabecular BMD was also weakly associated, whereas broadband ultrasound absorption was not. No significant association between SDI and structural indices were found at the tibia. Structural measures at the distal radius obtained in vivo by microMRI explained a significant portion of the variation in total spinal deformity burden in postmenopausal women independent of areal BMD.

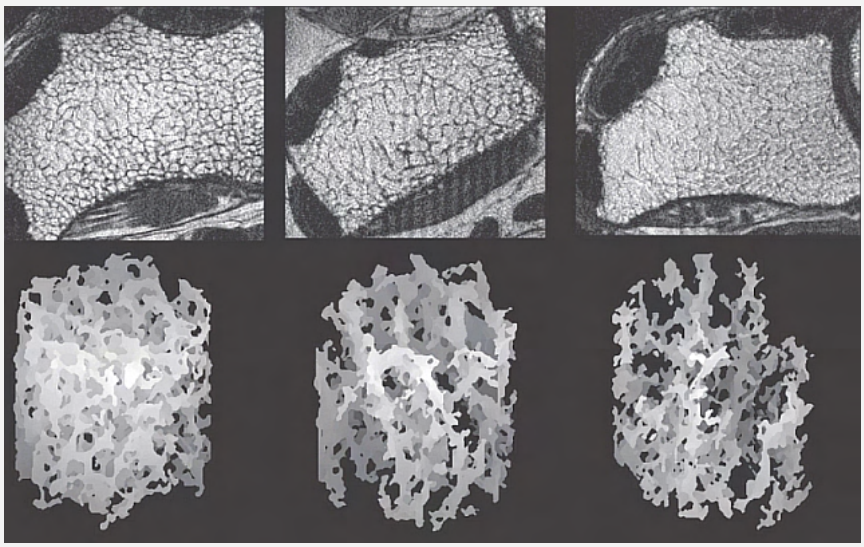

Fig. 9.2.43 μMRIs of the distal radius (top row) with their respective virtual cores (bottom row) along with structural parameters

from three subjects exemplifying a wide range in bone quality represented by the topological parameters that vary by over an order of magnitude between the extremes: (A) 68-yr old woman having a well connected bone structure; (B) 69-yr old woman with less dense trabecular network; (C) 87-yr old woman with sparse trabeculae and disconnected network. Reproduced from J Bone Miner Res 2008;23:64-74 with permission of the American Society for Bone and Mineral Research.

9.2.44 Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women

Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD
J Bone Miner Res 2008;23:392-9

In 33 postmenopausal women with a prior history of fragility wrist fracture and 33 age-matched controls from the OFELY cohort, radius aBMD was measured by DXA and pQCT. Areal and volumetric densities, cortical thickness, trabecular number, and mechanical parameters such as estimated failure load, stiffness, and the proportion of load carried by the trabecular bone at the distal and proximal sites were associated with wrist fracture ($p<0.05$). The PCA revealed five independent components that jointly explained 86.2% of the total variability of bone characteristics. The first PC included FE-estimated failure load, areal and volumetric BMD, and cortical thickness, explaining 51% of the variance with an OR for wrist fracture = 2.49 (95% CI, 1.32-4.72). The second PC included trabecular architecture, explaining 12% of the variance, with an OR=1.82 (95% CI, 0.94-3.52). The third PC included the proportion of the load carried by cortical versus trabecular bone, assessed by FEA, explaining 9% of the variance, and had an OR=1.61 (95% CI, 0.94-2.77). Thus, the proportion of load carried by cortical vs.rabecular bone seems to be associated with wrist fracture independently of BMD and microarchitecture (included in the first and second PC, respectively). Bone mechanical properties assessed by μFE may provide information about skeletal fragility and fracture risk not assessed by BMD or architecture measurements alone and are therefore likely to enhance the prediction of wrist fracture risk.

9.2.45 Race and ethnic variation in proximal femur structure and BMD among older men

Marshall LM, Zmuda JM, Chan BK, Barrett-Connor E, Cauley JA, Ensrud KE, Lang TF, Orwoll ES
J Bone Miner Res 2008;23:121-30

In a cross-sectional study, dimensions and vBMD in the femoral neck and shaft were obtained from QCT scans among 3,305 men ≥65 yr of age in the Osteoporotic Fractures in Men (MrOS) study. All groups had similar femoral neck integral volume. Among black and Asian men, mean cortical volume as a percent of integral volume was 6% greater, integral vBMD was 6-10% greater, and trabecular vBMD was 33-36% greater than means among whites. Shaft cross-sectional area was similar among blacks, but smaller among Asians, compared with whites. However, mean shaft cortical area was greater among blacks but similar among Asians and whites, resulting in mean cortical thickness being 5% greater among black and Asian men. Blacks also had greater mean cortical vBMD in both the femoral neck and shaft. Black and Asian men ≥65 yr of age have features in the proximal femur that may confer advantages for bone strength. Specifically, greater cortical thickness and higher trabecular vBMD among black and Asian men could help explain the lower hip fracture rates in these populations.

9.2.46 Age trends in proximal femur geometry in men: variation by race and ethnicity

Travison TG, Beck TJ, Esche GR, Araujo AB, McKinlay JB
Osteoporos Int 2008;19:277-87

Dual X-ray absorptiometry scans were obtained for 355 black, 394 Hispanic, and 441 white subjects. Measures were obtained for the narrow neck (NN), intertrochanter (IT) and shaft regions of the proximal femur via hip structural analysis. Black subjects exhibited greater age-specific BMD, CSA and Z, than their white counterparts. For instance, at age 50 y, NN BMD was approximately 11% higher among black men ($p<0.001$). Hispanic men exhibited sharper age-related differences in NN and IT BMD than did others. IT BMD, for instance, decreased by 2.4% with 10 y age among Hispanic subjects, but had virtually no age trend in others ($p<0.001$). These results imply greater bone strength among black American men than among their white counterparts, and may indicate elevated fracture risk among older Hispanic American subpopulations.

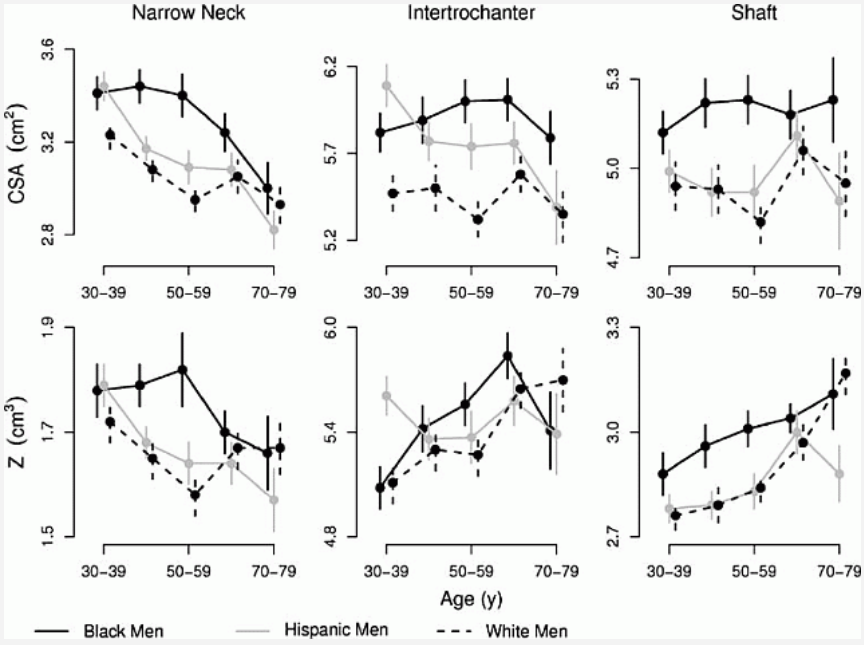

Fig. 9.2.46a Hip bone material (CSA) and bending strength (Z) vs. age, by region. Black men (dark solid lines) tend to have the highest CSA and Z, particularly with respect to their white counterparts. Differences in Z between black and white men are less substantial among the oldest men, while black/white differences in CSA are more consistent across the range of ages. In the narrow neck and intertrochanter regions, Hispanic men show greater cross-sectional decreases in both parameters with age. Horizontal position of symbols is staggered to enhance clarity. Reproduced from Osteoporos Int 2008; 19:277-87 wih permission from Springer.

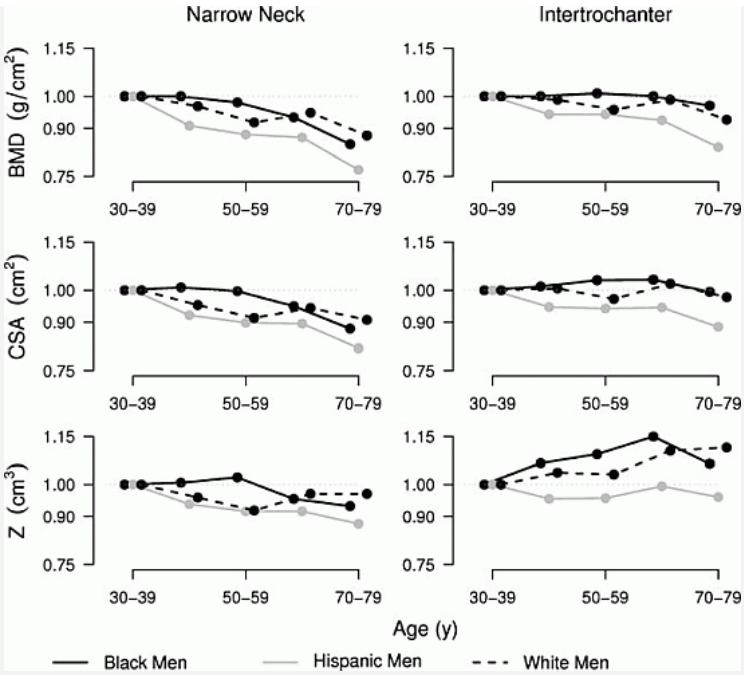

Fig. 9.2.46b Cross-sectional proportionate age trends in strength; narrow neck and intertrochanter regions. Figures depict mean bone density (BMD), material (CSA) and bending strength (Z) scaled to the race/ethnicity-specific means among 30-39 year old men in the sample. A value of 1.0 indicates a mean level equal to the mean among the 30-39 year old men. Hispanic men (gray lines) consistently exhibit the sharpest negative cross-sectional trend with increasing age. Horizontal position of symbols is staggered to enhance clarity. Reproduced from Osteoporos Int 2008; 19:277-87 wih permission from Springer.

9.2.47 Complete volumetric decomposition of individual trabecular plates and rods and its morphological correlations with anisotropic elastic moduli in human trabecular bone

Liu XS, Sajda P, Saha PK, Wehrli FW, Bevill G, Keaveny TM, Guo XE

J Bone Miner Res 2008;23:223-35

Seventy-one human trabecular bone samples from the femoral neck (FN), tibia, and vertebral body (VB) were imaged using μCT or serial milling. Complete volumetric decomposition was applied to segment trabecular bone microstructure into individual plates and rods. The orientation of each individual trabecula was determined, and the axial bone volume fractions (aBV/TV), axially aligned bone volume fraction along each orthotropic axis, were correlated with the elastic moduli. Longitudinal plates and transverse rods dominate at all three anatomic sites. aBV/TV along each axis showed a better correlation with the axial elastic modulus (r(2) = 0.95 approximately 0.99) compared with BV/TV (r(2) = 0.93 approximately 0.94). The plate-associated morphological parameters showed higher correlations with the corresponding standard morphological parameters than the rod-associated parameters. Multiple linear regression models of six elastic moduli with individual trabeculae segmentation (ITS)-based morphological parameters (adjusted r(2) = 0.95 approximately 0.98) performed equally well as those with standard morphological parameters (adjusted r(2) = 0.94 approximately 0.97) but revealed specific contributions from individual trabecular plates or rods. The ITS-based morphological analyses provide a better characterization of the morphology and trabecular orientation of trabecular bone. Results suggest that trabecular plates dominate the overall elastic properties of trabecular bone.

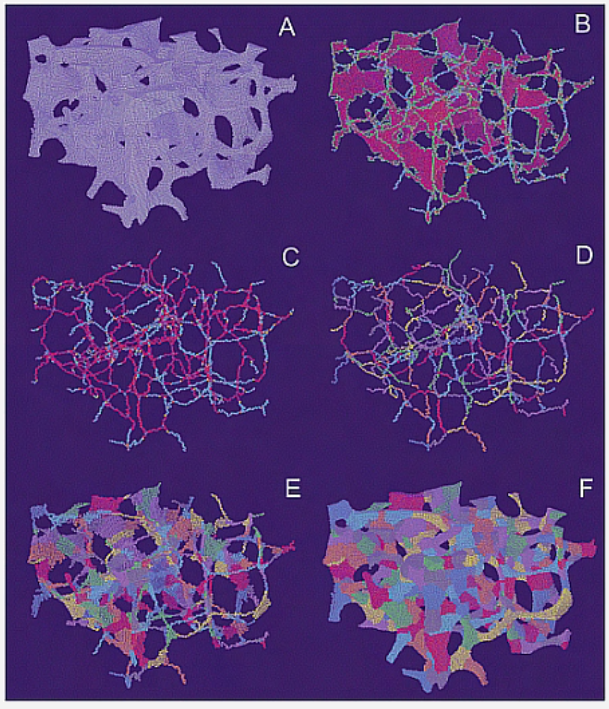

Fig. 9.2.47a Results of the complete volumetric decomposition procedure on image of vertebral trabecular bone sample (3.2×3.2×2.1 mm3). (A) An original image of a trabecular bone sample. (B) Results of skeletonization and topological classification of A. Inner surface voxels are shown as red, surface edge voxels in green, inner curve voxels in light blue, curve end voxels in pink, R-R junctions in orange, and P-R junctions in yellow. (C) Results of arc-skeletonization and topological classification of B. Arc

voxels are shown as red, inner curve voxels in light blue, curve end voxels in pink, P-P junctions in dark blue, R-R junctions in orange, and P-R junctions in yellow. (D) Results of the decomposition of C. (E) Intermediate result of reconstruction to B. (F) Result of complete reconstruction to A. Colors indicate different branches in D-F. Reproduced from J Bone Miner Res 2008;23:223-35 with permission of the American Society for Bone and Mineral Research.

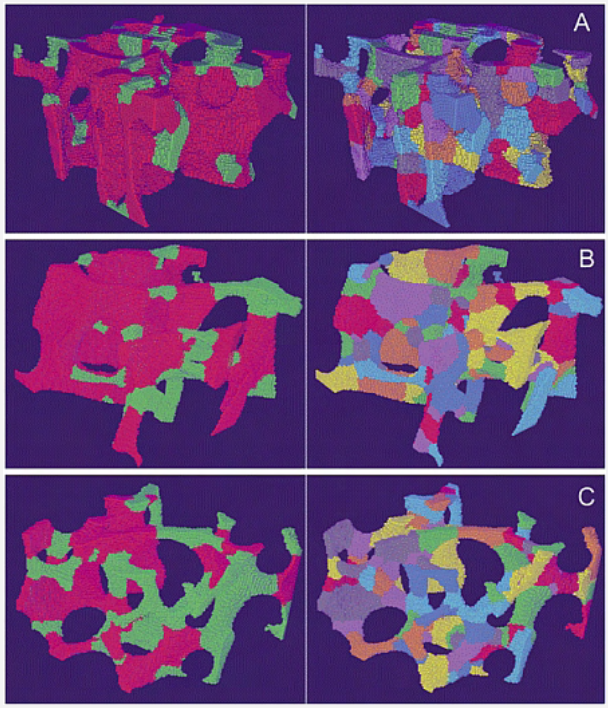

Fig. 9.2.47b Illustrations of complete volumetric decomposition on images of trabecular bone samples (2.1×2.1×1.3 mm3) from different anatomic sites: FN (A), tibia (B), and VB (C). (Left) Trabecular bone structures with the trabecular type labeled for each voxel. Plate voxels are shown in red, rod voxels in green. (Right) Completely decomposed trabecular bone structures with individual trabeculae labeled by color for each voxel. (A) 119 plates and 51 rods. (B) 72 plates and 46 rods. (C) 50 plates and 42 rods. Reproduced from J Bone Miner Res 2008;23:223-35 with permission of the American Society for Bone and Mineral Research.

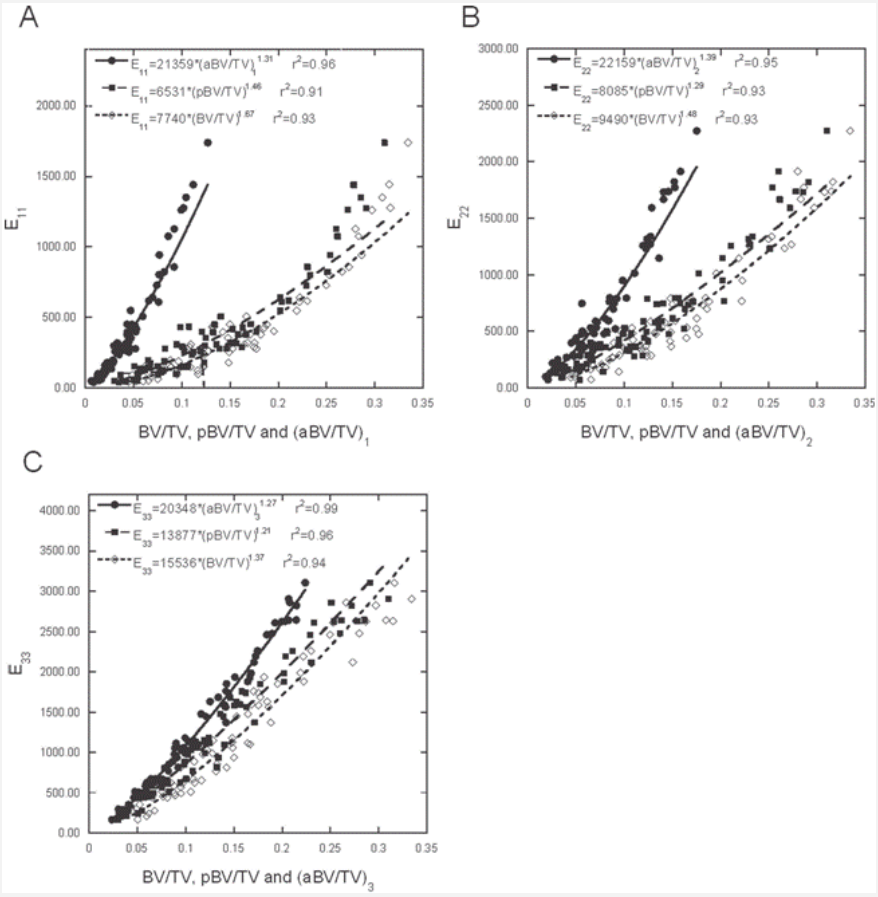

Fig. 9.2.47c Results of correlation analyses between axial elastic modulus Eii and bone volume fraction (BV/TV), plate bone volume fraction (pBV/TV), and Xi axial bone volume fraction (aBV/TV)i by nonlinear regression of power laws (i=1, 2, and 3). p<0.001 for all the correlations. Reproduced from J Bone Miner Res 2008;23:223-35 with permission of the American Society for Bone and Mineral Research.

9.2.48 Trabecular bone gradient in rat long bone metaphyses: mathematical modeling and application to morphometric measurements and correction of implant positioning

Gabet Y, Kohavi D, Kohler T, Baras M, Muller R, Bab I
J Bone Miner Res 2008;23:48-57

The mammalian metaphyseal trabecular bone is unevenly distributed. Hence, defining a standard reference volume is critical for morphometric analyses in metaphyseal sites. The distal femoral and proximal tibial metaphyses of adult orchietomized (ORX) or sham-ORX rats were scanned by μCT 6 wk postoperatively. The respective curve-fit analysis in both femur and tibia revealed decreasing linear/quadratic and logarithmic gradients for all morphometric parameters in the sham-ORX animals. The ORX animals showed similar gradients with roughly similar slopes but lower values. For the bone volume (BV/TV) and connectivity (Conn.D) densities, the magnitude of the ORX effect increased toward the diaphysis. The trabecular number was unaffected in ORX femora and tibias. The trabecular thickness showed a constant decrease in the femur and was unchanged in the tibia.

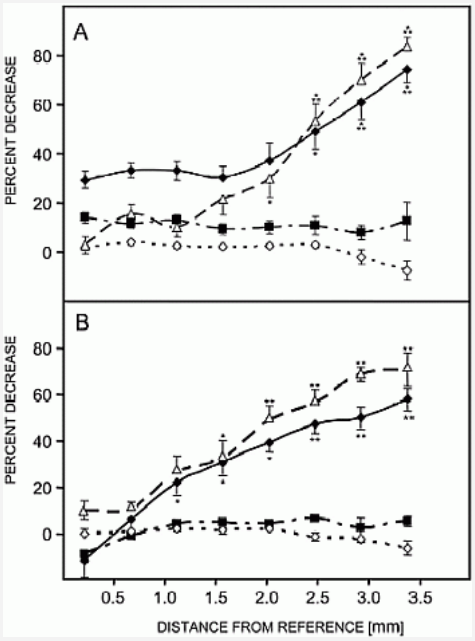

*Fig. 9.2.48 ORX-induced changes in trabecular bone parameters as function of distance from primary spongiosa. Abscissa is distance of layer midplane. Ordinate is ORX-induced percent decrease in the calculated value for corresponding layer in (A) femoral distal metaphysis and (B) tibial proximal metaphysis. ◆, BV/TV; ◇, Tb.N; ■, Tb.Th; △, Conn.D. Data are mean±SE obtained in eight animals per condition; *vs. first segment, p<0.05; **vs. segments 1-3, p<0.05; ***vs. segments 1-5, p<0.05. Reproduced from J Bone Miner Res 2008;23:48-57 with permission of the American Society for Bone and Mineral Research.*

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

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Histomorphology

9.2.49 Structural and cellular differences between metaphyseal and diaphyseal periosteum in different aged rats
Fan W, Crawford R, Xiao Y
Bone 2008;42:81-9

Four female Lewis rats from each group of juvenile (7 weeks old), mature (7 months old) and aged groups (2 years old) were sacrificed. The thickness and cell number in diaphyseal periosteum decreased with age ($p<0.001$). In comparison with diaphyseal area, the thickness and cell number in metaphyseal periosteum were much higher ($p<0.001$). There were no differences between the juvenile and aged groups in the thickness and cell number in the cambial layer of metaphyseal periosteum ($p>0.05$). However, the juvenile rats had more Stro1(+), F4/80(+) cells and blood vessels and fewer TRAP(+) cells in different periosteal areas compared with other groups ($p<0.001$). The aged rats showed much fewer Stro1(+) cells, but more F4/80(+), TRAP(+) cells and blood vessels in the cambial layer of metaphyseal periosteum ($p<0.001$). The metaphyseal periosteum of aged rats seems more destructive than diaphyseal part and other age groups.

Progress in
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Volume 9, Issue 2, 2008

Biomechanics

9.2.50 Biological co-adaptation of morphological and composition traits contributes to mechanical functionality and skeletal fragility
Tommasini SM, Nasser P, Hu B, Jepsen KJ
J Bone Miner Res 2008;23:236-46

Cross-sectional morphology, slenderness (Tt.Ar/Le), and tissue level mechanical properties were measured from tibias from 14 female (22-46 yr old) and 17 male (17-46 yr old) donors. A path analysis was conducted to test the hypothesis that Tt.Ar/Le is functionally related to mineralization (ash content) and the proportion of total area occupied by cortical bone. Ash content correlated negatively with several traits including Tt.Ar/Le and marrow area, indicating that slender bones were constructed of tissue with higher mineralization. Path analysis revealed that slender tibias were compensated by higher mineralization and a greater area fraction of bone. The results suggest that bone adapts by varying the relative amount of cortical bone within the diaphysis and by varying matrix composition.

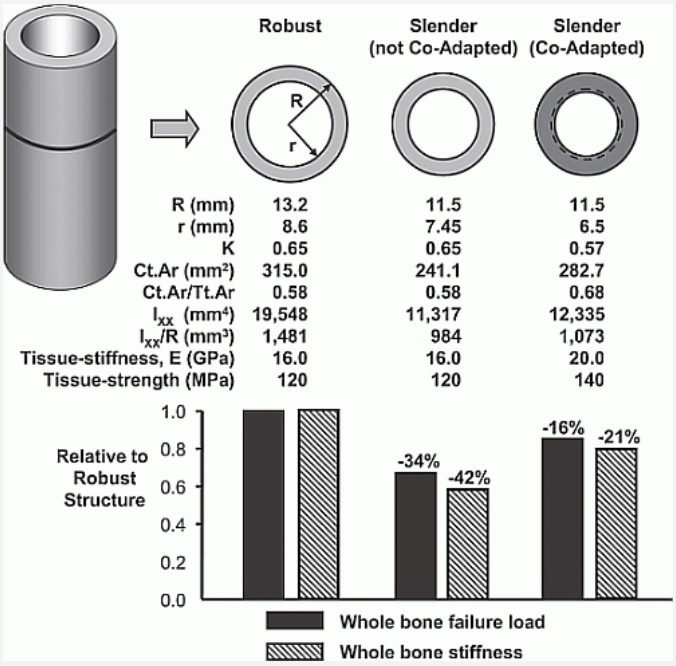

Fig. 9.2.50 Schematic illustration of how co-adaptation of morphological and compositional traits acts to increase overall stiffness and failure load of a slender cylindrical structure. The slender structure, without co-adapted traits, has the same tissue modulus (E), K, and Ct.Ar/Tt.Ar as the robust structure, but this results in a dramatically lower stiffness and failure load. The slender structure with co-adapted traits has a slightly smaller marrow area (lower K, higher Ct.Ar/Tt.Ar) and larger tissue modulus and tissue strength compared with the robust structure. These small changes increase the stiffness and failure load of the slender bone so that they are closer to the robust structure. Reproduced from J Bone Miner Res 2008;23:236-46 with permission of the American Society for Bone and Mineral Research.

9.2.51 An in vitro model to test the contribution of advanced glycation end products to bone biomechanical properties
Viguet-Carrin S, Farlay D, Bala Y, Munoz F, Bouxsein ML, Delmas PD
Bone 2008;42:139-49

In this in vitro model, young bovine cortical bone specimens were incubated in phosphate buffered saline (PBS)±ribose (RIB, an inducer of AGEs formation)±AMG for 15 days at 37 degrees C. (i) incubation±-treatments did not induce collagen denaturation compared to specimens that were not incubated; (ii) neither treatment or incubation time effected the concentration of trivalent enzymatic crosslinks pyridinoline and deoxypyridinoline. The nonenzymatic crosslink PEN was undetectable in specimens that were not incubated or that were incubated in PBS or AMG alone. However, PEN concentration increased in specimens incubated with RIB, whereas ribose-induced PEN formation was markedly inhibited by AMG. (iii) Incubation±treatments did not change the mineral maturity, crystallinity or microhardness assessed by X-ray diffraction, X-ray microscopy analyses, FTIRM and microindentation tests. (iv) PEN concentration was not associated with biomechanical properties assessed by 3-point bending. AMG inhibits ribose-induced formation of PEN crosslinks in bone. AGE concentration did not influence bending mechanical properties; however, the simple 3-point bending test we used was likely inadequate to demonstrate effects of AGEs on mechanical properties.

9.2.52 Validity of serial milling-based imaging system for microdamage quantification
Bigley RF, Singh M, Hernandez CJ, Kazakia GJ, Martin RB, Keaveny TM
Bone 2008;42:212-5

The goal for this study was to compare two-dimensional, surface-based measures of microdamage extracted from this new imaging system against those from more conventional histological section analyses. Human vertebral trabecular cores were isolated, stained en bloc with a series of chelating fluorochromes, monotonically loaded, and underwent microdamage quantification via the two methods. Bone area fraction measured by the new system correlated to that measured by histological

point counting (p<0.001, R(2)=0.80). Additionally, the new system produced statistically equivalent (p=0.021) measures of damage fraction (mean±SD), Dx.AF=0.047±0.021, to that obtained from stereological point counting, Dx.AF=0.048±0.017, at a 10% difference level. These results demonstrate that this serial milling-based fluorescent imaging system provides a destructive yet practical alternative to more conventional histologic section analysis in addition to its ability to provide a better understanding of the three-dimensional nature of microdamage.

9.2.53 Trabecular shear stress amplification and variability in human vertebral cancellous bone: Relationship with age, gender, spine level and trabecular architecture
Yeni YN, Zelman EA, Divine GW, Kim DG, Fyhrie DP
Bone 2008;42:591-6

9.2.54 Proximal femur mechanical adaptation to weight gain in late adolescence: A six-year longitudinal study
Petit MA, Beck TJ, Hughes JM, Lin HM, Bentley C, Lloyd T
J Bone Miner Res 2008;23:180-8

9.2.55 Load distribution in the healthy and osteoporotic human proximal femur during a fall to the side
Verhulp E, van Rietbergen B, Huiskes R
Bone 2008;42:30-5

9.2.56 Correlation between hydroxyapatite crystallite orientation and ultrasonic wave velocities in bovine cortical bone
Yamato Y, Matsukawa M, Yanagitani T, Yamazaki K, Mizukawa H, Nagano A
Calcif Tissue Int 2008;82:162-9

9.2.57 Multi-modality study of the compositional and mechanical implications of hypomineralization in a rabbit model of osteomalacia
Anumula S, Magland J, Wehrli SL, Ong H, Song HK, Wehrli FW
Bone 2008;42:405-13

Progress in
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Growth

9.2.58 Intrauterine programming of bone. Part 1: Alteration of the osteogenic environment
Lanham SA, Roberts C, Cooper C, Oreffo RO
Osteoporos Int 2008;19:147-56

Epidemiological studies suggest skeletal growth is programmed during intrauterine and early postnatal life. Dams received either 18% w/w (control) or 9% w/w (low protein) diet during pregnancy, and the offspring were studied. Alkaline phosphatase activity in controls reached peak levels from 8 to 20 weeks of age. In contrast, restricted diet offspring were at peak levels from 4 weeks of age. Peak levels were similar in both groups. Serum IGF-1 levels were lower in female restricted diet offspring at 4 weeks of age, and serum osteocalcin was higher at 4 weeks of age in male and female offspring from mothers fed the restricted diet, whereas serum 25-OH vitamin D was lower in restricted diet males at 8, 12, and 20 weeks of age. These data indicate that a low protein diet in utero affected the osteogenic environment in the offspring with effects that persist into late adulthood. The nutritional environment in early development on programming of skeletal development with implicit consequences in later life.

9.2.59 Intrauterine programming of bone. Part 2: Alteration of skeletal structure
Lanham SA, Roberts C, Perry MJ, Cooper C, Oreffo RO
Osteoporos Int 2008;19:157-67

Dams received either 18% w/w (control) or w/w 9% (low protein) diet during pregnancy, and the offspring were studied. Using µCT, we found that at 75 weeks of age female offspring from mothers fed a restricted protein diet during pregnancy had femoral heads with thinner, less dense trabeculae, femoral necks with closer packed trabeculae, vertebrae with thicker, denser trabeculae and midshaft tibiae with denser cortical bone. Mechanical testing showed the femoral heads and midshaft tibiae to be structurally weaker, whereas the femoral necks and vertebrae were structurally stronger.

9.2.60 Impact of maternal veiling during pregnancy and socioeconomic status on offspring's musculoskeletal health
Nabulsi M, Mahfoud Z, Maalouf J, Arabi A, Fuleihan GE
Osteoporos Int 2008;19:295-302

This study investigates the effects of maternal veiling during pregnancy, a surrogate for low vitamin D level, and socioeconomic status (SES), a surrogate of nutritional status, on their offspring's bone mass at adolescence. Three hundred and twenty-six healthy adolescents aged 13.1(2.0) years and their mothers were studied. In boys, adjusted analyses revealed that both maternal veiling during pregnancy and SES were predictors of bone mass, at multiple skeletal sites. In girls, SES but not maternal veiling during pregnancy was a significant predictor of bone mass at multiple sites. Maternal veiling during pregnancy was associated with decreased musculoskeletal parameters of boys, but not girls. SES was a significant predictor of bone mass in both genders. These findings may have profound implications on children's bone health.

9.2.61 Fetal growth velocity, size in early life and adolescence, and prediction of bone mass: Association to the GH-IGF axis
Jensen RB, Vielwerth S, Frystyk J, Veldhuis J, Larsen T, Molgaard C, Greisen G, Juul A
J Bone Miner Res 2008;23:439-46

A longitudinal cohort of 16- to 19-year old adolescents (n=123) with data on third trimester fetal growth velocity (FGV) was assessed by serial ultrasound measurements, birth weight (BW), and weight at 1 yr. A follow-up study included DXA scan, anthropometric measurements, and measurements of the growth hormone (GH)-IGF-I axis in a representative subpopulation (n=30). BW and weight at 1 yr were positively associated with whole body BMC (p=0.02 and p<0.0001, respectively), lumbar spine BMC (p=0.001 and p=0.03, respectively), and lumbar spine BMD (p=0.04). After correction for adolescent height and weight, no association remained significant. There was no relation between IGF-I and IGF binding protein 3 (IGFBP-3) levels in adolescence and size in early life or bone mass. In the subpopulation, GH secretion (median, 2.58 vs. 4.05), GH pulse mass (median, 10.7 vs. 19.4 mU/liter), and total GH (median, 74.9 vs. 108.8 mU/liter/12 h) were decreased in the small for gestational age (SGA) group compared with the appropriate for gestational age (AGA) group; this did not reach statistical significance. Likewise, there were no differences in IGF-I, IGF-II, and IGFBP-1, -2, and -3 levels between the SGA and AGA groups. A statistically significant positive association between FGV and adolescent IGF-II was found (B=199.9, p=0.006). Significant negative associations between GH measurement and BMC, as well as BMD, were found (B=-0.008, p=0.005 and B=-0.008, p=0.006, respectively).

9.2.62 Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma
Clark EM, Ness AR, Tobias JH
J Bone Miner Res 2008;23:173-9

Total body DXA scan results obtained at 9.9 yr of age were linked to reported fractures over the following 2 yr in children. Of the 6204 children with available data, 549 (8.9%) reported at least one fracture over the follow-up period, and trauma level was assigned in 280 as follows: slight trauma, 56.1%; moderate trauma, 41.0%; severe trauma, 2.9%. Compared with children without fractures, after adjustment, children with fractures from both slight and moderate/severe trauma had a reduced bone size relative to body size (1133 cm(2) in nonfractured children versus 1112 cm(2) for slight trauma fractures, p<0.001; 1112 cm(2) for moderate/severe trauma fractures, p=0.001) and reduced humeral vBMD (0.494 g/cm(3) in nonfractured children versus 0.484 g/cm(3) for slight trauma fractures, p=0.036; and 0.482g/cm(3) for moderate/severe trauma fractures, p=0.016). Skeletal fragility contributes to fracture risk in children, not only in fractures caused by slight trauma but also in those that result from moderate or severe trauma.

9.2.63 Fractures during growth: Potential role of a milk-free diet
Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E

Osteoporos Int 2007;18:1601-7

In this case-control study 57 boys and 34 girls aged 2.5-20 years with fractures (cases) were randomly matched by age and sex with 171 boys and 102 girls without fractures (controls). In girls, 29.4% of cases and 11.8% of controls had a history of milk-free diet producing an odds ratio (OR) for fracture associated with a milk-free diet of 4.6 (95% CI: 1.4-15.5, p<0.01). In boys, 23% of cases and 19% of controls had a history of a milk-free diet; OR=1.3 (95% CI: 0.6-2.7, NS). If the prevalence of CMA in the population is 5%, only 6.7% of the fractures occurring are attributable to CMA and the associated nutritional deficit. Cow's milk allergy is associated with increased fracture risk in girls. Whether this association is due to the illness, calcium deficit or a deficit in other milk nutrients is uncertain. The contribution of milk-free diet to fracture liability among children and adolescents is modest.

9.2.64 High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys
Chevalley T, Bonjour JP, Ferrari S, Rizzoli R
J Bone Miner Res 2008;23:131-42

In 232 healthy prepubertal boys (age: 7.4±0.4 [SD]), the correlation r with BMC of the various skeletal sites were as follows: physical activity, from 0.26 (p=0.0001) to 0.40 (p=0.0001); protein intake, from 0.18 (p=0.005) to 0.27 (p=0.0001); calcium intake, from 0.09 (p=0.181) to 0.17 (p=0.007). By multiple regression analysis, the beta-adjusted values remained correlated with BMC, ranging as follows: physical activity, from 0.219 (p=0.0007) to 0.340 (p<0.0001); protein intake, from 0.120 (p=0.146) to 0.217 (p=0.009). In contrast, it was not correlated for calcium intake: from -0.069 (p=0.410) to 0.001 (p=0.986). With protein intake (mean=2.0 g/kg body weight/d) above the median, increased physical activity from 168 to 321 kcal/d was associated with greater mean BMC Z-score (+0.6, p=0.0005). In contrast with protein intake (mean=1.5 g/kg body weight/d) below the median, increased physical activity from 167 to 312 kcal/d was not associated with a greater mean BMC Z-score (+0.2, p=0.371). The interaction between physical activity and protein intake was close to statistical significance for mean BMC Z-score (p=0.055) and significant for femoral neck BMC (p=0.012). Increased physical activity on mean BMC Z-score was not influenced by difference in calcium intake above (mean=945 mg/d) and below (mean=555 mg/d) the median.

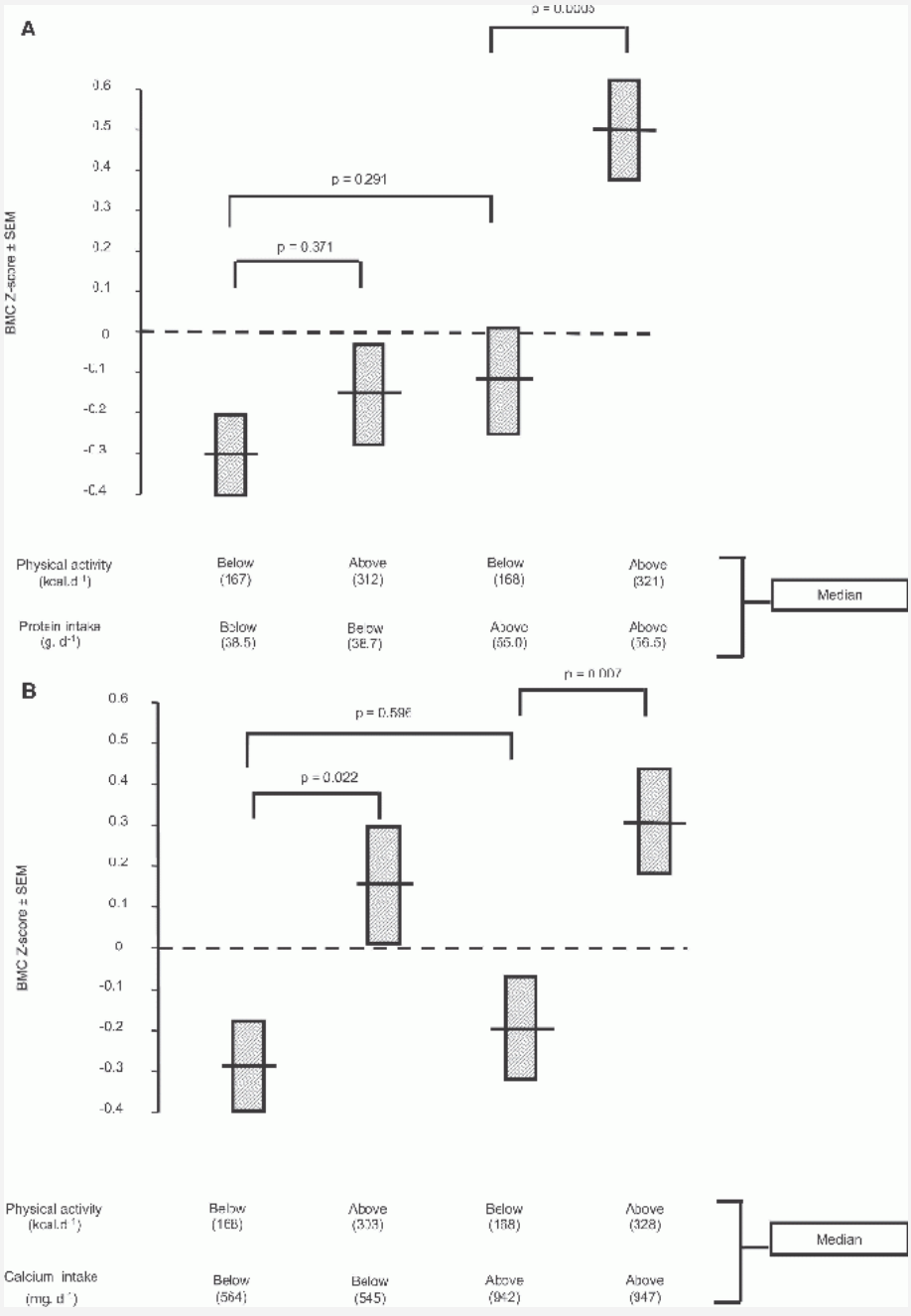


Fig. 9.2.64 Influence of protein vs. calcium intake on the impact of increased physical activity on BMC in prepubertal boys. (A) Increased physical activity is associated with a significant increase in mean BMC Z-score in subjects having protein intake above but not below the median. (B) The positive impact of increased physical activity was not significantly modified by the calcium intake. The means of physical activity and protein and calcium intakes below and above their respective median are indicated in parentheses. Analyzed by ANOVA, the interaction between physical activity and protein intake was very close to statistical significance (p=0.055). No interaction was found between physical activity and calcium intake (p=0.754). Reproduced from

J Bone Miner Res 2008;23:131-42 with permission of the American Society for Bone and Mineral Research.

9.2.65 Calcium supplementation and bone mineral accretion in adolescent girls: An 18-mo randomized controlled trial with 2-y follow-up
Lambert HL, Eastell R, Karnik K, Russell JM, Barker ME
Am J Clin Nutr 2008;87:455-62

An 18-mo randomized trial of calcium supplementation (792 mg/d) with follow-up 2 y after supplement withdrawal in 96 girls (mean age: 12 y) with low calcium intakes (mean: 636 mg/d) showed that the mean additional calcium intake in the supplemented group was 555 mg/d. Compared with the control group, the supplemented group showed (P<0.05) greater gains in BMC (except at the total hip site) over the 18-mo study. BMD change was (P<0.05) greater for all skeletal sites, and concentrations of resorption markers and parathyroid hormone were (P<0.01) lower in the supplemented group than in the control group after 18 mo. After 42 mo, gains in BMC and BMD and differences in bone resorption were no longer evident. Calcium supplementation enhances bone mineral accrual in teenage girls, but the effect is short lived. The likely mechanism for the effect of the calcium is suppression of bone turnover, which is reversed upon supplement withdrawal.

9.2.66 Polymorphisms in the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with peak bone mass in non-sedentary men: Results from the Odense Androgen Study
Brixen K, Beckers S, Peeters A, Piters E, Balemans W, Nielsen TL, Wraae K, Bathum L, Brasen C, Hagen C, Andersen M, Van Hul W, Abrahamsen B
Calcif Tissue Int 2007;81:421-9

The Odense Androgen Study (OAS) is a population-based study comprising 783 Caucasian men aged 20-30 years. The CC, CT, and TT genotypes in Ala1330Val were found in 75.6%, 21.8%, and 2.6% of the participants, respectively. Similarly, the GG, GA, and AA genotypes of Val667Met were found in 89.7%, 9.8%, and 0.5%, respectively. For the Ala1330Val polymorphism, no significant differences were found in BMD. However, when analysis was restricted to non-sedentary men (n=589), a significant association between the number of T-alleles and BMD in the spine and whole body were found. Each copy of the T-allele changed the Z-score of the spine by (median and 95% CI) -0.21 [95% CI: -0.40; -0.03] (p<0.02). Analysis suggested an association between the AA genotype in the Val667Met polymorphism and increased body height and decreased BMD of the femoral neck; however, no significant gene-dose effect of the A-allele could be demonstrated in the whole population. When the analysis was restricted to nonsedentary subjects, however, each number of A-alleles was associated with a change in Z-score of -0.26 [95% CI: -0.51; -0.01] (p=0.04). The Ala1330Val and Val667Met polymorphisms in the LRP5 gene are associated with peak bone mass in physically active men.

9.2.67 Impaired growth plate function in bmp-6 null mice
Perry MJ, McDougall KE, Hou SC, Tobias JH
Bone 2008;42:216-25

Bone morphogenetic protein 6 (BMP-6) is expressed by osteoblasts and growth plate chondrocytes suggesting roles in bone formation and growth regulation. Ten-week-old female littermate bmp-6 null and wild-type (WT) mice were administered E(2) by daily sc injection for 28 days. Tibia area as measured by DXA was reduced in vehicle-treated bmp-6 null mice compared with WT. Vehicle-treated bmp-6 null mice had a reduced cross-sectional area at the tibial middiaphysis whereas cancellous bone indices were unaffected. Histomorphometry of the proximal tibial metaphysis demonstrated a defect in bone formation immediately adjacent to the growth plate in bmp-6 null mice following E(2). E(2) was also associated with a dose-responsive decrease in longitudinal growth rate, and proliferative and hypertrophic zone parameters of the growth plate (p<0.0001). Significantly greater reductions following E(2) were observed in longitudinal growth rate (p<0.01), proliferating and hypertorphic zone widths (p<0.001), and proliferating (p<0.0002) and hypertrophic (p<0.002) cells per column of bmp-6 null mice compared to WT mice. BMP-6 may have a role in periosteal but not trabecular bone formation. Moreover, growth plate function was reduced in bmp-6 null mice receiving estrogen, leading to an impaired cancellous bone response to estrogen at the highest dose, suggesting that BMP-6 also plays a physiological role in maintaining growth plate function.

9.2.68 Nutrition-induced catch-up growth increases hypoxia inducible factor 1alpha RNA levels in the growth plate
Even-Zohar N, Jacob J, Amariglio N, Rechavi G, Potievsky O, Phillip M, Gat-Yablonski G
Bone 2008;42:505-15

To study the mechanisms governing catch-up growth in the growth plate, prepubertal rats had 10 days of 40% food restriction, followed by a renewal of the regular food supply. The expression level of 550 genes decreased during food restriction and increased during catch-up growth, starting already one day after refeeding. HIF-1alpha, as well as several of its downstream targets, was found among these genes. Immunohistochemistry showed a similar pattern for HIF-1alpha protein abundance. Additionally, HIF-1alpha mRNA and protein levels were higher in the proliferating than in the hypertrophic zone, and this distribution was unaffected by nutritional status. These findings indicate that nutrition has a profound effect on gene expression level during growth plate growth, and suggest an important role for HIF-1alpha in the growth plate and its response to nutritional manipulation.

9.2.69 Comparisons of body size, composition, and whole body bone mass between North American and South African children
Micklesfield LK, Norris SA, Nelson DA, Lambert EV, van der Merwe L, Pettifor JM
J Bone Miner Res 2007;22:1869-77

9.2.70 Which bone mass measures discriminate adolescents who have fractured from those who have not?
Jones G, Boon P
Osteoporos Int 2008;19:251-5

9.2.71 Growth and bone mineral accretion during puberty in Chinese girls: A five-year longitudinal study
Zhu K, Greenfield H, Zhang Q, Du X, Ma G, Foo LH, Cowell CT, Fraser DR
J Bone Miner Res 2008;23:167-72

9.2.72 Perinatal bone turnover in term pregnancies: The influence of intrauterine growth restriction
Briana DD, Gourgiotis D, Boutsikou M, Baka S, Hassiakos D, Vraila V-M, Creatsas G, Malamitsi-Puchner A
Bone 2008;42:307-13

9.2.73 Murine and chicken chondrocytes regulate osteoclastogenesis by producing RANKL in response to BMP2
Usui M, Xing L, Drissi H, Zuscik M, O'Keefe R, Chen D, Boyce BF
J Bone Miner Res 2008;23:314-25

9.2.74 Thyroid hormone interacts with the Wnt/beta-catenin signaling pathway in the terminal differentiation of growth plate chondrocytes
Wang L, Shao YY, Ballock RT
J Bone Miner Res 2007;22:1988-95

9.2.75 Involvement of nuclear factor I transcription/replication factor in the early stage of chondrocytic differentiation
Uchihashi T, Kimata M, Tachikawa K, Koshimizu T, Okada T, Ihara-Watanabe M, Sakai N, Kogo M, Ozono K, Michigami T
Bone 2007;41:1025-35

9.2.76 Bcl-2-associated athanogene-1 (BAG-1): A transcriptional regulator mediating chondrocyte survival and differentiation during endochondral ossification
Tare RS, Townsend PA, Packham GK, Inglis S, Oreffo RO
Bone 2008;42:113-28

9.2.77 P2Y receptors activated by diadenosine polyphosphates reestablish Ca(2+) transients in achondroplasic chondrocytes
Guzman-Aranguez A, Irazu M, Yayon A, Pintor J
Bone 2008;42:516-23

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

Volume 9, Issue 2, 2008

Remodelling Markers

9.2.78 Short-term changes in serum PINP predict long-term changes in trabecular bone in the rat ovariectomy model
Rissanen JP, Suominen MI, Peng Z, Morko J, Rasi S, Risteli J, Halleen JM
Calcif Tissue Int 2008;82:155-61

Volume 9, Issue 2, 2008

Bone Formation

9.2.79 Osteoblast-targeted expression of sfrp4 in mice results in low bone mass
Nakanishi R, Akiyama H, Kimura H, Otsuki B, Shimizu M, Tsuboyama T, Nakamura T
J Bone Miner Res 2008;23:271-7

Single nucleotide polymorphisms in the secreted frizzled-related protein 4 (Sfrp4) gene are responsible for low peak BMD in senescence-accelerated mouse (SAM) P6. In vitro studies revealed inhibition of osteoblast proliferation by Sfrp4, which is supposed to be mediated by canonical Wnt signaling. The authors examined the expression of Sfrp4 in neonate long bones by in situ hybridization and generated transgenic mice in which Sfrp4 was overexpressed in osteoblasts under the control of a 2.3-kb Col1a1 osteoblast-specific promoter. Hemizygous Sfrp4 TG mice exhibited a 30% reduction of trabecular bone mass at 8 wk of age, and histomorphometrical analysis showed decreases in both osteoblast numbers and bone formation rate. betaChet mice exhibited a 17% reduction of trabecular bone mass in distal femora caused by an increase in the osteoclast number and a decrease in bone formation rate. LiCl rescued the bone phenotype of Sfrp4 TG mice. Expression of Sfrp4 in periosteum and bone tissues suggested the role of Sfrp4 in osteoblasts. Overexpression of Sfrp4 in osteoblasts suppressed osteoblast proliferation, resulting in a decrease in bone formation in vivo. Partial suppression of beta-catenin/canonical Wnt signaling also impaired bone formation, and activation of the signaling restored low bone mass of Sfrp4 TG mice. Thus, these results indicate that Sfrp4 decreases bone formation at least in part by attenuating canonical Wnt signaling in vivo.

9.2.80 Knee loading accelerates bone healing in mice
Zhang P, Sun Q, Turner CH, Yokota H
J Bone Miner Res 2007;22:1979-87

9.2.81 Activation of the hypoxia-inducible factor-1alpha pathway accelerates bone regeneration
Wan C, Gilbert SR, Wang Y, Cao X, Shen X, Ramaswamy G, Jacobsen KA, Alaql ZS, Eberhardt AW, Gerstenfeld LC, Einhorn TA, Deng L, Clemens TL
Proc Natl Acad Sci U S A 2008;105:686-91

9.2.82 Bone regeneration is regulated by wnt signaling
Kim JB, Leucht P, Lam K, Luppen C, Ten Berge D, Nusse R, Helms JA
J Bone Miner Res 2007;22:1913-23

9.2.83 Extracellular matrix made by bone marrow cells facilitates expansion of marrow-derived mesenchymal progenitor cells and prevents their differentiation into osteoblasts
Chen XD, Dusevich V, Feng JQ, Manolagas SC, Jilka RL
J Bone Miner Res 2007;22:1943-56

9.2.84 Osteogenic differentiation of human adipose tissue-derived stem cells is modulated by the miR-26a targeting of the SMAD1 transcription factor
Luzi E, Marini F, Sala SC, Tognarini I, Galli G, Brandi ML
J Bone Miner Res 2008;23:287-95

9.2.85 Cell surface expression of stem cell antigen-1 (sca-1) distinguishes osteo-, chondro-, and adipoprogenitors in fetal mouse calvaria
Steenhuis P, Pettway GJ, Ignelzi MA, Jr.
Calcif Tissue Int 2008;82:44-56

9.2.86 Ucma, a novel secreted cartilage-specific protein with implications in osteogenesis
Surmann-Schmitt C, Dietz U, Kireva T, Adam N, Park J, Tagariello A, Onnerfjord P, Heinegard D, Schlotzer-Schrehardt U, Deutzmann R, von der Mark K, Stock M
J Biol Chem 2008;283:7082-93

9.2.87 Histone deacetylase 7 associates with Runx2 and represses its activity during osteoblast maturation in a deacetylation-independent manner
Jensen ED, Schroeder TM, Bailey J, Gopalakrishnan R, Westendorf JJ
J Bone Miner Res 2008;23:361-72

9.2.88 General transcription factor IIA-{gamma} increases osteoblast-specific osteocalcin gene expression via activating transcription factor 4 and runt-related transcription factor 2
Yu S, Jiang Y, Galson DL, Luo M, Lai Y, Lu Y, Ouyang HJ, Zhang J, Xiao G
J Biol Chem 2008;283:5542-53

9.2.89 Interaction of galectin-9 with lipid rafts induces osteoblast proliferation through the c-Src/ERK signaling pathway

Tanikawa R, Tanikawa T, Okada Y, Nakano K, Hirashima M, Yamauchi A, Hosokawa R, Tanaka Y
J Bone Miner Res 2008;23:278-86

9.2.90 A 4 bp deletion mutation in DLX3 enhances osteoblastic differentiation and bone formation in vitro
Choi SJ, Song IS, Ryu OH, Choi SW, Hart PS, Wu WW, Shen RF, Hart TC
Bone 2008;42:162-71

9.2.91 Wnt10b increases postnatal bone formation by enhancing osteoblast differentiation
Bennett CN, Ouyang H, Ma YL, Zeng Q, Gerin I, Sousa KM, Lane TF, Krishnan V, Hankenson KD, MacDougald OA
J Bone Miner Res 2007;22:1924-32

9.2.92 The protein tyrosine phosphatase Rptpzeta is expressed in differentiated osteoblasts and affects bone formation in mice
Schinke T, Gebauer M, Schilling AF, Lamprianou S, Priemel M, Mueldner C, Neunaber C, Streichert T, Ignatius A, Harroch S, Amling M
Bone 2008;42:524-34

9.2.93 Lipoxygenase metabolites are mediators of PTH-dependent human osteoblast growth
Somjen D, Tordjman K, Katzburg S, Knoll E, Sharon O, Limor R, Naidich M, Naor Z, Hendel D, Stern N
Bone 2008;42:491-7

9.2.94 Osteoblasts express NLRP3, a nucleotide-binding domain and leucine-rich repeat region containing receptor implicated in bacterially induced cell death
McCall SH, Sahraei M, Young AB, Worley CS, Duncan JA, Ting JP, Marriott I
J Bone Miner Res 2008;23:30-40

9.2.95 The essential role of fetuin in the serum-induced calcification of collagen
Toroian D, Price PA
Calcif Tissue Int 2008;82:116-26

9.2.96 Calcospherulites isolated from the mineralization front of bone induce the mineralization of type I collagen
Midura RJ, Vasanji A, Su X, Wang A, Midura SB, Gorski JP
Bone 2007;41:1005-16

9.2.97 Extracellular calcium regulates parathyroid hormone-related peptide expression in osteoblasts and osteoblast progenitor cells
Ahlstrom M, Pekkinen M, Riehle U, Lamberg-Allardt C
Bone 2008;42:483-90

9.2.98 HtrA1 inhibits mineral deposition by osteoblasts: Requirements for the protease and PDZ domains
Hadfield KD, Rock CF, Inkson CA, Dallas SL, Sudre L, Wallis GA, Boot-Handford RP, Canfield AE
J Biol Chem 2008;283:5928-38

9.2.99 Scavenger receptor of class B expressed by osteoblastic cells are implicated in the uptake of cholesteryl ester and estradiol from LDL and HDL3
Brodeur MR, Brissette L, Falstrault L, Luangrath V, Moreau R
J Bone Miner Res 2008;23:326-37

9.2.100 The GPCR modulator protein RAMP2 is essential for angiogenesis and vascular integrity
Ichikawa-Shindo Y, Sakurai T, Kamiyoshi A, Kawate H, Iinuma N, Yoshizawa T, Koyama T, Fukuchi J, Iimuro S, Moriyama N, Kawakami H, Murata T, Kangawa K, Nagai R, Shindo T
J Clin Invest 2008;118:29-39

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

Volume 9, Issue 2, 2008

Bone Resorption

9.2.101 Identification of angiogenin as the osteoclastic bone resorption-inhibitory factor in bovine milk
Morita Y, Matsuyama H, Serizawa A, Takeya T, Kawakami H
Bone 2008;42:380-7

A factor responsible for inhibiting osteoclast-mediated bone resorption in the basic protein fraction of bovine milk (milk basic protein, MBP) was purified from MBP based on its activity to prevent unfractionated rabbit bone cells from forming pits on dentine slices nd was identical to that of bovine angiogenin. The purified bovine angiogenin inhibited the pit-forming activity of both unfractionated bone cells and purified osteoclasts in a dose-dependent manner, and the inhibitory activity was suppressed by treatment with anti-bovine angiogenin antibody. The inhibitory activity was confirmed in mice both in vitro and in vivo. Treatment of osteoclasts with bovine angiogenin resulted in an impairment of the formation F-actin ring and a reduction in the mRNA levels of TRAP and cathepsin K, both known to be essential for the bone resorption activity of osteoclasts. Angiogenin is the substance mainly responsible for the inhibitory effect of bovine milk on osteoclast-mediated bone resorption, and that it exerts its activity by acting directly on the osteoclasts.

9.2.102 NOTCH1 regulates osteoclastogenesis directly in osteoclast precursors and indirectly via osteoblast lineage cells
Bai S, Kopan R, Zou W, Hilton MJ, Ong CT, Long F, Ross FP, Teitelbaum SL
J Biol Chem 2008;283:6509-18

9.2.103 Identifying the relative contributions of rac1 and rac2 to osteoclastogenesis
Wang Y, Lebowitz D, Sun C, Thang H, Grynpas MD, Glogauer M
J Bone Miner Res 2008;23:260-70

9.2.104 Extracellular acidification enhances osteoclast survival through an NFAT-independent, protein kinase C-dependent pathway
Pereverzev A, Komarova SV, Korcok J, Armstrong S, Tremblay GB, Dixon SJ, Sims SM
Bone 2008;42:150-61

9.2.105 NHA-oc/NHA2: A mitochondrial cation-proton antiporter selectively expressed in osteoclasts
Battaglino RA, Pham L, Morse LR, Vokes M, Sharma A, Odgren PR, Yang M, Sasaki H, Stashenko P
Bone 2008;42:180-92

9.2.106 Secreted tartrate-resistant acid phosphatase 5b is a marker of osteoclast number in human osteoclast cultures and the rat ovariectomy model
Rissanen JP, Suominen MI, Peng Z, Halleen JM
Calcif Tissue Int 2008;82:108-15

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

Volume 9, Issue 2, 2008

Osteocytes

9.2.107 Osteocytes as mechanosensors in the inhibition of bone resorption due to mechanical loading
You L, Temiyasathit S, Lee P, Kim CH, Tummala P, Yao W, Kingery W, Malone AM, Kwon RY, Jacobs CR
Bone 2008;42:172-9

Osteocytes support osteoclast formation and activation when cocultured with osteoclast precursors. Mechanical stimulation of MLO-Y4 osteocyte-like cells decreases their osteoclastogenic-support potential when cocultured with RAW264.7 monocyte osteoclast precursors; soluble factors released by these mechanically stimulated MLO-Y4 cells inhibit osteoclastogenesis induced by ST2 bone marrow stromal cells or MLO-Y4 cells; and soluble RANKL and OPG were released by MLO-Y4 cells, and the expressions of both were found to be mechanically regulated. Mechanical loading decreases the osteocyte's potential to induce osteoclast formation by direct cell-cell contact. Mechanically stimulated osteocytes release soluble factors that can inhibit osteoclastogenesis induced by other supporting cells including bone marrow stromal cells.

9.2.108 Mechanical stimulation of bone in vivo reduces osteocyte expression of sost/sclerostin
Robling AG, Niziolek PJ, Baldridge LA, Condon KW, Allen MR, Alam I, Mantila SM, Gluhak-Heinrich J, Bellido TM, Harris SE, Turner CH
J Biol Chem 2008;283:5866-75

Sclerostin, the protein product of the Sost gene, inhibits bone formation. Among bone cells, sclerostin is found nearly exclusively in the osteocytes, the cell type that has is implicated in sensing and initiating mechanical signaling. The recent discovery of sclerostin's antagonistic effects on Lrp5 receptor signaling-a crucial mediator of skeletal mechanotransduction-provides a potential mechanism for the osteocytes to control mechanotransduction, by adjusting their sclerostin (Wnt inhibitory) signal output to modulate Wnt signaling in the effector cell population. Sost transcripts and sclerostin protein levels were dramatically reduced by ulnar loading. Portions of the ulnar cortex receiving a greater strain stimulus were associated with a greater reduction in Sost staining intensity and sclerostin-positive osteocytes (revealed via in situ hybridization and immunohistochemistry, respectively) than were lower-strain portions of the tissue. Hindlimb unloading yielded a significant increase in Sost expression in the tibia. Modulation of sclerostin levels appears to be a finely-tuned mechanism by which osteocytes coordinate regional and local osteogenesis in response to increased mechanical stimulation, perhaps via releasing the local inhibition of Wnt/Lrp5 signaling.

9.2.109 Aberrant Phex function in osteoblasts and osteocytes alone underlies murine X-linked hypophosphatemia
Yuan B, Takaiwa M, Clemens TL, Feng JQ, Kumar R, Rowe PS, Xie Y, Drezner MK
J Clin Invest 2008;118:722-34

9.2.110 Hormonal, pH, and calcium regulation of connexin 43-mediated dye transfer in osteocytes in chick calvaria
Ishihara Y, Kamioka H, Honjo T, Ueda H, Takano-Yamamoto T, Yamashiro T
J Bone Miner Res 2008;23:350-60

Volume 9, Issue 2, 2008

Systemic Factors

9.2.111 Relationships between insulin-like growth factor-I (IGF-I) and OPG, RANKL, bone mineral density in healthy Chinese women

Zhao HY, Liu JM, Ning G, Zhao YJ, Chen Y, Sun LH, Zhang LZ, Xu MY, Chen JL

Osteoporos Int 2008;19:221-6

BMDs at lumbar spine and proximal femur in 504 pre- and postmenopausal women were measured by DXA. Age was negatively correlated with serum levels of IGF-I (r=-0.702, p<0.001). IGF-I was negatively correlated with OPG and OPG/RANKL ratio, but positively correlated with RANKL. The relationship between IGF-I and BMDs disappeared after adjustment for age. In postmenopausal women, IGF-I was lower in women with osteoporosis than in those with normal BMD (p=0.056), but no differences were found among OPG, RANKL and OPG/RANKL ratio. Serum levels of OPG in the highest quintile of IGF-I were lower than those in the lowest quintile of IGF-I, while no difference was found in RANKL. In the multiple regression analysis model, serum levels of IGF-I were the main determinants of the bone mass in Chinese women.

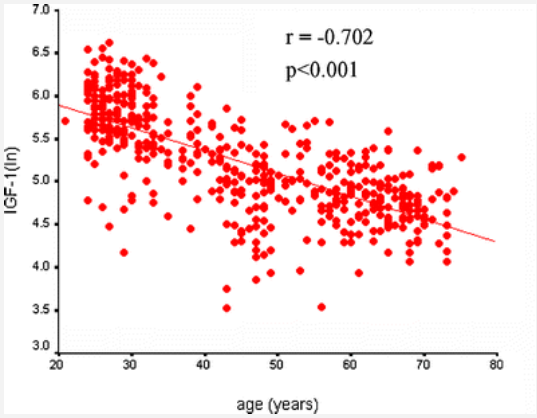
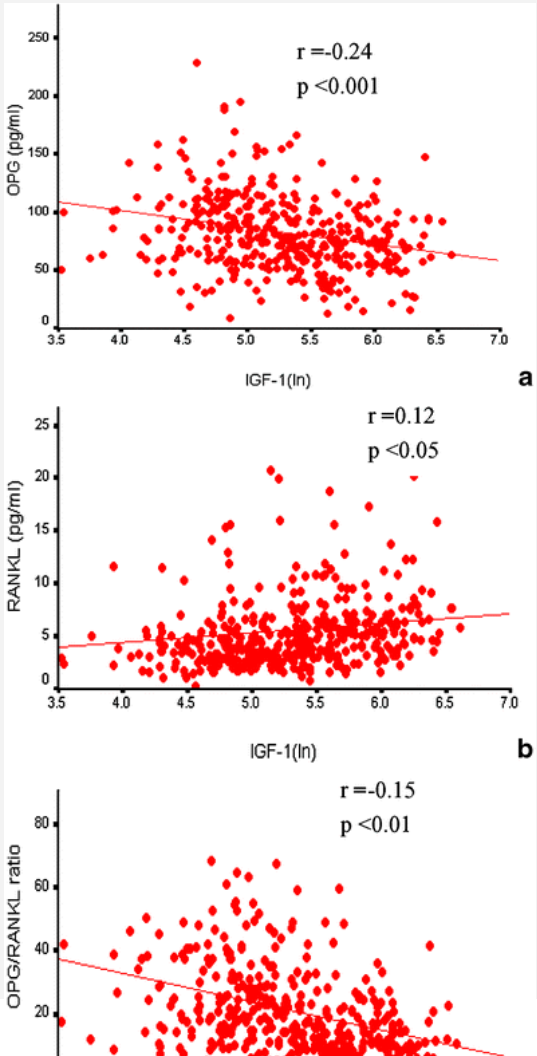


Fig. 9.2.111a Scatter plot of serum level IGF-I (ln) against age IGF-I (ln): logarithmically transformed IGF-I. Reproduced from Osteoporos Int 2008; 19:221-6 wih permission from Springer.



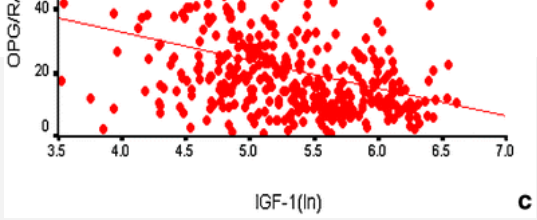


Fig. 9.2.111b Scatter plot of serum levels of IGF-I (ln) vs. OPG (a), RANKL (b) and OPG/RANKL ratio (c). Reproduced from Osteoporos Int 2008; 19:221-6 wih permission from Springer.

9.2.112 The role of IGF-I and IGFBP-1 status and secondary hyperparathyroidism in relation to osteoporosis in elderly Swedish women
Salminen H, Saaf M, Ringertz H, Strender LE
Osteoporos Int 2008;19:201-9

9.2.113 Parathyroid hormone is predictive of low bone mass in Canadian Aboriginal and White women
Weiler HA, Leslie WD, Bernstein CN
Bone 2008;42:498-504

9.2.114 Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio
Seriwatanachai D, Thongchote K, Charoenphandhu N, Pandaranandaka J, Tudpor K, Teerapornpuntakit J, Suthiphongchai T, Krishnamra N
Bone 2008;42:535-46

9.2.115 Variations along the 24-hour cycle of circulating osteoprotegerin and soluble RANKL: A rhythmometric analysis
Dovio A, Generali D, Tampellini M, Berruti A, Tedoldi S, Torta M, Bonardi S, Tucci M, Allevi G, Aguggini S, Bottini A, Dogliotti L, Angeli A
Osteoporos Int 2008;19:113-7

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

Volume 9, Issue 2, 2008

Local Factors

9.2.116 Transgenic over-expression of plasminogen activator inhibitor-1 results in age-dependent and gender-specific increases in bone strength and mineralization
Nordstrom SM, Carleton SM, Carson WL, Eren M, Phillips CL, Vaughan DE
Bone 2007;41:995-1004

9.2.117 Callus mineralization and maturation are delayed during fracture healing in interleukin-6 knockout mice
Yang X, Ricciardi BF, Hernandez-Soria A, Shi Y, Pleshko Camacho N, Bostrom MP
Bone 2007;41:928-36

9.2.118 Bone morphogenetic proteins signal through the transforming growth factor-beta type III receptor
Kirkbride KC, Townsend TA, Bruinsma MW, Barnett JV, Blobe GC
J Biol Chem 2008;283:7628-37

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

Volume 9, Issue 2, 2008

Risk Factors

9.2.119 Long-term risk of incident vertebral fractures
Cauley JA, Hochberg MC, Lui LY, Palermo L, Ensrud KE, Hillier TA, Nevitt MC, Cummings SR
Jama 2007;298:2761-7

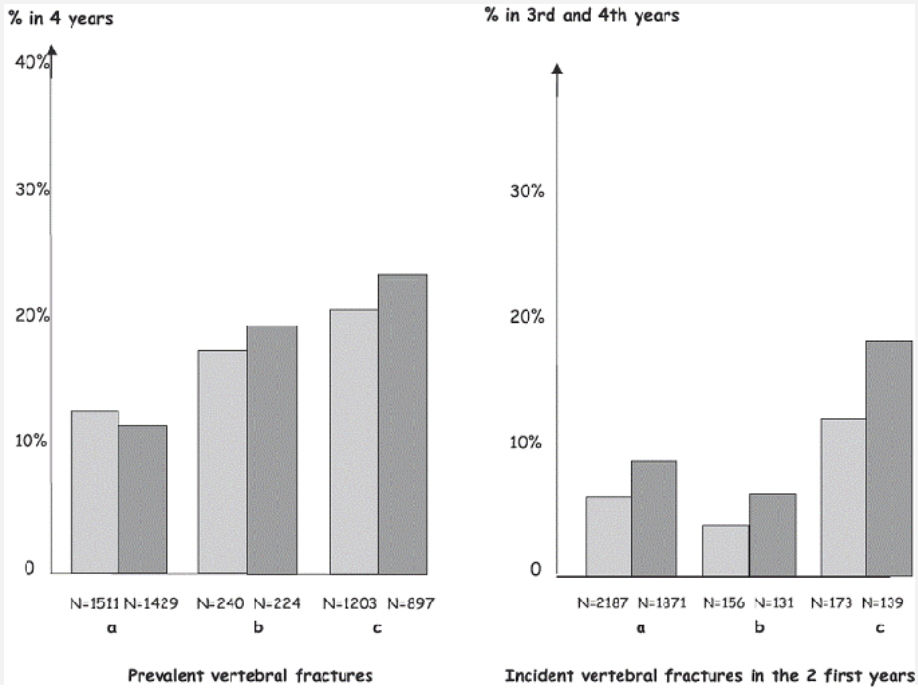
2680 attended a clinic visit an average of 14.9 years after baseline; mean age of 68.8 years at entry and 83.8 years at follow-up. 487 (18.2%) had an incident vertebral fracture including 163 of the 394 (41.4%) with a prevalent vertebral fracture at baseline and 324 of the 2286 (14.2%) without a prevalent vertebral fracture at baseline (odds ratio, 4.21; 3.33-5.34). Low BMD was associated with an increased risk of incident vertebral fracture (1 SD decrease in total hip BMD, 1.78 [1.58-2.00]). The absolute risk of vertebral fracture ranged from 56% among women with total hip BMD T-score of -2.5 or less and a prevalent vertebral fracture to 9% in women with normal BMD and no prevalent vertebral fracture. Low BMD and prevalent vertebral fractures are independently related to new vertebral fractures over 15 years of follow-up.

9.2.120 Assessing population risk for postmenopausal osteoporosis: A new strategy using data from the Behavioral Risk Factor Surveillance System (BRFSS)
Schneyer CR, Lopez H, Concannon M, Hochberg MC
J Bone Miner Res 2008;23:151-8

Using the Osteoporosis Self-Assessment Tool Index (OST Index; [self-reported weight in kg - age] x 0.2) to analyze data from 62,882 women ≥50 yr of age who participated in the 2002 Behavioral Risk Factor Surveillance System (BRFSS) to assess an individual's risk of disease, has has modest positive and high negative predictive value for osteoporosis defined by BMD criteria. Based on this index, women from each state were distributed among high-, moderate-, and low-risk OST categories. Comparison of unweighted BRFSS-OST results and NHANES BMD data revealed similar percentages of osteoporosis among all women ≥50 yr of age (BRFSS, 18.5%; NHANES, 18.0%; p=0.47) and also among white women (BRFSS, 19.0%; NHANES, 20.0%; p=0.28). However, the percentages of osteoporosis among blacks and Hispanics did not correspond. Analysis of readily available BRFSS data with the OST index formula is a simple, no-cost technique that provides state prevalence estimates of postmenopausal osteoporosis that could be used to guide allocation of resources to statewide osteoporosis prevention programs.

9.2.121 Mild prevalent and incident vertebral fractures are risk factors for new fractures
Roux C, Fechtenbaum J, Kolta S, Briot K, Girard M
Osteoporos Int 2007;18:1617-24

Three thousand three hundred and fifty-eight patients, aged 74±6 years, with postmenopausal osteoporosis included in the placebo groups of two clinical trials of strontium ranelate were followed for 4 years. The RR of vertebral fracture in 4 years was 1.8 (1.3-2.4) p<0.001, and 2.7 (2.3-3.3) p<0.001 for patients having only mild vertebral fractures and at least one grade ≥2 fracture at baseline respectively. The RR of vertebral fracture in the 3rd and 4th years of follow-up was 1.7 (1.1-2.6) p=0.01, and 1.9 (1.3-2.6) p<0.001 for patients having during the first 2 years incident mild fractures only, and for patients having at least one grade ≥2 incident fracture respectively. The RR of nonvertebral fracture in 4 years was 1.3 (0.9-1.9) p=0.15 and 1.7 (1.4-2.1) p<0.001 for patients having only mild or at least one grade ≥2 vertebral fracture at baseline respectively. For patients aged more than 70 years, these RR were 1.45 (0.99-2.11) (p=0.06), and 1.72 (1.36-2.18) p<0.001, respectively. The RR of nonvertebral fracture in the 3rd and 4th years was 1.68 (1.36-2.09) p<0.001 for patients having at least one grade ≥2 incident fracture during the 2 first years of follow-up. Mild vertebral fractures are a risk factor for subsequent vertebral and nonvertebral fracture in postmenopausal women with osteoporosis; 1 out of 4 patients with an incident mild vertebral fracture in 2 years will fracture again within the 2 next years.



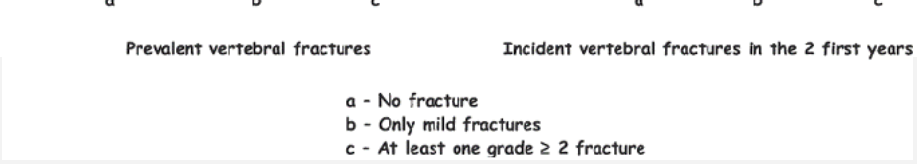


Fig. 9.2.121 Incidence of new non-vertebral fracture by severity of prevalent and incident vertebral fractures. a-No fracture. b-Only mild fractures. c-At least one grade ≥2 fracture. Reproduced from Osteoporos Int 2007; 18:1617-24 wih permission from Springer.

9.2.122 Risk factors for vertebral and nonvertebral fracture over 10 years: A population-based study in women

Finigan J, Greenfield DM, Blumsohn A, Hannon RA, Peel NF, Jiang G, Eastell R

J Bone Miner Res 2008;23:75-85

In a 10-yr prospective population-based study of 375 women who were 50-85 yr of age initially, 70 subjects sustained one or more nonvertebral fractures and 29 sustained one or more vertebral fractures. Risk factors that predicted both types of fracture included increasing age, decreasing BMD at all sites, prevalent vertebral fracture, and shorter estrogen exposure. For nonvertebral fractures only, the risk factors included low urinary creatinine and less frequent use of stairs. The factors for vertebral fractures included lighter weight, reduced body fat, heavy smoking, lower serum calcium, albumin, and thyroid T(3), weak grip strength, and poor physical capability. In a multivariate model, weight, fat mass, serum calcium and T(3), prevalent vertebral fracture, and physical capability remained significant. Furthermore, grip strength, serum albumin, weight loss, and physical capability were associated with rate of bone loss at the femoral neck, and a fast rate of bone loss was also associated with vertebral fractures.

9.2.123 Combining clinical factors and quantitative ultrasound improves the detection of women both at low and high risk for hip fracture

Durosier C, Hans D, Krieg MA, Ruffieux C, Cornuz J, Meunier PJ, Schott AM

Osteoporos Int 2007;18:1651-9

We pooled two Caucasian cohorts, EPIDOS and SEMOF, into a large database named "EPISEM", in which 12,064 women, 70 to 100 years old, were analyzed. Risk score was formed by combining the QUS-derived heel stiffness index (SI), patient age, body mass index (BMI), fracture history, fall history, diabetes history, chair-test results, and past estrogen treatment. Using the composite SI-CRF score, 42% of the women who did not report a hip fracture were found to be at low risk at baseline, and 57% of those who subsequently sustained a fracture were at high risk. Using the SI alone, corresponding percentages were 38% and 52%; using CRF alone, 34% and 53%. The number of subjects in the intermediate group was reduced from 5,400 (including 112 hip fractures) and 5,032 (including 111 hip fractures) to 4,549 (including 100 including fractures) for the CRF and QUS alone versus the combination score. Combining clinical risk factors to heel bone ultrasound appears to correctly identify more women at low risk for hip fracture than either the stiffness index or the CRF alone; it improves the detection of women both at low and high risk.

9.2.124 A population-based assessment of rates of bone loss at multiple skeletal sites: Evidence for substantial trabecular bone loss in young adult women and men

Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S

J Bone Miner Res 2008;23:205-14

In an age- and sex-stratified population sample (n=553), volumetric BMD (vBMD) of trabecular and cortical bone by QCT was measured annually for up to 3 yr at the distal radius (DR) and distal tibia (DT) (n=552) and trabecular vBMD at baseline and 3 yr at the lumbar spine (LS) (n=474). Substantial cortical bone loss began in middle life in women but began mainly after age 75 in men. Trabecular bone loss began in young adult women and men at all three skeletal sites and continued throughout life with acceleration during perimenopause in women. Women experienced 37% and men experienced 42% of their total lifetime trabecular bone loss before age 50 compared with 6% and 15%, respectively, for cortical bone. Median rates of change in trabecular bone (%/yr) were -0.40, -0.24, and -1.61 in young adult women and -0.38, -0.40, and -0.84 in young adult men at the DR, DT, and LS, respectively (all p<0.001). In postmenopausal women and, to a lesser extent, in older men, higher rates of cortical and trabecular bone loss were associated with lower levels of biologically active sex steroids and with higher levels of follicle stimulating hormone and bone turnover markers.

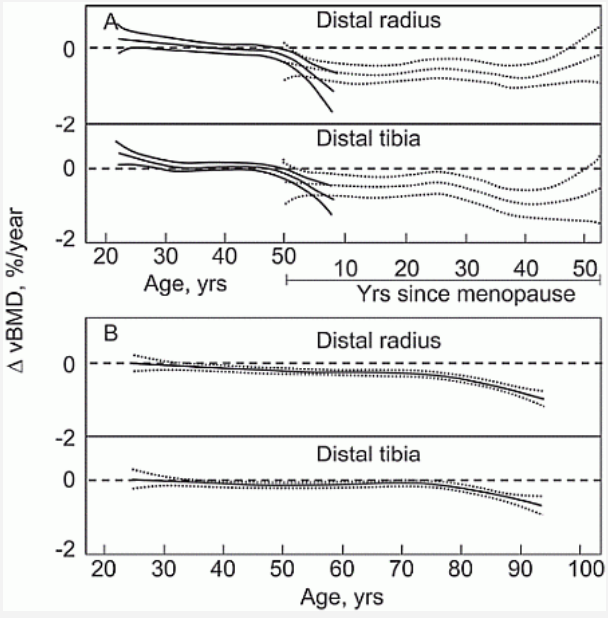


Fig. 9.2.124a Age-specific changes in vBMD at cortical scanning sites at DR and DT in (A) women and (B) men. Data are shown with a smoothing spline and the 95% CI. Premenopausal women (solid lines) are plotted against age in years, whereas postmenopausal women (broken lines) are plotted against years since menopause. Flaring of confidence limits at beginning and end of regression plots is a statistical artifact caused by smaller numbers of subjects at these ages. Reproduced from J Bone Miner Res 2008;23:205-14 with permission of the American Society for Bone and Mineral Research.

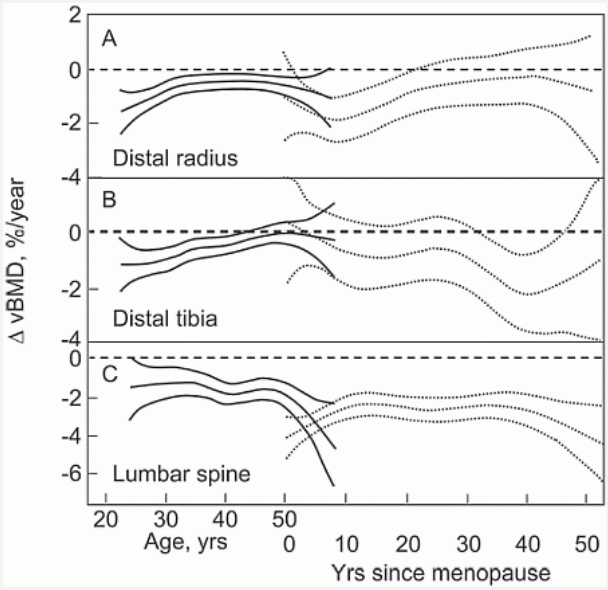


Fig. 9.2.124b Age-specific changes in vBMD at trabecular scanning sites in women at the (A) DR, (B) DT, and (C) LS. Data are shown with a smoothing spline and the 95% CI. Premenopausal women (solid lines) are plotted against age in years, whereas postmenopausal women (broken lines) are plotted against years since menopause. Reproduced from J Bone Miner Res 2008;23:205-14 with permission of the American Society for Bone and Mineral Research.

9.2.125 Prediction of clinical non-spine fractures in older black and white men and women with volumetric BMD of the spine and areal BMD of the hip: The Health, Aging, and Body Composition Study

Mackey DC, Eby JG, Harris F, Taaffe DR, Cauley JA, Tylavsky FA, Harris TB, Lang TF, Cummings SR

J Bone Miner Res 2007;22:1862-8

Areal BMD (aBMD) predicts clinical non-spine fractures. The predictive ability of vertebral trabecular volumetric BMD (TrvBMD) for clinical non-spine fractures has never been tested or compared with hip aBMD. In 1446 elderly black and white adults (70-79 yr) in the Health, Aging, and Body Composition Study, 152 clinical non-spine fractures were confirmed during an average of 6.4 yr. Vertebral TrvBMD and hip aBMD were both associated with risk of non-spine fracture in black and white women and black men. The age-adjusted HR of fracture per SD decrease in BMD was highest in black men (hip aBMD: HR=2.04, 95% CI=1.03, 4.04; vertebral TrvBMD: HR=3.00, 95% CI=1.29, 7.00) and lowest in white men (hip aBMD: HR=1.23, 95% CI=0.85, 1.78; vertebral TrvBMD: HR=1.06, 95% CI=0.73, 1.54). Adjusted for age, sex, and race, each SD decrease in hip aBMD was associated with a 1.67-fold (95% CI=1.36, 2.07) greater risk of fracture, and each SD decrease in vertebral TrvBMD was associated with a 1.47-fold (95% CI=1.18, 1.82) greater risk. Low BMD measured by either spine QCT or hip DXA predicts non-spine fracture in older black and white women and black men. Vertebral TrvBMD is not a stronger predictor than hip aBMD of non-spine fracture.

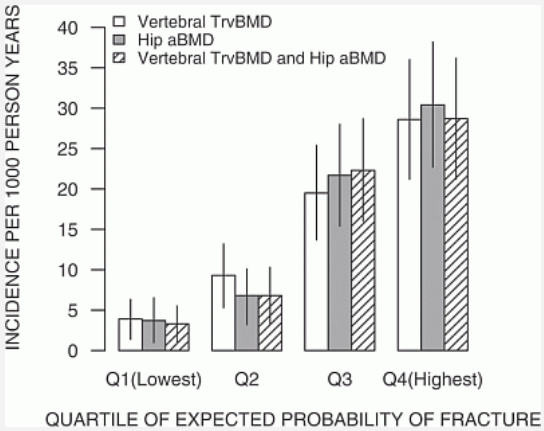


Fig. 9.2.125 Incidence of clinical non-spine fracture by quartile of expected probability of fracture. Expected probabilities were calculated from logistic regression models based on measurement of vertebral TrvBMD, total hip aBMD, and the combination of vertebral TrvBMD and total hip aBMD. Reproduced from J Bone Miner Res 2007;22:1862-8 with permission of the American Society for Bone and Mineral Research.

9.2.126 Measured height loss predicts fractures in middle-aged and older men and women: The EPIC-Norfolk prospective population study

Moayyeri A, Luben RN, Bingham SA, Welch AA, Wareham NJ, Khaw KT

J Bone Miner Res 2008;23:425-32

Height change can be easily measured and may contribute to fracture risk prediction. We assessed measured height loss and fracture incidence in a prospective population study. Height was measured between 1993 and 1997 and repeated between 1997 and 2000. Incident fractures to 2006 were ascertained by hospital record linkage. In 14,921 men and women 42-82 yr of age, during a mean follow-up period of 7.1 yr, there were 390 fractures, including 122 hip fractures. Prior annual height loss in those who had an incident fracture (1.8± 0.3 [SD] mm) was greater than other participants (0.9±0.2 mm; p<0.001). Participants with annual height loss >0.5 cm had an age- and sex-adjusted hazard ratio of any fracture of 1.76 (95% CI, 1.16-2.67) and of hip fracture of 2.08 (95% CI, 1.07-4.05). Each 1 cm/yr height loss was associated with a hazard ratio of 1.86 (95% CI, 1.28-2.72) for all fractures and 2.24

(95% CI, 1.23-4.09) for hip fracture after adjustment for age, sex, past history of fracture, smoking, body mass index, alcohol intake, and heel ultrasound measures. Annual height loss of 1 cm was comparable to having a past history of fracture and equivalent to being approximately 14 yr older in chronological age in terms of the magnitude of relationship with fracture risk. Middle-aged and older men and women with annual height loss >0.5 cm are at increased risk of hip and any fracture.

9.2.127 Decreased bone mineral density is correlated with increased subclinical atherosclerosis in older, but not younger, Mexican American women and men: The San Antonio Family Osteoporosis Study
Shaffer JR, Kammerer CM, Rainwater DL, O'Leary DH, Bruder JM, Bauer RL, Mitchell BD
Calcif Tissue Int 2007;81:430-41

In 535 women and 335 men significant inverse correlations of IMT and BMD at all bone sites in women >60 years of age (P<0.001) and modest positive correlations (not significant) of IMT on hip BMD (P<0.1) in women <60 years of age. Similarly, we observed negative correlations between IMT and forearm BMD in men >60 years of age (P<0.001) and positive correlations in men <60 years of age (P=0.05). Variation in risk factors for CVD, including serum levels of low- and high-density lipoprotein cholesterol, low-density lipoprotein particle size, triglycerides, paraoxonase 1 activity, and CRP did not account for the relationship between BMD and IMT in either older or younger men or women.

9.2.128 Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: The diabetes heart study
Carr JJ, Register TC, Hsu FC, Lohman K, Lenchik L, Bowden DW, Langefeld CD, Xu J, Rich SS, Wagenknecht LE, Freedman BI
Bone 2008;42:43-52

To determine the relationships between atherosclerotic calcified plaque (CP) and BMD in subjects with type 2 diabetes mellitus (DM2) 1023 diabetics were studied. Subjects were 53.8% female, 85% European American (EA) and 15% African American (AA). After adjustment for age, inverse associations between CP and vBMD persisted in EA men (correlations between -0.11 and -0.16, all p<0.05 with the exception of carotid CP vs. T-vBMD, p=0.076) and in AA women, excluding aortic CP (correlations between -0.16 and -0.25, all p<0.05). Estrogen use in AA but not EA women was associated with an inverse relation between CP and vBMD. Inverse relationships between CP and vBMD were observed in EA men and AA women with DM2 after adjusting for age and other covariates. QCT determined vBMD was more strongly related to CP than aBMD by DXA.

9.2.129 Bone formation in spontaneously diabetic Torii-newly established model of non-obese type 2 diabetes rats
Fujii H, Hamada Y, Fukagawa M
Bone 2008;42:372-9

To examine the bone abnormalities in non-obese type 2 diabetes, Spontaneously Diabetic Torii (SDT) rats and Sprague-Dawley (SD) rats were used as a control group (n = 17). SDT rats were divided into two groups: the diabetic (DM) group (n=18) and the DM+insulin (INS) group (n=18) at 20 weeks of age. The DM+INS group received subcutaneously implanted insulin pellets every 2 weeks. Despite renal function not being impaired, BMD and bone strength were lower in the DM group. Osteoid volume per bone volume, osteoblast surface per bone surface, eroded surface per bone surface, osteoclast surface per bone surface, the mineral apposition rate, and the bone formation rate per bone surface were lower in the DM group than in the control and DM +INS groups. The mRNA expression of ALP and OCN was lower in the DM group than in the control group. Furthermore, 8-hydroxydeoxyguanosine, which is an oxidative stress marker, was elevated in the DM group. These abnormalities were recovered by insulin therapy. Non-obese type 2 diabetes is associated with a low turnover of bone and that the abnormalities are ameliorated by insulin.

9.2.130 Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: Results from the third National Health and Nutrition Examination Survey
Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V
Am J Clin Nutr 2008;87:136-41

Blood pressure was normotensive SBP (<110 mm Hg) high-normal SBP (110-119 mm Hg). Lower 25(OH)D was associated with a higher blood pressure in whites (P<0.001); however, when controlling for age, the association was no longer significant. Concentrations of 25(OH)D >80 nmol/L decreased the age-related increase in SBP by 20% compared with participants having 25(OH)D <50 nmol/L (P<0.001). Only 8% of blacks had 25(OH)D >80 nmol/L. SBP is inversely associated with serum vitamin D in nonhypertensive white persons in the United States.

9.2.131 Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D
Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, Reitz R, Salameh W, Ameri A, Tannenbaum AD
J Clin Endocrinol Metab 2008;93:677-81

This was a randomized, placebo-controlled, double-blinded study of healthy adults ages 18-84 years who received placebo, 1,000 IU vitamin D3, 1,000 IU vitamin D2, or 500 IU of vitamin D2 plus 500 IU of vitamin D3 daily for 11 weeks at the end of the winter. Sixty percent of the healthy adults were vitamin D deficient at the start. The circulating 25-hydroxyvitamin D increased to the same extent in the groups that received 1,000 IU daily as D2 (baseline 16.9±10.5 ng/ml; 11 weeks 26.8±9.6 ng/ml); vitamin D3 (baseline 19.6±11.1 ng/ml; 11 weeks 28.9±11.0 ng/ml) or a

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9.2.132 Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults
Looker AC, Mussolino ME
J Bone Miner Res 2008;23:143-50

1917 white men and women ≥65 yr of age were examined in NHANES III, 1988-1994. There were 156 incident hip fracture cases. Cases were older, had lower BMD and body mass index, more prevalent spine or wrist fractures and weight loss before baseline, and ate fewer kilocalories and less calcium than noncases. After adjusting, serum 25(OH)D exceeding 60 nM were related to hip fracture risk. For example, the multivariate-adjusted RR was 0.64 (95% CI, 0.46-0.89) among individuals with serum 25(OH)D values ≥62.5 nM compared with those with values below this level. When grouped into quartiles, the multivariate-adjusted RR for the second, third, and fourth vs. the first quartile of serum 25(OH)D were 0.50 (95% CI, 0.25-1.00), 0.41 (95% CI, 0.24-0.70), and 0.50 (95% CI, 0.29-0.86), respectively. Serum 25(OH)D was related to a lower hip fracture riskafter adjusting for confounding variables.

9.2.133 Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study

Nakamura K, Tsugawa N, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, Maruyama K, Oshiki R, Kobayashi R, Nashimoto M, Yoshihara A, Ozaki R, Okano T, Yamamoto M

Bone 2008;42:271-7

Among 600 ambulatory postmenopausal women the mean serum 25(OH)D was 55.6 nmol/L (SD 14.6). Serum 25(OH)D was linearly associated with BMD of the femoral neck (R2=0.020, P=0.003), not spine. Odds ratios (ORs) for low BMD (defined as t score ≤ -2.5 SD) were calculated for strata defined by 25(OH)D concentration. The prevalence of low BMD of the lumbar spine was higher in the 40- to 50-nmol/L 25(OH)D group (adjusted OR=3.0, 95% CI: 1.3-7.0) compared to the reference group (≥70 nmol/L). Prevalence of low BMD for the femoral neck was higher in the 30- to 40 nmol/L (adjusted OR=3.6, 95% CI: 1.1-12.1) and the 40- to 50 nmol/L (adjusted OR=7.6, 95% CI: 2.5-23.2) groups compared to the reference group (≥70 nmol/L). The mean serum PTH was higher in subjects with serum 25(OH)D <50 nmol/L compared to those with serum 25(OH)D ≥50 nmol/L. A serum 25(OH)D of at least 70 nmol/L is needed to obtain high BMD of the femoral neck, and that of at least 50 nmol/L is needed to achieve normal PTH levels and prevent low BMD in home-dwelling postmenopausal Japanese women.

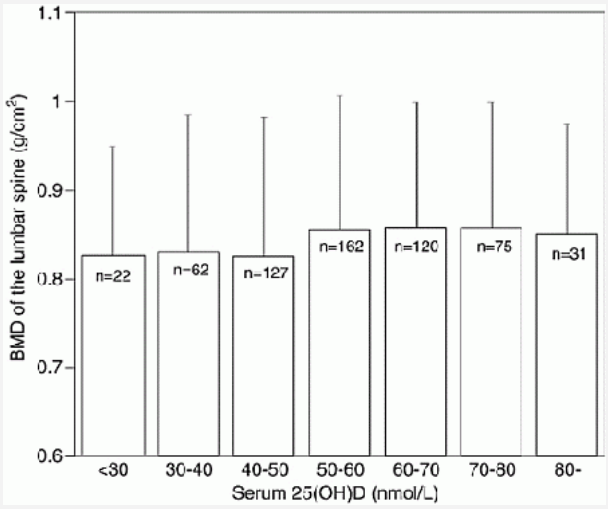


Fig. 9.2.133a Mean (plus SD) values of BMD of the lumbar spine for each 10 nmol/L increment in the serum 25(OH)D concentration. The serum 25(OH)D concentration was not linearly associated with BMD at the lumbar spine (P=0.1322), although 50 nmol/L may be an inflection point. Reproduced from Bone, 42:271-7, Copyright (2008), with permission from Elsevier.

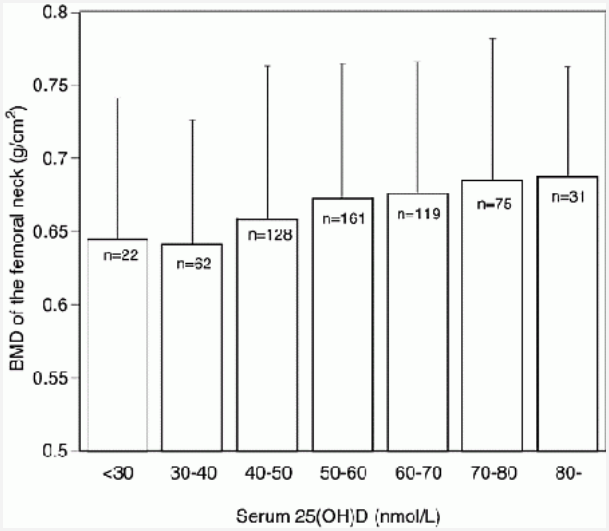


Fig. 9.2.133b Mean (plus SD) values of BMD of the femoral neck for each 10 nmol/L increment in the serum 25(OH)D concentration. BMD becomes higher as the 25(OH)D level becomes higher beginning from the 40-50 nmol/L group of serum 25(OH) D. Reproduced from Bone, 42:271-7, Copyright (2008), with permission from Elsevier.

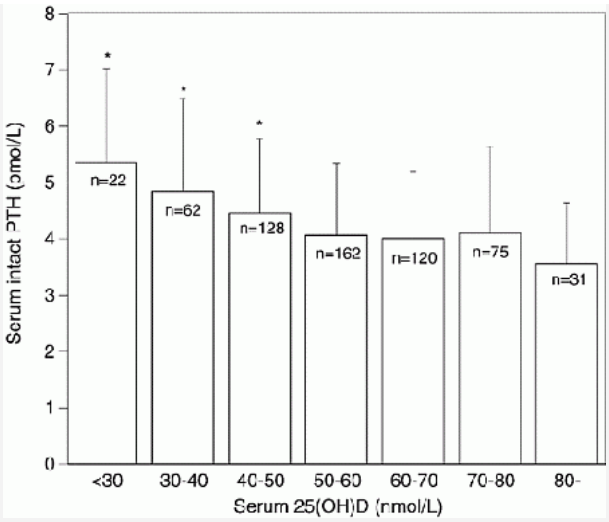


Fig. 9.2.133c Mean (plus SD) values of the serum intact PTH concentration for each 10 nmol/L increment in the serum 25(OH) D concentration. Mean serum intact PTH concentrations for 25(OH)D <30 nmol/L, 30-39 nmol/L, and 40-49 nmol/L, indicated with an asterisk (*), are significantly higher than those for serum 25(OH)D concentrations ≥50 nmol/L, as assessed by ANOVA with the Dunnett multiple comparison. Reproduced from Bone, 42:271-7, Copyright (2008), with permission from Elsevier.

9.2.134 Vitamin D deficiency as a risk factor for osteoporotic fractures
van Schoor NM, Visser M, Pluijm SMF, Kuchuk N, Smit JH, Lips P
Bone 2008;42:260-6

1311 community-dwelling older men and women had serum 25(OH)D determined and fractures assessed during six years. 11.3% had a serum 25(OH)D below 10 ng/ml, 48.4% below 20 ng/ml, and 82.4% below 30 ng/ml. 115 (8.5%) had one or more osteoporotic fractures. A cut point of 12 ng/ml giving the best discrimination between persons with and without fractures (17.5% of the persons fell below this cut point). The lowest percentage of fractures (5.6%) was found above 30 ng/ml. Analyses were conducted separately for persons aged 65-75 years (n=656) and for persons aged 75-89 years (n=664). After adjustment for age, and other factors serum 25(OH)D below or equal to 12 ng/ml was associated with an increased fracture risk in the youngest age group (HR=3.1; 95% CI: 1.4-6.9), not in the oldest age group (HR=1.3; 95% CI: 0.7-2.2). For commonly used cut points of serum 25(OH)D (<10 ng/ml, 10-19.9 ng/ml, 20-29.9 ng/ml, ≥30 ng/ml), no associations were found after adjustment. Serum 25(OH)D levels below or equal to 12 ng/ml were associated with an increased fracture risk in persons aged 65-75 years.

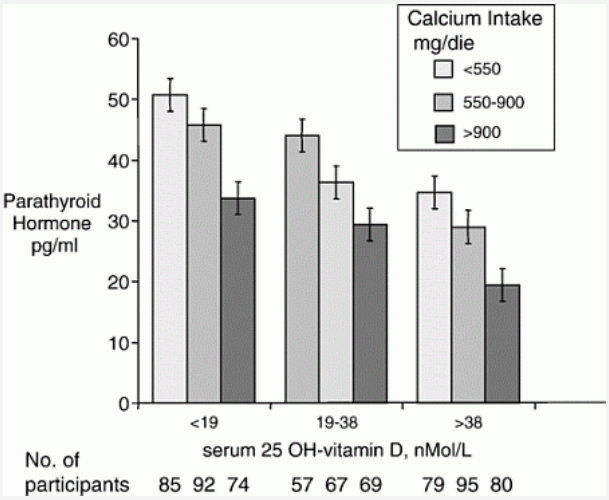


Fig. 9.2.134 Risk of fractures using the optimal cut point of serum 25(OH)D. Presented are the hazard ratios and 95% confidence intervals for fractures comparing serum 25(OH)D ≤12 ng/ml vs. serum 25(OH)D >12 ng/ml in the age groups <75 years (a) and ≥75 years (b). In the youngest age group, 53 persons had a serum 25(OH)D ≤12 ng/ml and 595 persons had a serum 25 (OH)D >12 ng/ml. In the oldest age group, 177 persons had a serum 25(OH)D level ≤12 ng/ml and 486 persons had a serum 25(OH) D >12 ng/ml. Model 1: univariate. Model 2: adjusted for age, sex, season. Model 3: Model 2+education, body mass index, number of chronic diseases, creatinine level, cognition, smoking, alcohol use. Model 4: Model 3+physical activity, physical performance. These variables can both act as a confounder and as a mediator. Reproduced from Bone, 42:260-6, Copyright (2008), with permission from Elsevier.

9.2.135 Severe vitamin D deficiency in Swiss hip fracture patients
Bischoff-Ferrari HA, Can U, Staehelin HB, Platz A, Henschkowski J, Michel BA, Dawson-Hughes B, Theiler R
Bone 2008;42:597-602

222 consecutive hip fracture patients were investigated over a 12 month period. Mean age of patients was 86 years and 77% were women. Mean serum 25(OH)D levels were low among hip fracture patients admitted from home (34.6 nmol/l), from assisted living (27.7 nmol/l), and from nursing homes (24 nmol/l). Severe vitamin D deficiency below 30 nmol/l was present in 60%, 80% were below 50 nmol/l, and less than 4% reached desirable levels of at least 75 nmol/l. Consistently, only 10% of hip fracture patients had any vitamin D supplementation on admission to acute care with significantly higher 25(OH)D levels among individuals supplemented with 800-880 IU/day (63.5 nmol/l). Controlling for age and gender, vitamin D supplementation, type of dwelling, and season were independently and significantly associated with 25(OH)D levels. These data provide evidence that current guidelines for the prevention of hip fractures need further effort to be translated into clinical practice.

9.2.136 Prevalence of vitamin D depletion among subjects seeking advice on osteoporosis: A five-year cross-sectional study with public health implications
Guardia G, Parikh N, Eskridge T, Phillips E, Divine G, Rao DS
Osteoporos Int 2008;19:13-9

In a cross-sectional study of 2924 patients seen for osteoporosis, 25-OHD level was 24.6±10 ng/ml and mean PTH was 48.4±32 pg/ml. The prevalence of vitamin D depletion was 15% with a cut-off level of <15 ng/ml, and rose to 32% and 72% with cut-off levels <20 ng/ml and <30 ng/ml, respectively. The prevalence was higher in men and blacks and remained constant over 5 years, regardless of the cut-off level. The expected inverse relationship between 25-OHD and PTH was observed irrespective of gender or ethnicity. The prevalence of vitamin D depletion in patients seeking advice for osteoporosis is high and did not change over the 5 years of the study.

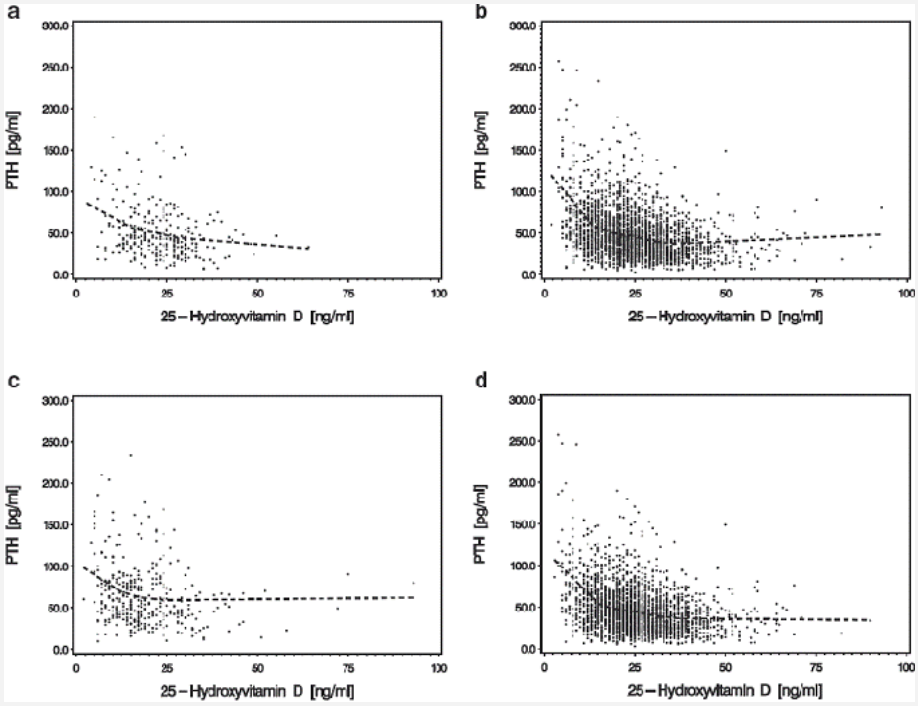


Fig. 9.2.136 Relationship between serum PTH and 25-hydroxyvitamin D levels by gender (a: Men & b: Women) and ethnicity (c: Blacks & d: Whites) with Loess curve fit. Reproduced from Osteoporos Int 2008; 19:13-9 wih permission from Springer.

9.2.137 Parathyroid response to vitamin D insufficiency: relations to bone, body composition, and to lifestyle characteristics
Rejnmark L, Vestergaard P, Brot C, Mosekilde L
Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

In 405 recent postmenopausal women with vitamin D insufficiency, plasma 25-hydroxyvitamin were higher ($p<0.05$) in SHPT compared with FHPT. SHPT was associated with higher osteocalcin and bone-specific alkaline phosphatase, whereas whole body BMD and hip and lumbar spine BMD were reduced. Subjects with SHPT had a 7% ($p<0.01$) higher body weight and a 23% higher fat mass ($p<0.01$) than subjects with FHPT, whereas lean tissue mass did not differ. In SHPT, fat mass was increased by 14% ($p<0.001$) at the upper and lower extremities and by 33% ($p<0.001$) at the trunk. In a regression model, predictors of fat mass was P-PTH ($r(p)=0.248$, $p<0.01$) and P-osteocalcin ($r(p) = -0.115$, $p=0.02$), with no effects of P-25OHD or P-creatinine levels. Effects of vitamin D insufficiency on bone is associated with the PTH responses. The increased body weight and fat mass in SHPT compared with FHPT may imply that PTH excess contributes to fat accumulation.

9.2.138 Relationship between serum parathyroid hormone, vitamin D sufficiency, age, and calcium intake
Adami S, Viapiana O, Gatti D, Idolazzi L, Rossini M
Bone 2008;42:267-70

697 women were available for analysis. Serum PTH correlated with age, 25(OH)D and calcium intake ($p<0.001$) and in a multivariate model they all contributed to explain PTH variance ($R2=24.4\%$). In 39 elderly osteoporotic women on a low calcium intake and given vitamin D supplements (2000-3000 IU daily for >8 months) able to increase 25(OH)D levels above 110 nMol/l, PTH levels were below 35 pg/mL. The minimum 25(OH)D to be recommended depends largely on the age and the calcium intake. In elderly individuals not taking calcium supplements in order to keep serum PTH levels strictly within the normal range 25(OH) D serum levels should be maintained above ca. 120 nMol/L.

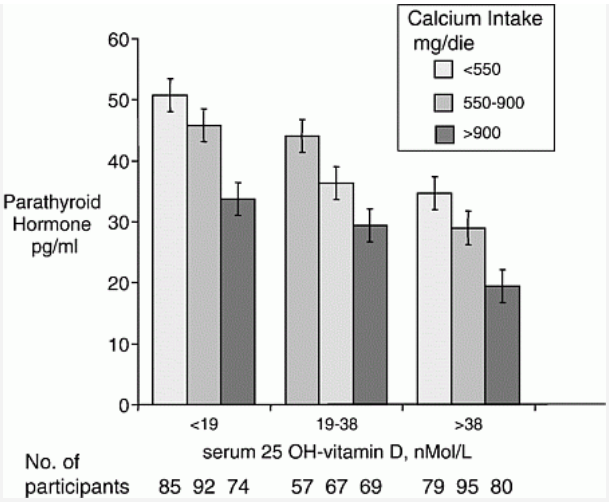


Fig. 9.2.138 Age adjusted mean serum parathyroid hormone values according to serum 25-hydroxyvitamin D values and calcium intake. Reproduced from Bone, 42:267-70, Copyright (2008), with permission from Elsevier.

9.2.139 Low prevalence of vitamin D deficiency among adolescents with anorexia nervosa
Haagensen AL, Feldman HA, Ringelheim J, Gordon CM
Osteoporos Int 2008;19:289-94

Fifty adolescents with AN and 200 controls were compared. The prevalence of deficiency (<20 ng/mL) was 2% in the AN group vs. 24% among controls (p=0.003). 25OHD was similar among white participants with AN and white controls (39.5 vs. 36.0 ng/mL, p=0.20), but higher than in non-white controls (20.6 ng/mL). Significantly more girls with AN reported vitamin D supplementation (86%) than the full control (14%) or white subgroup (27%) (p<0.001). Participants with AN had lower PTH concentrations than controls, (27.8 vs. 47.4 pg/mL, p=0.009), a trend that lost significance after age and race adjustment (41.7 pg/mL, p=0.12). Compared to healthy controls, adolescents with AN had a lower prevalence of vitamin D deficiency and PTH concentration. However, 25OHD and PTH concentrations were similar after adjustment for race and age. The trend of lower PTH levels in adolescents with AN, accompanied by exceptional compliance with supplementation, may have bone health implications for these patients.

9.2.140 Dietary protein intake and bone mineral content in adolescents: The Copenhagen Cohort Study
Budek AZ, Hoppe C, Ingstrup H, Michaelsen KF, Bugel S, Molgaard C
Osteoporos Int 2007;18:1661-7

This was a cross-sectional study of 17-year old girls (n=63) and boys (n=46) participating in the second follow-up of The Copenhagen Cohort Study. The mean total protein intake (approximately 1.2 g/kg) was modestly higher than that recommended. Total and milk (approximately 0.3 g/kg) protein intake, but not meat protein intake (approximately 0.4 g/kg), was positively associated with size-adjusted BMC (P≤0.05). The positive association between milk protein intake and size-adjusted BMC remained after correction for energy, calcium, and physical activity (P≤0.01) and did not seem to be mediated via current serum IGF-I.

9.2.141 Dietary intake of folate, but not vitamin B(2) or B(12), is associated with increased bone mineral density 5 Years after the menopause: Results from a 10-year follow-up study in early postmenopausal women
Rejnmark L, Vestergaard P, Hermann AP, Brot C, Eiken P, Mosekilde L
Calcif Tissue Int 2008;82:1-11

In 1,869 perimenopausal women associations between intakes and BMD were assessed at baseline and after 5 years. At year 5, but not at baseline, cross-sectional analyses showed positive correlations between daily intake from diet and from diet plus supplements of folate and BMD at the femoral neck (P<0.01). However, no associations were found between intakes and changes in BMD. During 10 years of follow-up, 360 subjects sustained a fracture. Compared with 1,440 controls, logistic regression analyses revealed no difference in intakes between cases and controls.

9.2.142 Effect of dietary B vitamins on BMD and risk of fracture in elderly men and women: The Rotterdam Study
Yazdanpanah N, Zillikens MC, Rivadeneira F, de Jong R, Lindemans J, Uitterlinden AG, Pols HA, van Meurs JB
Bone 2007;41:987-94

Elevated homocysteine (Hcy) is a modifiable risk factor for fractures. Elevated Hcy can have a nutritional cause, such as inadequate intake of folate, riboflavin, pyridoxine or cobalamin, which serve as cofactors or substrates for the enzymes involved in the Hcy metabolism. We examined the association between intake of Hcy-related B vitamin (riboflavin, pyridoxine, folate and cobalamin) and FN-BMD and the risk of fracture in 5304 individuals aged 55 years and over from the Rotterdam Study. During 7.4 years, with vertebral fractures assessed by X-rays during a mean of 6.4 years small associations between dietary pyridoxine (beta=0.09, p=1x10(-8)) and riboflavin intake (beta=0.06, p=0.002) and baseline FN-BMD were found. Pyridoxine intake was inversely correlated to fracture risk. As compared to the three lowest quartiles, individuals in the highest quartile of age- and energy-adjusted dietary pyridoxine intake had a decreased risk of non-vertebral fractures (HR=0.77, 95% CI=0.65-0.92) and of fragility fractures (HR=0.55, 95% CI=0.40-0.77). Increased dietary riboflavin and pyridoxine intake was associated with higher FN-BMD. Furthermore, a reduction in risk of fracture in relation to dietary pyridoxine intake independent of BMD was found.

9.2.143 Chronic ethanol consumption inhibits postlactational anabolic bone rebuilding in female rats
Shankar K, Hidestrand M, Liu X, Chen JR, Haley R, Perrien DS, Skinner RA, Lumpkin CK, Jr., Badger TM, Ronis MJ
J Bone Miner Res 2008;23:338-49

Female Sprague-Dawley rats (n=7-9 per group) were fed EtOH-containing diets (13 g/kg/d) for 1, 2, or 4 wk after weaning of their offspring. EtOH abolished the anabolic bone rebuilding that occurred after lactation. Decreased BMD and BMC were associated with decreased bone formation not increased osteoclast activity. EtOH-fed rats showed greater proportion of fat

volume/bone volume and expression of adipocyte-specific genes. EtOH-induced skeletal effects were mitigated by the dietary antioxidant, N-acetyl cysteine or by blocking TNF-alpha signaling. These data suggest EtOH in the period immediately postweaning may impair the mother's skeletal health and lead to long-term osteopenia.

9.2.144 Increased cathepsin K and tartrate-resistant acid phosphatase expression in bone of streptozotocin-induced diabetic rats
Hie M, Shimono M, Fujii K, Tsukamoto I
Bone 2007;41:1045-50

The effect of insulin-dependent diabetes mellitus (IDDM) on bone metabolism was evaluated using the streptozotocin (STZ)-induced diabetic rat 1 week after the induction of diabetes. The urine N- NTx and Dpd increased to 3.6-fold and 1.2-fold. The amount of hydroxyproline and calcium in the distal femur of diabetic rats decreased to 76% and 90%. The levels of serum osteocalcin and alkaline phosphatase (ALP) activity in the distal femur were reduced to about 40% and 70% of the control levels, respectively. The decrease in the expression osteocalcin was observed in distal femur of the diabetic rats, although the level of ALP mRNA was unchanged. The activity and the mRNA level of tartrate-resistant acid phosphatase (TRAP) increased to 1.5- and 2.3-fold the control level, respectively, in distal femur. The activity, protein, and mRNA levels of cathepsin K were also elevated to about 2-, 2.3-, and 2-fold. IDDM contributes to bone loss through changes in gene expression of TRAP and cathepsin K in osteoclasts as well as osteocalcin in osteoblasts resulting in increased resorptive activity and decreased bone formation.

9.2.145 The association between cysteine, bone turnover, and low bone mass
Baines M, Kredan MB, Davison A, Higgins G, West C, Fraser WD, Ranganath LR
Calcif Tissue Int 2007;81:450-4

In 328 postmenopausal British women grouped according to their BMD measurement subjects with low BMD had a lower plasma Cys (146.3 vs. 177.7 mumol/l, p<0.0001), a higher recent fracture rate (30.9% vs. 16.4%, p=0.017), and a higher percentage of current smokers (26.4% vs. 7.3%. p=0.003) than those with normal BMD. Additionally, they had a lower plasma Cys, and higher plasma tHcy and CTX, than those with osteopenia. In the whole population, Cys was associated with BMD, weight, height, smoking habit, log creatinine, Cys-Gly, log tHcy, and log folate, but the significant positive association of Cys with BMD was maintained after correction for all other variables (r=0.197, p=0.003). After weight, Cys was the next most significant predictor of BMD in a stepwise multiple linear regression model.

9.2.146 Fracture incidence in GH-deficient patients on complete hormone replacement including GH
Holmer H, Svensson J, Rylander L, Johannsson G, Rosen T, Bengtsson BA, Thoren M, Hoybye C, Degerblad M, Bramnert M, Hagg E, Engstrom BE, Ekman B, Thorngren KG, Hagmar L, Erfurth EM
J Bone Miner Res 2007;22:1842-50

Eight hundred thirty-two patients with GHD and 2581 matched population controls answered a questionnaire about fractures. Incidence rate ratio (IRR) for first fracture were estimated. The median time on GH therapy for childhood onset (CO) GHD men and women was 15 and 12 yr, respectively, and 6 and 5 yr for adult onset (AO) GHD men and women, respectively. A more than doubled risk (IRR, 2.29; 95% CI, 1.23-4.28) for nonosteoporotic fractures was recorded in women with CO GHD, whereas no risk increase was observed among CO GHD men (IRR, 0.61) and AO GHD women (IRR, 1.08). A decreased incidence of fractures (IRR, 0.54; 95% CI, 0.34-0.86) was recorded in AO GHD men. Increased fracture risk in CO GHD women can most likely be explained by interaction between oral estrogen and the GH-IGF-I axis. The adequate substitution rate of testosterone (90%) and GH (94%) may have resulted in significantly lower fracture risk in AO GHD men.

9.2.147 Does diabetes increase the risk for fractures after solid organ transplantation? A nested case-control study
Rakel A, Sheehy O, Rahme E, Lelorier J
J Bone Miner Res 2007;22:1878-84

Diabetes has been associated with osteoporosis in the general population. However, among patients receiving solid organ transplantation, the association between pretransplant diabetes and post-transplant fractures is not clear. The study included 238 cases and 873 controls. Pretransplant diabetes was present in 30% of the cases and 22% of the controls (crude OR: 2.16; 95% CI: 1.7-2.8). Diabetes remained a risk factor for fractures (adjusted OR: 1.94; 95% CI: 1.5-2.6). Use of narcotics (OR: 3.0; 95% CI: 2.0-4.4) and antidepressants (OR: 1.9; 95% CI: 1.2-3.1) in the month preceding the index date and use of loop diuretics in the year preceding the index date (OR: 1.4; 95% CI: 1.1-1.9) were also associated with increased risks of fractures.

9.2.148 Lean mass and not fat mass is associated with male proximal femur strength
Travison TG, Araujo AB, Esche GR, Beck TJ, McKinlay JB
J Bone Miner Res 2008;23:189-98

Data from N=1171 community-dwelling subjects, lean mass, fat mass, and BMI were each positively associated with hip strength. However, controlling for lean mass was sufficient to remove the positive, and induce a negative, association for fat mass or BMI. Associations between lean mass and hip strength were strongest and resistant to control for other measures. Lean mass alone was sufficient to account for a substantial proportion of racial/ethnic difference in hip strength measures, whereas fat mass exhibited no comparable explanatory power. The positive association between relative weight and proximal femur strength is accounted for by lean mass, suggesting that, in men, the protective effect of BMI in preventing fracture is mediated not by adipose tissue but by the influence of increased muscle mass accompanying elevated BMI.

9.2.149 Recovery of spaceflight-induced bone loss: Bone mineral density after long-duration missions as fitted with an exponential function
Sibonga JD, Evans HJ, Sung HG, Spector ER, Lang TF, Oganov VS, Bakulin AV, Shackelford LC, Leblanc AD
Bone 2007;41:973-8

Changes in BMD (between 56 different sets of pre- and postflight measurements) were plotted as a function of days after landing. BMD changes were fitted to an exponential mathematical function that estimated: (i) BMD change on landing day (day 0) and (ii) the number of days after landing when 50% of the lost bone would be recovered ("50% recovery time") in the lumbar spine, trochanter, pelvis, femoral neck and calcaneus. Averaged losses of bone mineral after long-duration spaceflight ranged between 2% and 9% across all sites with the recovery model predicting a 50% restoration of bone loss for all sites to be within 9 months.

9.2.150 Baseline bone morphometry and cellular activity modulate the degree of bone loss in the appendicular skeleton during disuse
Squire M, Brazin A, Keng Y, Judex S
Bone 2008;42:341-9

Adult mice (4 months old, BALB/cByJ x C3H/HeJ) were assigned to male and female baseline controls, age-matched controls or disuse. All baseline controls were sacrificed (0 day). Age-matched control and disuse mice were sacrificed (21 days). Following 21 days of unloading, trabecular bone loss in the distal femur and proximal tibia was 3-fold greater in the metaphyses than in the epiphyses and 2-fold greater in females than in males. Disuse-induced changes in cortical bone were 2-fold smaller than trabecular bone losses and were more apparent in females. Bone loss was inversely related to baseline bone volume fraction (R2=0.51 for females and 0.43 for males) and directly related to baseline bone surface to volume ratio (R2=0.69 for females and 0.60 for males). Additionally, trabecular bone loss correlated with baseline mineral apposition rates and osteoclast surface to bone surface ratios (R2=0.86 and 0.46, respectively, genders combined). These data demonstrate that baseline bone morphology and cellular activity modulate bone loss and that, independent of gender, anatomical regions with low bone quantity, high surface-to-volume ratios, and high levels of osteoblastic and osteoclastic activity are particularly susceptible to disuse.

9.2.151 Decreased bone turnover with balanced resorption and formation prevent cortical bone loss during disuse (hibernation) in grizzly bears (Ursus arctos horribilis)
McGee ME, Maki AJ, Johnson SE, Nelson OL, Robbins CT, Donahue SW
Bone 2008;42:396-404

Cortical bone turnover during hibernation with balanced formation and resorption in grizzly bear femurs avoids bone loss. Hibernating grizzly bear femurs were less porous and more mineralized, and did not demonstrate any changes in cortical bone geometry or whole bone mechanical properties. The activation frequency of intracortical remodeling was 75% lower during hibernation than during periods of physical activity, but the normalized mineral apposition rate was unchanged. These data indicate that bone turnover decreases during hibernation, but osteons continue to refill at normal rates. There were no changes in regional variation of porosity, geometry, or remodeling indices in femurs from hibernating bears, indicating that hibernation did not preferentially affect one region of the cortex. Thus, grizzly bears prevent bone loss during disuse by decreasing bone turnover and maintaining balanced formation and resorption, which preserves bone structure and strength. These results support the idea that bears possess a biological mechanism to prevent disuse osteoporosis.

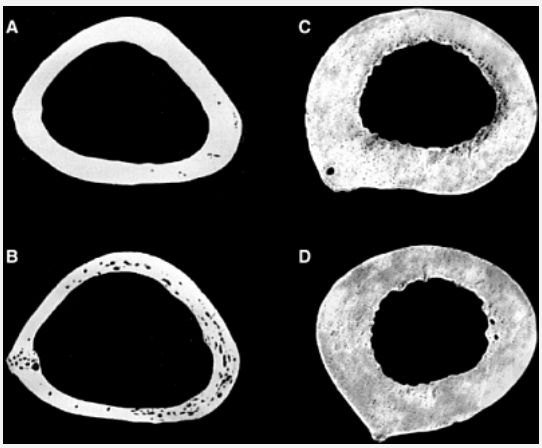


Fig. 9.2.151 Bone geometry and intracortical porosity do not respond similarly to disuse in turkeys (A, B) and grizzly bears (C, D). A: Control turkey ulna, B: turkey ulna immobilized for 8 weeks, C: active grizzly bear femur, D: grizzly bear femur after 17 weeks of hibernation. Large intracortical pores and thinning of the bone cortex, which occur during disuse in the turkey ulna, are not seen in the hibernating grizzly bear femur. In contrast, grizzly bear bone becomes less porous during physical inactivity. Reproduced from Bone, 42:396-404, Copyright (2008), with permission from Elsevier.

9.2.152 Abdominal aortic calcification detected on lateral spine images from a bone densitometer predicts incident myocardial infarction or stroke in older women
Schousboe JT, Taylor BC, Kiel DP, Ensrud KE, Wilson KE, McCloskey EV
J Bone Miner Res 2008;23:409-16

Among participants in a randomized controlled trial (women; age >75 yr) of clodronate versus placebo, those who sustained an MI or stroke during the median 4-yr follow-up study period were selected as cases (n=408), and 408 controls were randomly selected from the remainder of the parent study population. Baseline VFA images were scored for AAC, The OR of incident MI or stroke for those in the middle and top tertiles, respectively, compared with the bottom tertile of AAC score were 1.14 (95% CI, 0.79-1.66) and 1.74 (95% CI, 1.19-2.56) for the 24-point scale and 1.42 (95% CI, 0.98-2.05) and 1.77 (95% CI, 1.22-2.55) for the 8-point scale, adjusted for age, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, blood pressure, smoking, renal function, health status, and baseline diagnoses of diabetes mellitus, hypertension, angina, and prior stroke. AAC scored on VFA images is independently associated with incident MI or stroke. Because bone densitometry is indicated for all women ≥65 yr of age, VFA imaging offers an opportunity to capture this CVD risk factor in postmenopausal women undergoing bone densitometry at very little additional cost.

9.2.153 Association of left ventricular function with bone mineral density in older women: A population-based study
Laudisio A, Marzetti E, Antonica L, Cocchi A, Bernabei R, Zuccala G
Calcif Tissue Int 2008;82:27-33

In 312 subjects aged 75 and over living in Tuscania, Italy, LVEF was associated with T score (beta=0.02, 95% CI 0.01-0.05; P=0.033), Z score (beta=0.02, 95% CI 0.01-0.04; P=0.038), and stiffness index (beta=0.25, 95% CI 0.02-0.48; P=0.036). No significant associations were observed in men. In linear discriminant analysis, the LVEF cutoff level that best predicted osteoporosis was ≤49%. Left ventricular function is directly and independently associated with all of the ultrasonographic BMD parameters in older women.

9.2.154 Serum insulin-like growth factor-I level is associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes mellitus
Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Yano S, Sugimoto T
Osteoporos Int 2007;18:1675-81

A total of 131 postmenopausal women with type 2 diabetes were recruited. Either IGF-I or C-peptide was not correlated with BMD at any site or bone metabolic markers, such as osteocalcin (OC) and urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX). However, serum IGF-I level was lower in subjects with vertebral fractures than in those without fractures (mean ±SD: 106.9±50.0 vs. 142.8±50.8 ng/ml, p=0.0006). IGF-I was selected as an index affecting the presence of vertebral fractures (odds ratio=0.436, 95% confidential interval 0.234-0.814 per SD increase, p=0.0092). This significance was almost the same after additional adjustment for lumbar BMD or C-peptide. Serum IGF-I level could be clinically useful for assessing the risk of vertebral fractures independent of BMD in postmenopausal women with type 2 diabetes.

9.2.155 Nutritional impact of elevated calcium transport activity in carrots
Morris J, Hawthorne KM, Hotze T, Abrams SA, Hirschi KD
Proc Natl Acad Sci U S A 2008;105:1431-5

9.2.156 Chocolate consumption and bone density in older women
Hodgson JM, Devine A, Burke V, Dick IM, Prince RL
Am J Clin Nutr 2008;87:175-80

9.2.157 Dietary restraint and low bone mass in female adolescent endurance runners
Barrack MT, Rauh MJ, Barkai HS, Nichols JF
Am J Clin Nutr 2008;87:36-43

9.2.158 Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure
Moan J, Porojnicu AC, Dahlback A, Setlow RB
Proc Natl Acad Sci U S A 2008;105:668-73

9.2.159 Vitamin D insufficiency underlies unexpected hypocalcemia following high dose glucocorticoid therapy
Kinoshita Y, Masuoka K, Miyakoshi S, Taniguchi S, Takeuchi Y
Bone 2008;42:226-8

9.2.160 Low dietary riboflavin but not folate predicts increased fracture risk in postmenopausal women homozygous for the MTHFR 677 T allele
Yazdanpanah N, Uitterlinden AG, Zillikens MC, Jhamai M, Rivadeneira F, Hofman A, de Jonge R, Lindemans J, Pols HA, van Meurs JB
J Bone Miner Res 2008;23:86-94

9.2.161 Relation of folates, vitamin B12 and homocysteine to vertebral bone mineral density change in postmenopausal women: A five-year longitudinal evaluation
Cagnacci A, Bagni B, Zini A, Cannoletta M, Generali M, Volpe A
Bone 2008;42:314-20

9.2.162 Homocysteine, bone mineral density, and fracture risk over 2 years of followup in women with and without systemic lupus erythematosus
Rhew EY, Lee C, Eksarko P, Dyer AR, Tily H, Spies S, Pope RM, Ramsey-Goldman R
J Rheumatol 2008;35:230-6

9.2.163 Bone mineral density in postmenopausal female subjects is associated with serum antioxidant carotenoids
Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Ando F, Yano M
Osteoporos Int 2008;19:211-9

9.2.164 The importance of calculating absolute rather than relative fracture risk
Tucker G, Metcalfe A, Pearce C, Need AG, Dick IM, Prince RL, Nordin BE
Bone 2007;41:937-41

9.2.165 Bone mineral density changes during the menopause transition in a multiethnic cohort of women
Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, Lo JC, Johnston JM, Cauley JA, Danielson ME, Neer RM
J Clin Endocrinol Metab 2008;93:861-8

9.2.166 The relationship between body composition and bone mineral content: Threshold effects in a racially and ethnically diverse group of men
Travison TG, Araujo AB, Esche GR, McKinlay JB
Osteoporos Int 2008;19:29-38

9.2.167 Association between height loss and bone loss, cumulative incidence of vertebral fractures and future quality of life: The Miyama study
Yoshimura N, Kinoshita H, Takijiri T, Oka H, Muraki S, Mabuchi A, Kawaguchi H, Nakamura K, Nakamura T
Osteoporos Int 2008;19:21-8

9.2.168 Flattening of sagittal spinal curvature as a predictor of vertebral fracture
Kobayashi T, Takeda N, Atsuta Y, Matsuno T
Osteoporos Int 2008;19:65-9

9.2.169 Prognostic indicators of changes in bone density measures in adolescent girls with anorexia nervosa-II
Misra M, Prabhakaran R, Miller KK, Goldstein MA, Mickley D, Clauss L, Lockhart P, Cord J, Herzog DB, Katzman DK, Klibanski A
J Clin Endocrinol Metab 2007;[Epub ahead of print]

9.2.170 Reduced attenuation of bone resorption after oral glucose in type 2 diabetes
Chailurkit LO, Chanprasertyothin S, Rajatanavin R, Ongphiphadhanakul B
Clin Endocrinol (Oxf) 2007;[Epub ahead of print]

9.2.171 Risk factors for fractures and falls in older women with type 2 diabetes mellitus
Patel S, Hyer S, Tweed K, Kerry S, Allan K, Rodin A, Barron J
Calcif Tissue Int 2008;82:87-91

9.2.172 Short-term changes in bone and mineral metabolism following gastrectomy in gastric cancer patients
Baek KH, Jeon HM, Lee SS, Lim DJ, Oh KW, Lee WY, Rhee EJ, Han JH, Cha BY, Lee KW, Son HY, Kang SK, Kang MI
Bone 2008;42:61-7

9.2.173 Shwachman-Diamond syndrome is associated with low-turnover osteoporosis
Toiviainen-Salo S, Mayranpaa MK, Durie PR, Richards N, Grynpas M, Ellis L, Ikegawa S, Cole WG, Rommens J, Marttinen E, Savilahti E, Makitie O
Bone 2007;41:965-72

9.2.174 Underdeveloped trabecular bone microarchitecture is detected in children with cerebral palsy using high-resolution magnetic resonance imaging
Modlesky CM, Subramanian P, Miller F
Osteoporos Int 2008;19:169-76

9.2.175 Low bone mineral density and high bone metabolism turnover in premenopausal women with unipolar depression
Petronijevic M, Petronijevic N, Ivkovic M, Stefanovic D, Radonjic N, Glisic B, Ristic G, Damjanovic A, Paunovic V
Bone 2008;42:582-90

9.2.176 Selective serotonin reuptake inhibitors and osteoporosis: pathomechanism and clinical relevance remain to be established
Schulte-Herbruggen O, Anghelescu I
Arch Intern Med 2008;168:110

9.2.177 Selective serotonin reuptake inhibitors and other antidepressants and risk of fracture
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2008;82:92-101

9.2.178 Anxiolytics and sedatives and risk of fractures: Effects of half-life
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2008;82:34-43

9.2.179 Increased augmentation index and central aortic blood pressure in osteoporotic postmenopausal women
Mangiafico RA, Alagona C, Pennisi P, Parisi N, Mangiafico M, Purrello F, Fiore CE
Osteoporos Int 2008;19:49-56

9.2.180 Evaluation of osteoporosis using skin thickness measurements
Patel R, Blake GM, Fogelman I
Calcif Tissue Int 2007;81:442-9

9.2.181 Effects of depot medroxyprogesterone acetate on bone density and bone metabolism before and after peak bone mass: A case-control study
Walsh JS, Eastell R, Peel NF
J Clin Endocrinol Metab 2008;[Epub ahead of print]

9.2.182 Specific effects of gamma-linolenic, eicosapentaenoic, and docosahexaenoic ethyl esters on bone post-ovariectomy in rats
Poulsen RC, Firth EC, Rogers CW, Moughan PJ, Kruger MC
Calcif Tissue Int 2007;81:459-71

9.2.183 Phenotypic characteristics of bone in carbonic anhydrase II-deficient mice
Margolis DS, Szivek JA, Lai LW, Lien YH
Calcif Tissue Int 2008;82:66-76

9.2.184 Deterioration of bone quality by long-term magnetic field with extremely low frequency in rats
Gurgul S, Erdal N, Yilmaz SN, Yildiz A, Ankarali H
Bone 2008;42:74-80

Volume 9, Issue 2, 2008

Treatment

9.2.185 Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis
Delmas PD, McClung MR, Zanchetta JR, Racewicz A, Roux C, Benhamou CL, Man Z, Eusebio RA, Beary JF, Burgio DE, Matzkin E, Boonen S
Bone 2008;42:36-42

Women with osteoporosis were randomly assigned to risedronate 5 mg daily (n=642) or 150 mg once a month (followed by daily placebo) (n=650) double-blind fashion for 2 years. 538 patients in the daily group (83.8%) and 556 patients in the once-a-month group (85.5%) completed 1 year. The mean percent change in lumbar spine bone mineral density was 3.4% in the daily group and 3.5% in the once-a-month group. The once-a-month regimen was non-inferior to the daily regimen. The mean percent changes in bone mineral density at sites in the hip (total proximal femur, femoral neck, femoral trochanter) were also similar in both dose groups, as were the changes in biochemical markers of bone turnover. The incidence of adverse events, adverse events leading to withdrawal, and upper gastrointestinal tract adverse events were similar in the 2 treatment groups. Both regimens were well tolerated; the percent of patients who withdrew from treatment as a result of an adverse event was 9.5% in the daily group and 8.6% in the once-a-month group.

9.2.186 Fracture risk remains reduced one year after discontinuation of risedronate
Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, Grauer A
Osteoporos Int 2008;19:365-72

Patients who received risedronate 5 mg daily (N=398) or placebo (N=361) during the VERT-NA study stopped therapy per protocol after 3 years but continued taking vitamin D (if levels at study entry were low) and calcium and were reassessed one year later. In the year off treatment, spine BMD decreased, but remained higher than baseline (p≤0.001) and placebo (p<0.001), with similar findings at the femoral neck and trochanter. Urinary NTX and bone-specific alkaline phosphatase, which decreased with treatment, were not different from placebo after 1 year off treatment. Despite the changes in intermediate markers, the incidence of new morphometric vertebral fractures was 46% lower in the former risedronate group compared with the former placebo group (RR 0.54 [95% CI, 0.34, 0.86, p=0.009]). Despite the apparent resolution of effect on BMD and BTM, the risk reduction of new vertebral fractures remained in the year after treatment with risedronate was stopped.

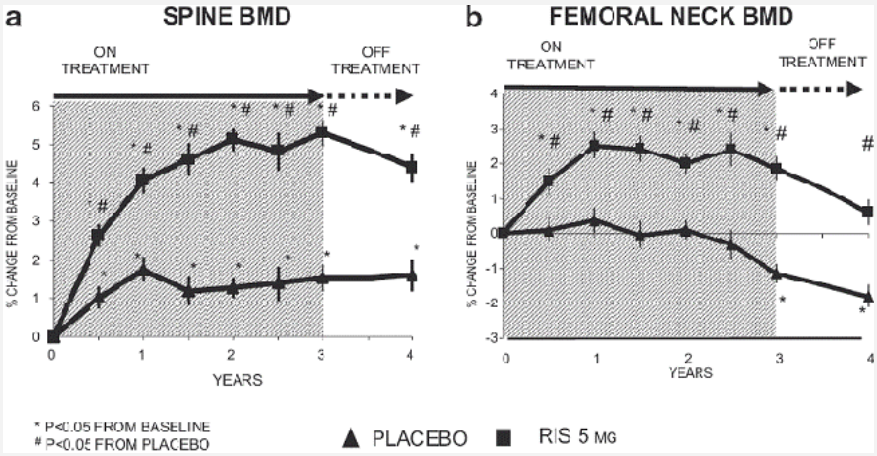


Fig. 9.2.186a (a) Mean percent change in lumbar spine BMD during 3 years of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment with calcium (and vitamin D, if needed). Asterisk indicates significant change from baseline (p<0.05) based upon a paired t-test. (b) Mean percent change in femoral neck BMD during 3 years of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment with calcium (and vitamin D, if needed). An asterisk indicates significant change from baseline (p<0.05) based upon a paired t-test. Reproduced from Osteoporos Int 2008; 19:365-72 wih permission from Springer.

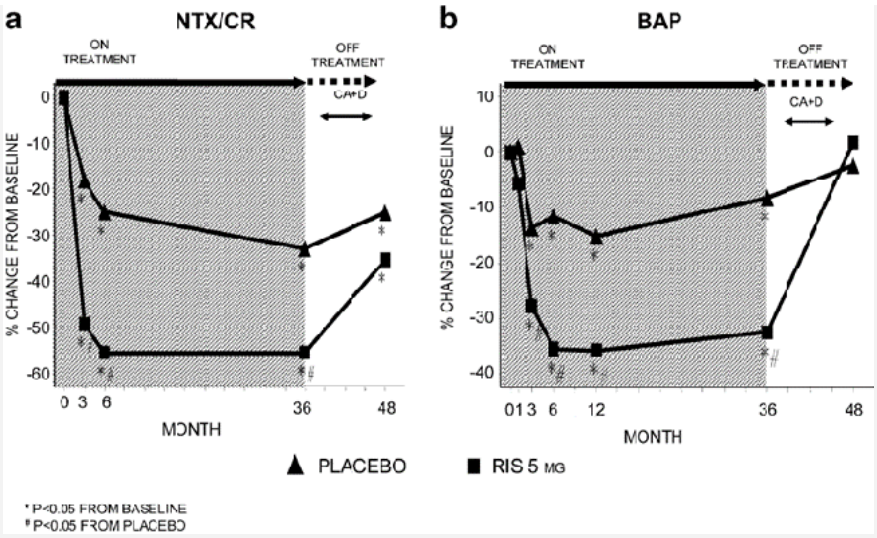


Fig. 9.2.186b (a) Median percent change in urinary NTX excretion during 3 years of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment with calcium (and vitamin D, if needed). Asterisk indicates significant change from baseline (p<0.05) based upon a Signed Rank t-test. (b) Median percent change in bone-specific alkaline phosphatase during 3 years of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment with calcium (and vitamin D, if needed). Asterisk indicates significant change from baseline (p<0.05) based upon a Signed Rank test. Reproduced from Osteoporos Int 2008; 19:365-72 wih permission from Springer.

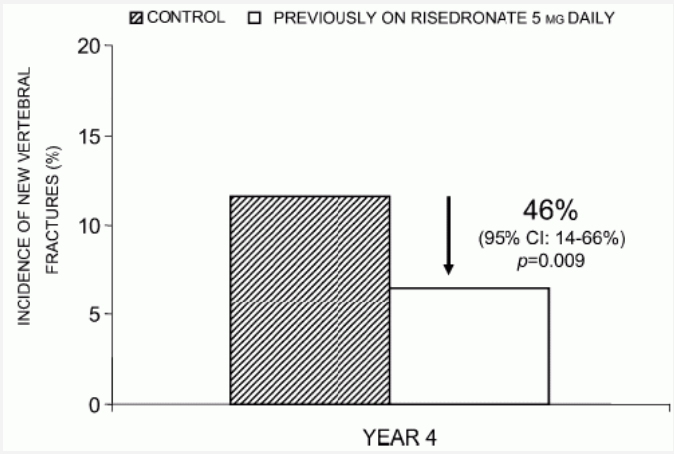


Fig. 9.2.186c New vertebral fractures in the subjects previously treated with risedronate and those in the control group in the year after discontinuation of risedronate 5 mg daily. Reproduced from Osteoporos Int 2008; 19:365-72 with permission from Springer.

9.2.187 Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial

Mok CC, Tong KH, To CH, Siu YP, Ma KM

Osteoporos Int 2008;19:357-64

Adults with medical diseases treated with high-dose prednisolone (>0.5 mg/kg/day) were randomized to risedronate (5 mg/day) or placebo for 6 months in a double-blind manner, along with elemental calcium (1,000 mg/day). 120 patients were recruited (82 women, age 42.8±14.3 years, 63% corticosteroid-naive, 30% women postmenopausal) and 103 completed the study. Baseline clinical characteristics and BMD were similar in the risedronate and placebo groups. At 6 months, a significant gain in spinal BMD was observed in the risedronate group (+0.7±0.3%; p=0.03) but a drop was detected in the placebo group (-0.7 ±0.4%; p=0.12). After adjustment for baseline BMD, age, gender, body mass index and cumulative prednisolone dosages, the intergroup difference in spinal BMD remained significant (1.4%; p=0.006). Both groups had a significant drop in hip BMD, but the magnitude was greater in the placebo arm (-0.8±0.4% in risedronate vs. -1.3±0.5% the in placebo).

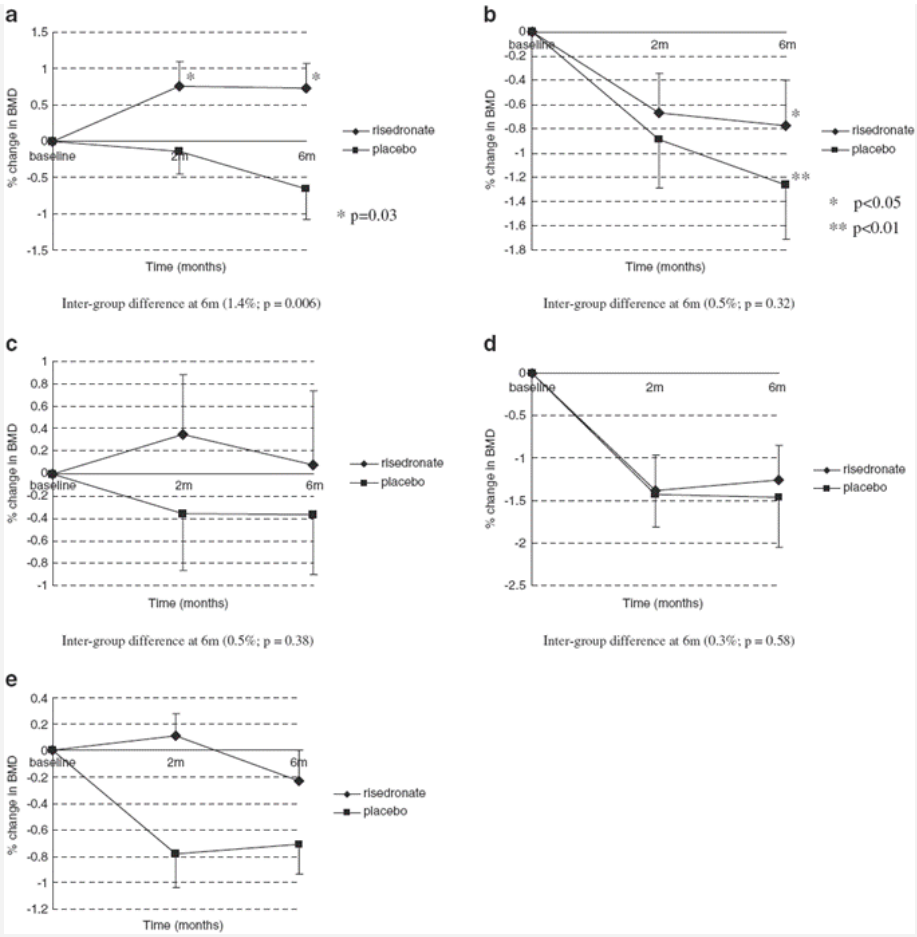


Fig. 9.2.187 Changes in bone mineral density (BMD) from baseline to 6 months: (a) Lumbar spine; (b) Hip; (c) Femoral neck; (d) Femoral trochanter; (e) Whole body. Error bars represent standard error of the mean (SEM). Reproduced from Osteoporos Int 2008; 19:357-64 with permission from Springer.

9.2.188 Risedronate reduces osteoclast precursors and cytokine production in postmenopausal osteoporotic women
D'Amelio P, Grimaldi A, Di Bella S, Tamone C, Brianza SZ, Ravazzoli MG, Bernabei P, Cristofaro MA, Pescarmona GP, Isaia G
J Bone Miner Res 2008;23:373-9

Bisphosphonates inhibit bone resorption by acting against osteoclasts. Some in vitro studies suggest that they induce osteoclast apoptosis; others suggest that they exert an effect on the production of pro-osteoclastogenic cytokines. This paper examined the influence of risedronate on the formation of osteoclast precursors and cytokine production within the compass of osteoclastogenesis in osteoporosis. In 38 osteoporotic women; 25 patients were treated with risedronate 5 mg/d, whereas 13 were treated with calcium 1 g/d and vitamin D 800 UI/d. After 3 mo of risedronate, there was a reduction in the number and degree of differentiation of osteoclast precursors, osteoclast formation, vitality and activity, and in the level of RANKL and TNF in cultures and of TNF and osteoprotegerin (OPG) in serum, whereas in the group treated with calcium and vitamin D, there were no significant changes. Risedronate lowers the number of circulating osteoclast precursors, their formation, vitality, and activity in cultures, and in reducing the level of pro-osteoclastogenic cytokines in culture supernatants and in serum.

9.2.189 Monthly oral ibandronate is effective and well tolerated after 3 years: The MOBILE long-term extension
Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster JY
Clin Rheumatol 2008;[Epub ahead of print]

The 2-year Monthly Oral iBandronate In LadiEs (MOBILE) registration study assessed BMD and turnover. Monthly oral ibandronate was as effective and well tolerated as a 2.5 mg daily oral regimen. 3 years treatment with monthly ibandronate. received 100 mg (n=359) or 150 mg (n=360) monthly oral ibandronate with a post hoc analysis included patients who received 100 mg (n=173) or 150 mg (n=169) monthly continuously. After one additional year mean spine BMD increased a 1.5% and 1.1% in the 150 and 100 mg arms, respectively. Total hip BMD changed by 0.3 and -0.08%, respectively. In the post hoc analysis, 3-year increases in lumbar spine BMD were 7.6%; p<0.0001 vs. baseline and 100 mg monthly (6.4%; p<0.0001 vs. baseline).

9.2.190 Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure
Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, Garcia-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF
J Bone Miner Res 2008;23:6-16

Bone biopsies were obtained in 152 patients on treatment or placebo at 3 yr after double tetracycline labeling. In five patients, only qualitative histology was performed, leaving 147 biopsy cores (79 treatment, 68 placebo) for µCT and histomorphometry. MicroCT revealed higher trabecular bone volume (BV/TV) in the zol group (median, 16.6% vs. 12.8%; p=0.02), higher trabecular numbers (p=0.008), decreased trabecular separation (p=0.011), and a trend toward improved connectivity density (p=0.062). Qualitative analysis revealed presence of tetracycline label in 81 of 82 biopsies on zoledronic acid and all 70 biopsies from placebo groups. Zoledronic acid induced a 63% median (71% mean) reduction of the activation frequency (Ac. f; p<0.0001) and reduced mineralizing surface (MS/BS; p<0.0001) and volume referent bone formation rate (BFR/BV). Mineral appositional rate was higher in the zoledronic acid group (p=0.0002), suggesting improved osteoblast function. Mineralization lag time was similar in the two groups, whereas osteoid volume (OV/BV; p<0.0001) and osteoid thickness (O. Th; p=0.0094) were lower in zoledronic acid-treated patients. Concomitant administration of other antiresorptives did not alter

the tissue level response to zoledronic acid.

9.2.191 Hip fractures in users of first- vs. second-generation bisphosphonates
Mamdani M, Kopp A, Hawker G
Osteoporos Int 2007;18:1595-600

Hip fracture rates among elderly women with a history of fracture dispensed first- and second generation bisphosphonates were compared. Administrative data from Ontario, Canada from 01 April 1998 to 31 March 2002 was used to identify population-based bisphosphonate-naive cohorts of subjects age 66 years and older initiated on first- (etidronate plus calcium; n=19,127) or second-generation (alendronate or risedronate; n=1,460) bisphosphonates. During over 23,000 person-years of follow-up, 293 hospital admissions for first hip fracture. The unadjusted event rates yielded approximately 12.5 hospital admissions for hip fracture per 1,000 person-years of follow-up in each study group. Relative to the etidronate plus calcium group, females in the alendronate or risedronate group were equally likely to be admitted for hip fracture (adjusted rate ratio=1.0; 95% CI 0.6-1.6).

9.2.192 Use of oral bisphosphonates and the risk of aseptic osteonecrosis: A nested case-control study
Etminan M, Aminzadeh K, Matthew IR, Brophy JM
J Rheumatol 2008;[Epub ahead of print]

Cases were hospitalizations secondary to AON at a nonspecified site. For each case, 10 controls were matched to the cases. The initial cohort consisted of 87,837 subjects. In the primary analysis, the adjusted RR for AON among bisphosphonate users was 2.87 (95% CI 1.71-5.05). The adjusted RR for alendronate, etidronate, and risedronate were 2.87 (95% CI 1.46-5.67), 2.43 (95% CI 1.05-5.62), and 3.34 (95% CI 1.04-10.67), respectively. There were no differences in RR for AON among current users and past users of bisphosphonates. An association was observed between oral bisphosphonate use and aseptic osteonecrosis.

9.2.193 Changes in vertebral strength-density and energy absorption-density relationships following bisphosphonate treatment in beagle dogs
Allen MR, Burr DB
Osteoporos Int 2008;19:95-9

aBMD and compressive mechanical properties (ultimate load and energy absorption) were assessed on lumbar vertebrae from skeletally mature beagle dogs treated with vehicle (VEH), alendronate (ALN), or risedronate (RIS). Neither treatment altered the strength-density relationship compared to VEH. The energy absorption-density relationship was altered by ALN, resulting in lower energy absorption capacity at a given aBMD compared to both VEH (-22%) and RIS (-14%). These data document that after adjusting for increased aBMD, vertebrae from animals treated with bisphosphonates have similar strength as those from untreated animals. Conversely, when adjusted for increased aBMD, alendronate, but not risedronate, reduces the energy required for vertebral fracture.

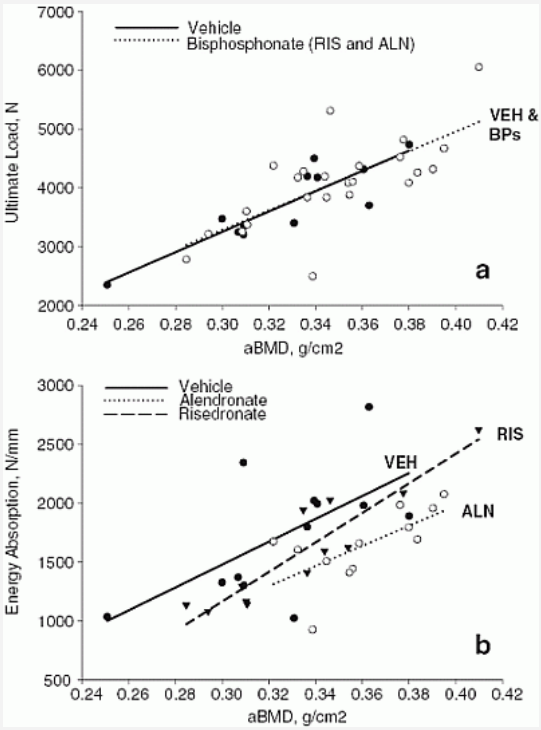


Fig. 9.2.193 Strength-density (a) and energy absorption-density (b) relationships of vertebral bone from beagles treated for 1 year with vehicle or clinical doses of risedronate, or alendronate. The strength-density relationship was similar for untreated (vehicle (●), y=17264 × −1927.2) and bisphosphonate-treated animals (pooled (○), y=16709 × −1724.8). BP-treated groups were combined as there was no difference between RIS (y=24551 × −4132) and ALN (y=10051 × +464) for the strength-density relationship. The energy absorption-density relationship differed from untreated (●, y=9717 × −1437) and risedronate-treated (▼, y=12559 × −2604) animals compared to those treated with alendronate (○, y=8542×−1439). Reproduced from Osteoporos Int 2008; 19:95-9 wih permission from Springer.

9.2.194 Bisphosphonates alter trabecular bone collagen crosslinking and isomerization in beagle dog vertebra
Allen MR, Gineyts E, Leeming DJ, Burr DB, Delmas PD
Osteoporos Int 2008;19:329-37

Skeletally mature female beagles were treated for one year with oral doses of vehicle (VEH), risedronate (RIS; 3 doses), alendronate (ALN; 3 doses), or raloxifene (RAL; 2 doses). The middle dose of RIS and ALN and the lower dose of RAL.

Vertebral trabecular bone matrix was assessed for collagen isomerization (ratio of alpha/beta C-telopeptide [CTX]), enzymatic (pyridinoline [PYD] and deoxypyridinoline [DPD]), and non-enzymatic (pentosidine [PEN]) cross-links. All doses of both RIS and ALN increased PEN (+34-58%) and the ratio of PYD/DPD (+14-26%), and decreased the ratio of alpha/beta CTX (-29-56%) compared to VEH. RAL did not alter any collagen parameters. Bone turnover rate correlated to PEN (R=-0.664), alpha/beta CTX (R=0.586), and PYD/DPD (R=-0.470). Bisphosphonate alters properties of bone collagen suggesting a contribution of the organic matrix to the anti-fracture efficacy of this drug class.

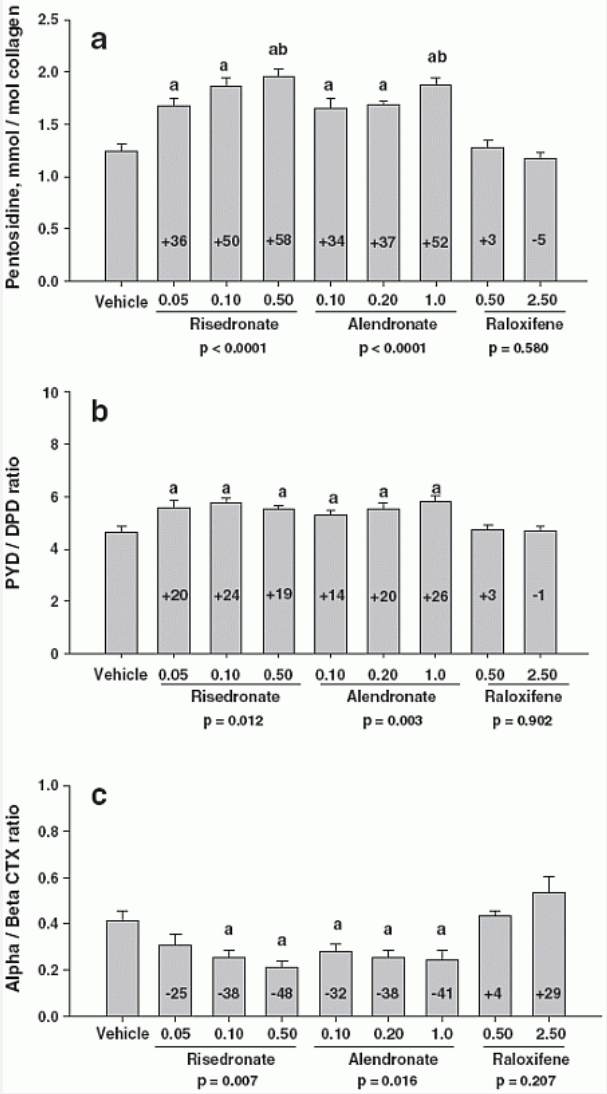
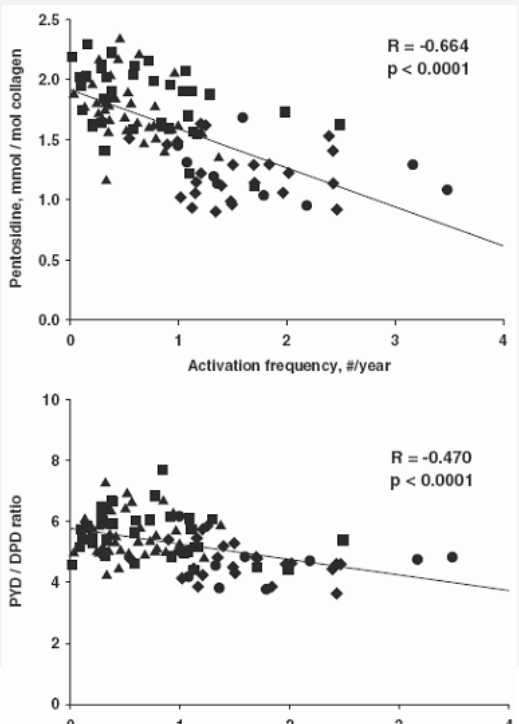


Fig. 9.2.194a Changes in collagen crosslinking and isomerization with anti-remodeling agents. Pentosidine (a), the ratio of PYD/DPD (b) and the ratio of α/β CTX (c) were assessed in trabecular bone from vertebrae of dogs treated for 1 year with vehicle, risedronate, alendronate, or raloxifene. An increase in the PYD/DPD ratio is indicative of increased enzymatic collagen crosslinks while a decrease in the α/β CTX ratio indicates increased collagen maturity. Data presented as mean ±SE. Numbers in bars represent percent difference compared to Vehicle. (a) p<0.05 vs. vehicle, (b) p<0.05 vs. low dose within drug. Reproduced from Osteoporos Int 2008; 19:329-37 wih permission from Springer.



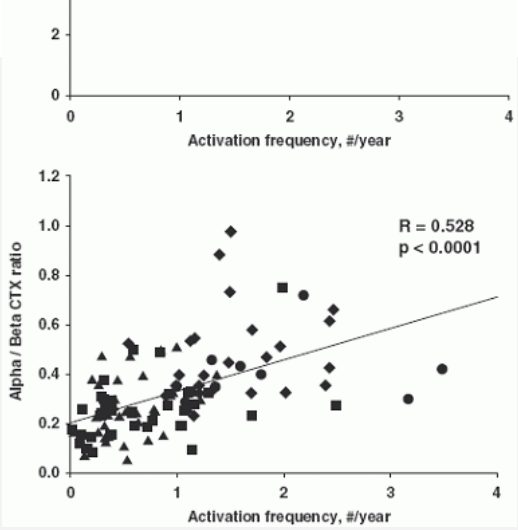


Fig. 9.2.194b Relationship between bone turnover and collagen crosslinking and isomerization. Significant linear relationships existed between the rate of vertebral bone turnover (activation frequency) and pentosidine (a), enzymatic crosslink ratio (b), and collagen isomerization (c). Vehicle (●), risedronate (■), alendronate (▲), raloxifene (◆). Reproduced from Osteoporos Int 2008; 19:329-37 wih permission from Springer.

9.2.195 Stainless steel screws coated with bisphosphonates gave stronger fixation and more surrounding bone. Histomorphometry in rats

Wermelin K, Suska F, Tengvall P, Thomsen P, Aspenberg P

Bone 2008;42:365-71

Coating of stainless steel screws with bisphosphonate in a fibrinogen matrix leads to an enhancement of the pullout strength 2 weeks after insertion in rat tibiae. This effect then increases over time until at least 8 weeks. The pullout force reflects the mechanical properties of the bone within the threads, which acts as a screw nut. Stainless steel screws served as uncoated control, controls coated with a layer of cross-linked fibrinogen, or screws further modified with bisphosphonates covalently linked and physically adsorbed to the fibrinogen layer. At 8 weeks, the part of the bisphosphonate screw that was located in the marrow cavity had become surrounded with bone, whereas there was almost no bone surrounding the controls. The bone area density in the threads along the entire bisphosphonate screw was increased by 40% compared with uncoated controls, and at 250 [mu]m distance it was more than doubled. At 1 week, coated screws had less implant-bone contact, but at 8 weeks there was no difference between uncoated and bisphosphonate-coated screws. The bisphosphonate screws had 50% increased removal torque at 2 weeks compared to uncoated screws. Howship's lacunae and osteoclasts were found near the screws with bisphosphonates at 8 weeks, suggesting that some bone remodeling took place near the implant, in spite of the presence of bisphosphonates.

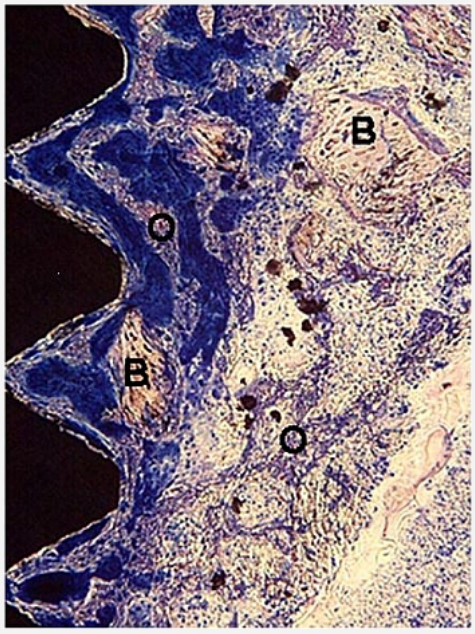


Fig. 9.2.195a Primitive bone or osteoid (O) and a fragment of old bone (B) in the marrow cavity at 1 week around a bisphosphonate screw. Reproduced from Bone, 42:365-71, Copyright (2008), with permission from Elsevier.

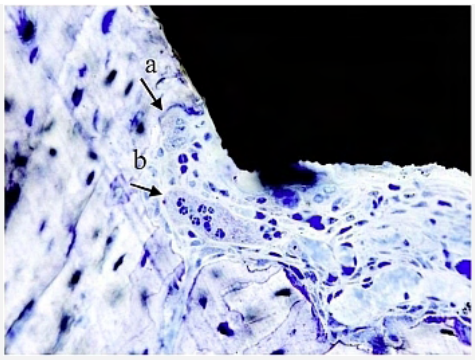


Fig. 9.2.195b A multinucleated cell in a resorption lacune (a), suggestive on ongoing bone resorption adjacent to a bisphosphonate-coated screw. There is also a multinucleated cell with lobulated nuclei (b), probably an apoptotic osteoclast. Reproduced from Bone, 42:365-71, Copyright (2008), with permission from Elsevier.

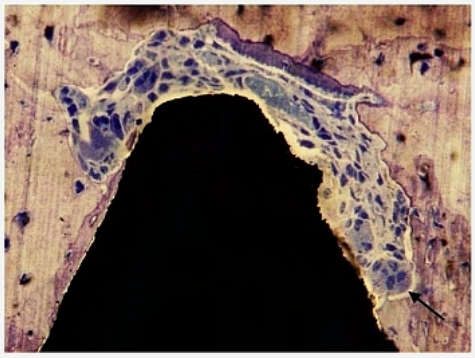


Fig. 9.2.195c Osteoclast (black arrow) resorbing newly synthesized bone at 8 weeks adjacent to a bisphosphonate screw in the medullary cavity. Reproduced from Bone, 42:365-71, Copyright (2008), with permission from Elsevier.

9.2.196 Bisphosphonate treatment increases the size of the mandibular condyle and normalizes growth of the mandibular ramus in osteoprotegerin-deficient mice
Kimura M, Miyazawa K, Tabuchi M, Maeda H, Kameyama Y, Goto S
Calcif Tissue Int 2008;82:137-47

OPG-deficient (OPG-/-) mice develop osteoporosis. Eight-week-old male OPG-/- mice and wild-type (WT) mice were administered bisphosphonate (1.25 mg/kg body weight) intraperitoneally once every 3 days for 30 days. All bone formation-related parameters and bone resorption-related parameters were lower in OPG-/- mice with bisphosphonate than in those without bisphosphonate. The volume of the whole condyle and the mandibular length in OPG-/- mice without bisphosphonate were smaller than in WT mice. Bisphosphonate treatment of the OPG-/- mice resulted in an increase in the volume of the mandibular condyle and mandibular ramus length. In fact, the mandibular ramus length in OPG-/- mice with bisphosphonate was similar to the length in WT mice without bisphosphonate. Histologically, the surface irregularity of the mandibular condyle that was observed in the OPG-/- mice without bisphosphonate tended to be less marked in the OPG-/- mice with bisphosphonate, and the proportion of the area of the cartilage layer relative to the whole condyle was significantly larger in OPG-/- mice with bisphosphonate than in those without bisphosphonate.

9.2.197 Effects of raloxifene on fracture risk in postmenopausal women: The raloxifene use for the heart trial
Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, Zhao Q, Agnusdei D, Cauley JA
J Bone Miner Res 2008;23:112-20

10,101 postmenopausal women ≥55 yr of age with coronary heart disease or at high risk for coronary events received 60 mg raloxifene daily or placebo for a median of 5.6 yr. There was no difference between raloxifene and placebo groups in risk of nonvertebral fractures (428 vs. 438 events; hazard ratio [HR], 0.96; 95% CI, 0.84-1.10), including hip/femur (89 vs. 103 events; HR, 0.85; 95% CI, 0.64-1.13) and wrist (107 vs. 111 events; HR, 0.95; 95% CI, 0.73-1.24) fractures. Women treated with raloxifene had a lower risk of clinical vertebral fractures (64 vs. 97 events; HR, 0.65; 95% CI, 0.47-0.89). In older women with or at high risk of coronary heart disease not selected on the basis of osteoporosis or increased fracture risk, treatment with raloxifene for 5 yr reduced the risk of clinical vertebral, not nonvertebral fractures.

9.2.198 Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis
Adami S, San Martin J, Munoz-Torres M, Econs MJ, Xie L, Dalsky GP, McClung M, Felsenberg D, Brown JP, Brandi ML, Sipos A
Osteoporos Int 2008;19:87-94

Following a year teriparatide 20 µg/day, women with osteoporosis were assigned to raloxifene 60 mg/day (n=157) or a placebo (n=172) for year 2, than a year of raloxifene. The raloxifene and placebo groups showed a decrease in spine (LS) BMD in year 2 (-1.0±0.3%, P=0.004; and -4.0±0.3%, P<0.001, respectively); the decrease was less with raloxifene (P<0.001). Open-label raloxifene reversed the LS BMD decrease with a placebo, resulting in similar decreases 2 years (-2.6±0.4% (raloxifene-raloxifene) and -2.7±0.4% (placebo-placebo). At study end, LS and femoral neck (FN) BMD were higher than pre-teriparatide levels, with no differences between the raloxifene-raloxifene and placebo-raloxifene groups, respectively (LS: 6.1±0.5% vs. 5.1±0.5%; FN: 3.4±0.6% vs. 3.0±0.5%). Sequential raloxifene prevented rapid bone loss at the LS and increased FN BMD whether raloxifene was started immediately or after a one-year delay following teriparatide.

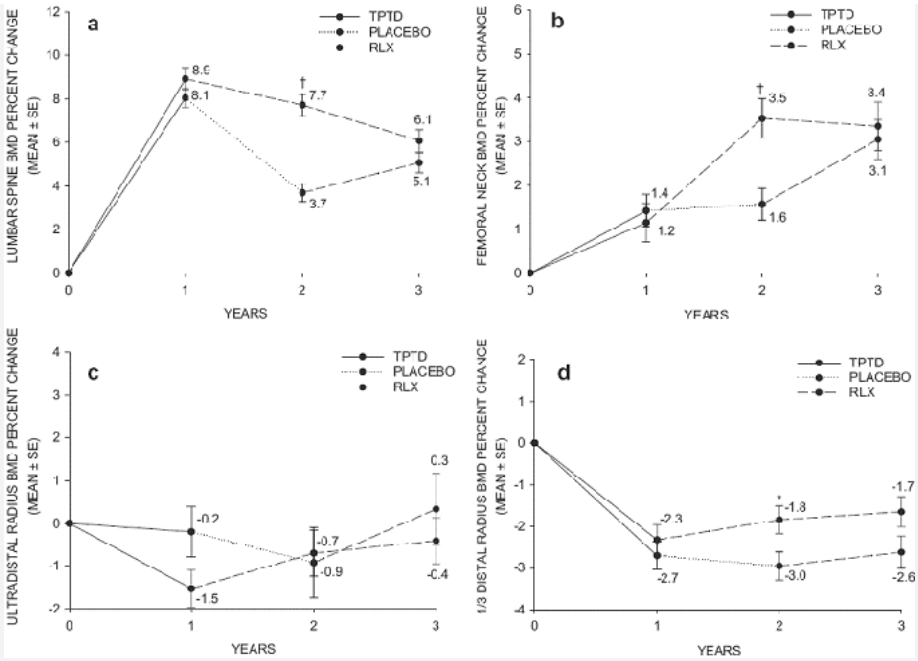


*Fig. 9.2.198a Percent change in bone mineral density during the 3-year sequential treatment. a. Lumbar spine; b. Femoral neck; c. Ultradistal radius; d. One-third distal radius. *P=0.021 vs. placebo, †P<0.001 vs. placebo. Reproduced from Osteoporos Int 2008; 19:87-94 wih permission from Springer.*

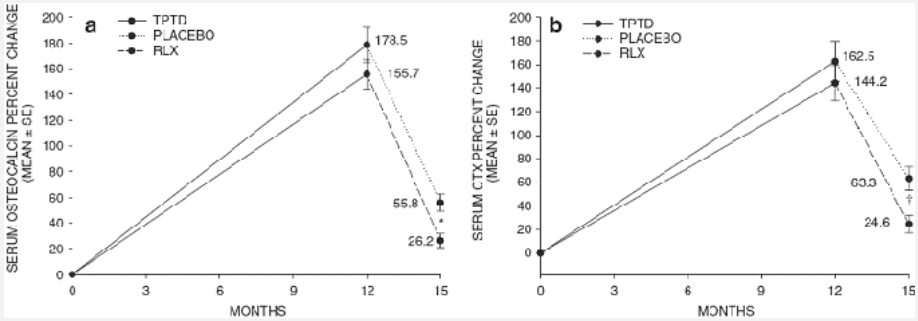


*Fig. 9.2.198b Percent change in serum osteocalcin (a) and serum CTX (b) 3 months after randomization. *P<0.001 vs. placebo, †P=0.002 vs. placebo. Reproduced from Osteoporos Int 2008; 19:87-94 wih permission from Springer.*

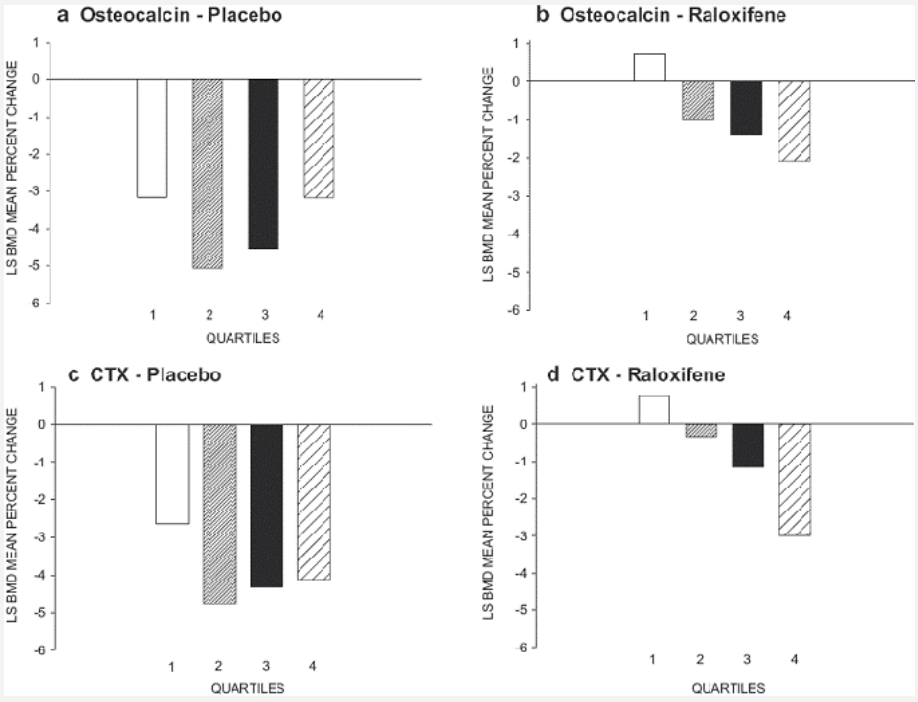


Fig. 9.2.198c Percent changes in lumbar spine BMD during the randomization year and quartiles of percent change in biochemical markers in 3 months after randomization. A. Osteocalcin-placebo quartiles: 1st: -75.1 to -50.8; 2nd: -50.8 to -39.5; 3rd: -39.5 to -25.6; 4th: -25.6 to +77.7. B. Osteocalcin-raloxifene quartiles: 1st: -77.3 to -59.7; 2nd: -59.7 to -49.5; 3rd: -49.5 to -36.3; 4th:-36.3 to +47.7. C. CTX-placebo quartiles: 1st: -84.6 to -51.9; 2nd: -51.9 to -35.0; 3rd: -35.0 to -10.6; 4th: -10.6 to +152.0. D. CTX-raloxifene quartiles: 1st: -86.1 to -58.4; 2nd: -58.4 to -45.3; 3rd: -45.3 to -24.1; 4th: -24.1 to +99.3. Homogeneity tests: osteocalcin-placebo, P=0.1370; osteocalcin-raloxifene, P=0.0303; CTX-placebo, P=0.1717; CTX-raloxifene, P=0.0012. Linear trend tests: osteocalcin-raloxifene, P=0.0047; CTX-raloxifene, P<0.0001. Reproduced from Osteoporos Int 2008; 19:87-94 wih permission from Springer.

9.2.199 Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis
Boonen S, Marin F, Obermayer-Pietsch B, Simoes ME, Barker C, Glass EV, Hadji P, Lyritis G, Oertel H, Nickelsen T, McCloskey EV
J Clin Endocrinol Metab 2008;93:852-60

245 women with osteoporosis had 2 years of teriparatide and were stratified by into alendronate (n=107), risedronate (n=59), etidronate (n=30), non-bisphosphonate (n=49). Significant increases in bone formation markers occurred in all groups after 1 month of teriparatide. Spine BMD increased while a transient decrease in hip BMD reversed. BMD change was similar in all prior antiresorptives. Prior etidronate users showed a higher increase at the spine not hip BMD. Duration of prior antiresorptive and lag time between stopping prior therapy and starting teriparatide did not affect the BMD response at any skeletal site. Teriparatide induces positive effects on BMD and markers of bone formation in postmenopausal women with established osteoporosis, regardless of prior long-term exposure to antiresorptive therapies.

9.2.200 Enhanced chondrogenesis and Wnt signaling in PTH-treated fractures
Kakar S, Einhorn TA, Vora S, Miara LJ, Hon G, Wigner NA, Toben D, Jacobsen KA, Al-Sebaei MO, Song M, Trackman PC, Morgan EF, Gerstenfeld LC, Barnes GL
J Bone Miner Res 2007;22:1903-12

Closed femoral fractures were generated in 8-wk-old male C57Bl/6 mice followed by daily systemic injections of either saline (control) or 30 µg/kg PTH(1-34) for 14 days after fracture. Bones were harvested at days 2, 3, 5, 7, 10, 14, 21, and 28 after fracture and analyzed at the tissue level by radiography and histomorphometry and at the molecular and biochemical levels level by RNase protection assay (RPA), real-time PCR, and Western blot analysis. PTH induced a larger callus cross-sectional area, length, and total volume compared with controls. Molecular analysis of the expression of extracellular matrix genes associated with chondrogenesis and osteogenesis showed that PTH treated fractures displayed a 3-fold greater increase in chondrogenesis relative to osteogenesis over the course of the repair process. In addition, chondrocyte hypertrophy occurred earlier in the PTH-treated callus tissues. Analysis of the expression of potential mediators of PTH actions showed that PTH treatment induced the expression of Wnts 4, 5a, 5b, and 10b and increased levels of unphosphorylated, nuclear localized beta-catenin protein, a central feature of canonical Wnt signaling. PTH-mediated enhancement of fracture repair is primarily associated with an amplification of chondrocyte recruitment and maturation and an increase in canonical Wnt signaling supporting the conclusion that PTH effects on bone repair are mediated at least in part through the activation of Wnt-signaling pathways.

9.2.201 Intermittent administration of human parathyroid hormone enhances bone formation and union at the site of cancellous bone osteotomy in normal and ovariectomized rats
Nozaka K, Miyakoshi N, Kasukawa Y, Maekawa S, Noguchi H, Shimada Y
Bone 2008;42:90-7

After a bilateral ovariectomy (OVX) cancellous bone osteotomy was performed on the right proximal tibia. After once-a-week hPTH (1-34) (100 µg/kg) or its vehicle for 4 weeks, bilateral tibiae including osteotomy and non-osteotomy sites were harvested. hPTH increased cancellous bone volume by stimulating bone formation in both normal and OVX rats and suppressed adipocyte volume ($p<0.05$). The percentage of PCNA-positive cells at the osteotomy site after PTH treatment was 2- to 3-fold higher than that of vehicle both in sham-operated and OVX rats ($p<0.05$). The magnitude of increase in the percentage of PCNA-positive cells after PTH at the osteotomy site was two times higher than that at the non-osteotomy site. PTH increased cancellous bone union after osteotomy both in sham-operated and OVX rats ($p<0.05$).

9.2.202 Interleukin-18 is regulated by parathyroid hormone and is required for its bone anabolic actions
Raggatt LJ, Qin L, Tamasi J, Jefcoat SC, Jr., Shimizu E, Selvamurugan N, Liew FY, Bevelock L, Feyen JH, Partridge NC
J Biol Chem 2008;283:6790-8

IL-18 expression is increased in UMR 106-01 rat osteoblastic cells in response to PTH. IL-18 mRNA increased by 2 h and had diminished after 12 h. Female IL-18 null mice and wild type littermate controls were injected with human 1-38 PTH for 4 weeks and the anabolic effect of PTH was abolished in trabecular bone not cortical bone.

9.2.203 Effectiveness of antiresorptive agents in the prevention of recurrent hip fractures
Morin S, Rahme E, Behlouli H, Tenenhouse A, Goltzman D, Pilote L
Osteoporos Int 2007;18:1625-32

Of 20,644 patients, 6,779 filled a prescription for antiresorptive agents. There were 992 recurrent hip fractures. Patients exposed to antiresorptives had a 26% reduction in the rate of recurrent fractures (adjusted hazard ratio 0.74; 95% CI, 0.64-0.86) compared to patients who were not. All subgroups experienced a reduction in recurrent fracture, except the very elderly.

9.2.204 Bone turnover and bone collagen maturation in osteoporosis: Effects of antiresorptive therapies
Byrjalsen I, Leeming DJ, Qvist P, Christiansen C, Karsdal MA
Osteoporos Int 2008;19:339-48

Participants were from cohorts of healthy postmenopausal women participating in double blind, placebo-controlled 2-year studies of alendronate, ibandronate, intranasal hormone replacement therapy (HRT), oral HRT, transdermal HRT, or raloxifene (n=427). The non-isomerized ααCTX and isomerized ββCTX were measured in urine samples obtained at baseline, and after 6, 12, and 24 months of therapy. Bone collagen maturation measured as the ratio between ααCTX and ββCTX showed that bisphosphonate treatment induced a collagen profile consistent with an older matrix with a 52% (alendronate) and 38% (ibandronate) reduction in the ratio between the two CTX isoforms vs. 3% and 15% with HRT or raloxifene, respectively. Anti-resorptive treatments had different effects on the endogenous profile of bone collagen maturation.

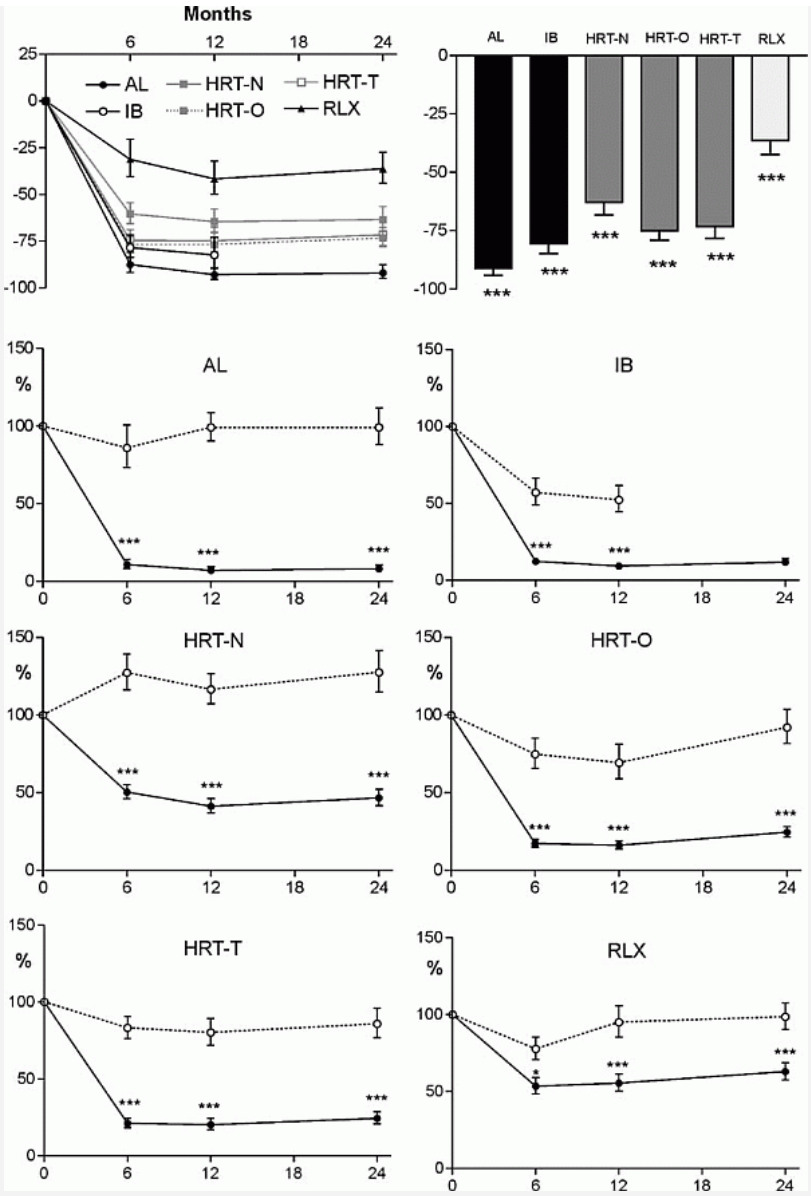
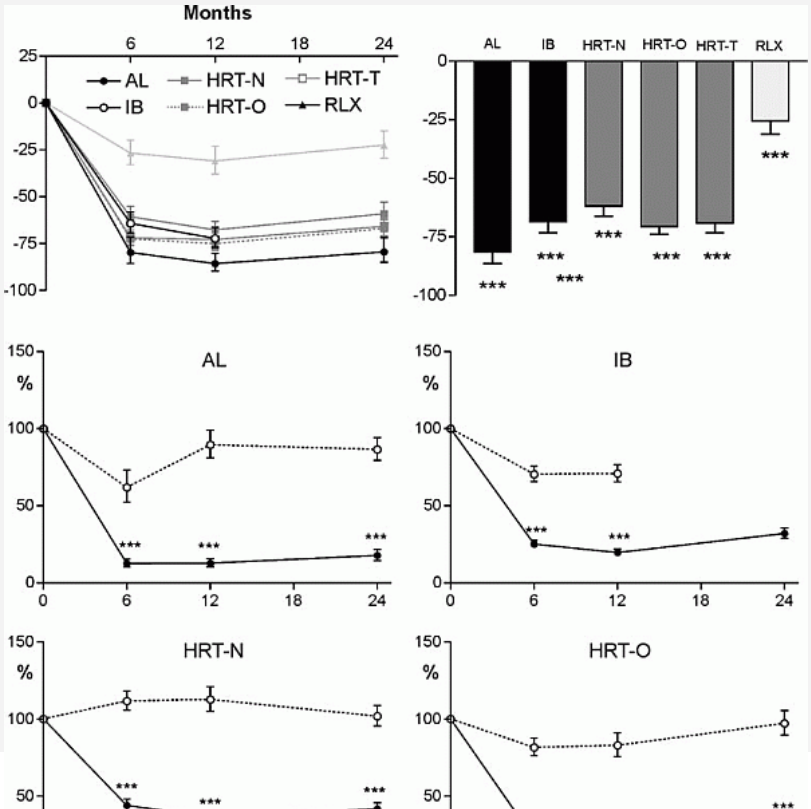


*Fig. 9.2.204a Urinary αCTX in percentage of baseline values in postmenopausal women during 24 months of anti-resorptive therapy. Upper left shows the placebo-corrected changes, and upper right the placebo-corrected time-averaged mean during the treatment period. The lower panels show values relative to baseline in each study in the placebo (○) and active treatment groups (●). AL (alendronate); IB (ibandronate); HRT-N (intranasal HRT); HRT-O (oral HRT); HRT-T (transdermal HRT); RLX (raloxifene). 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; 19:339-48 wih permission from Springer.*



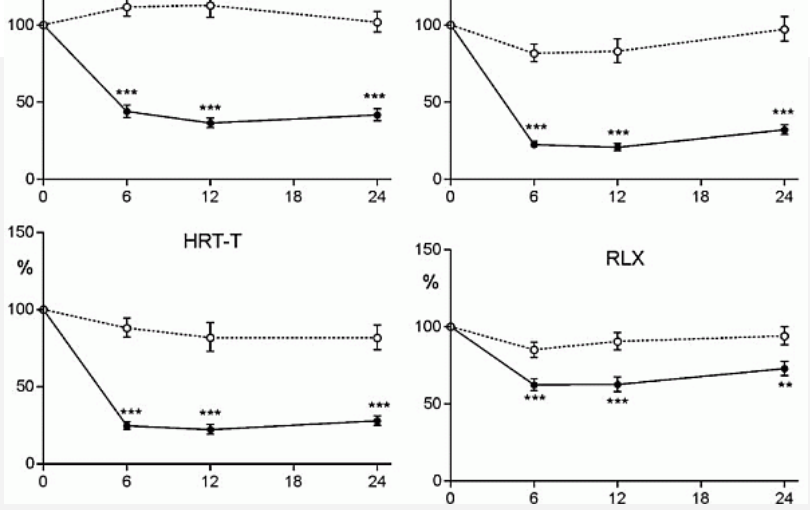


*Fig. 9.2.204b Urinary ββCTX in percentage of baseline values in postmenopausal women during 24 months of anti-resorptive therapy. Upper left shows the placebo-corrected changes, and upper right the placebo-corrected time-averaged mean during the treatment period. The lower panels show values relative to baseline in each study in the placebo (○) and active treatment groups (●). AL (alendronate); IB (ibandronate); HRT-N (intranasal HRT); HRT-O (oral HRT); HRT-T (transdermal HRT); RLX (raloxifene). Values shown are geometric mean±1SEM. The level of significance denotes difference from the placebo group: **p<0.01; ***p<0.001. Reproduced from Osteoporos Int 2008; 19:339-48 wih permission from Springer.*

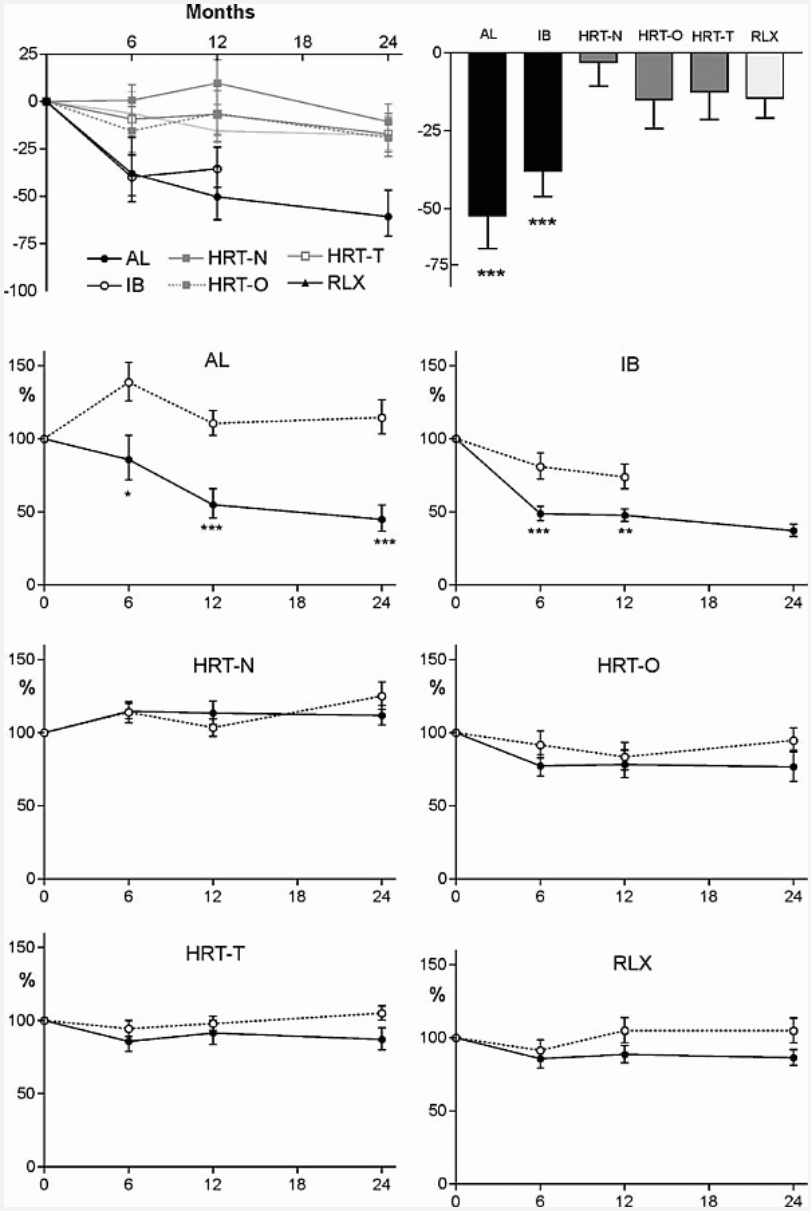


*Fig. 9.2.204c Urinary ααCTX/ββCTX ratio in percentage of baseline values in postmenopausal women during 24 months of anti-resorptive therapy. Upper left shows the placebo-corrected changes, and upper right the placebo-corrected time-averaged mean during the treatment period. The lower panels show values relative to baseline in each study in the placebo (○) and active treatment groups (●). AL (alendronate); IB (ibandronate); HRT-N (intranasal HRT); HRT-O (oral HRT); HRT-T (transdermal HRT); RLX (raloxifene). Values shown are geometric mean±1SEM. The level of significance denotes difference from the placebo group: *p<0.05; **p<0.01; ***p<0.001. Reproduced from Osteoporos Int 2008; 19:339-48 wih permission from Springer.*

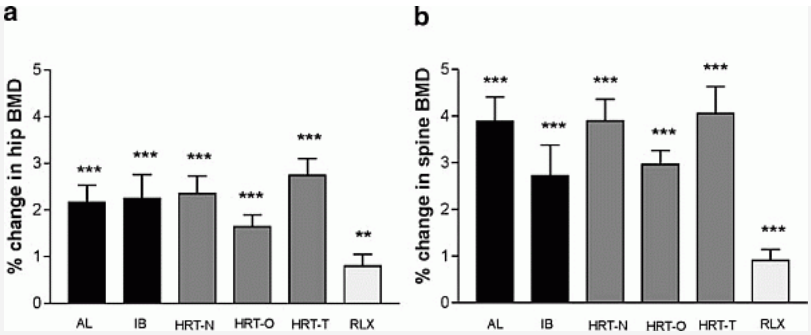


*Fig. 9.2.204d Changes in percentage per year in BMDhip (a) and BMDspine (b) in postmenopausal women during anti-resorptive therapy. AL (alendronate); IB (ibandronate); HRT-N (intranasal HRT); HRT-O (oral HRT); HRT-T (transdermal HRT); RLX (raloxifene). In the individual studies the values were adjusted for the corresponding placebo group. Values shown are mean±1SEM. The level of significance denotes difference from the placebo group: **p<0.01; ***p<0.001. Reproduced from Osteoporos Int 2008; 19:339-48 wih permission from Springer.*

9.2.205 Histomorphometric and muT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate

Arlot ME, Jiang Y, Genant HK, Zhao J, Burt-Pichat B, Roux JP, Delmas PD, Meunier PJ
J Bone Miner Res 2008;23:215-22

One hundred forty-one transiliac bone biopsies were obtained from 133 postmenopausal osteoporotic women: 49 biopsies after 1-5 yr of 2 g/d strontium ranelate and 92 biopsies at baseline or after 1-5 yr of placebo. Histomorphometry provided a 2D demonstration of the bone safety of strontium ranelate, with significantly higher mineral apposition rate (MAR) in cancellous bone (+9% vs. control, p=0.019) and borderline higher in cortical bone (+10%, p=0.056). Osteoblast surfaces were higher (+38% vs. control, p=0.047). 3D analysis of 3-yr biopsies with treatment (20 biopsies) and placebo (21 biopsies) using µCT showed changes in microarchitecture with, in the strontium ranelate group, higher cortical thickness (+18%, p=0.008) and trabecular number (+14%, p=0.05), and lower structure model index (-22%, p=0.01) and trabecular separation (-16%, p=0.04), with no change in cortical porosity.

9.2.206 Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia

Seeman E, Devogelaer JP, Lorenc R, Spector T, Brixen K, Balogh A, Stucki G, Reginster JY
J Bone Miner Res 2008;23:433-8

Data from the Spinal Osteoporosis Therapeutic Intervention study (SOTI; n=1649) and the TReatment Of Peripheral OSteoporosis (TROPOS; n=5091) were pooled to evaluate the antivertebral fracture efficacy of strontium ranelate in women with lumbar spine (LS) osteopenia with any BMD value at the femoral neck (FN; N=1166) and in 265 women with osteopenia at both sites (intention-to-treat analysis). The women were randomized to strontium ranelate 2 g/d orally or placebo for 3 yr. In women with LS osteopenia, treatment reduced the risk of vertebral fracture by 41%, by 59% (RR=0.41; 95% CI, 0.17-0.99) in the 447 patients with no prevalent fractures, and by 38% (RR=0.62; 95% CI, 0.44-0.88) in the 719 patients with prevalent fractures. In women with osteopenia at both sites, treatment reduced the risk of fracture by 52%. Strontium ranelate safely reduces the risk of vertebral fractures in women with osteopenia with or without a prevalent fracture.

9.2.207 Dual effect of strontium ranelate: Stimulation of osteoblast differentiation and inhibition of osteoclast formation and resorption in vitro

Bonnelye E, Chabadel A, Saltel F, Jurdic P
Bone 2008;42:129-38

In primary murine osteoblasts and osteoclasts derived from calvaria and spleen cells strontium ranelate continuously or during proliferation or differentiation phases of mouse calvaria cells, stimulates osteoblast formation. After 22 days of continuous treatment, expression of the osteoblast markers ALP, BSP and OCN increased, and was combined with an increase in bone nodule numbers. The number of mature osteoclasts decreased after treatment. Similarly to previous studies, we confirm that osteoclasts resorbing activity was also reduced but we found that strontium ranelate was associated with a disruption of the osteoclast actin-containing sealing zone.

9.2.208 Differential effects of D-hormone analogs and native vitamin D on the risk of falls: A comparative meta-analysis

Richy F, Dukas L, Schacht E
Calcif Tissue Int 2008;82:102-7

Fourteen trials including 21,268 subjects were included. Using double-blind data only, vitamin D-hormone analogs provided a statistically significant lower level of risk for falling compared to native vitamin D: RR=0.79 (95% confidence interval 0.64-0.96) vs. 0.94 (0.87-1.01) (intergroup difference P=0.049). The dropout rates observed in the two sets of trials were comparable: 0.33% per month. Upon current evidence, D-hormone analogs seem to prevent falls to a greater extent than their native compound.

9.2.209 Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women

Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K
Arch Intern Med 2008;168:103-8

A 1-year double-blind, randomized controlled trial of 302 community-dwelling ambulant older women aged 70 to 90 years with a serum 25-hydroxyvitamin <24.0 ng/mL and a history of falling in the previous year were randomized to ergocalciferol, 1000 IU/d, or placebo. Both groups received calcium citrate, 1000 mg/d. Ergocalciferol reduced the risk of at least 1 fall after adjustment for height (ergocalciferol, 53.0%; control, 62.9%; OR=0.61, 0.37-0.99). Ergocalciferol reduced the risk of having the first fall in winter and spring ergocalciferol group, 25.2%; control, 35.8%; OR, 0.55 (0.32-0.96) but not in summer and autumn, and reduced the risk of having 1 fall (ergocalciferol 21.2%; control 33.8%; OR, 0.50; (0.28-0.88) but not multiple falls. Patients with a history of falling and vitamin D insufficiency in sunny climates benefit from ergocalciferol and calcium, which is associated with a 19% reduction in the relative risk of falling, mostly in winter.

9.2.210 Effects of calcium and vitamin d supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: A five-year randomized controlled trial
Zhu K, Devine A, Dick IM, Wilson SG, Prince RL
J Clin Endocrinol Metab 2008;93:743-9

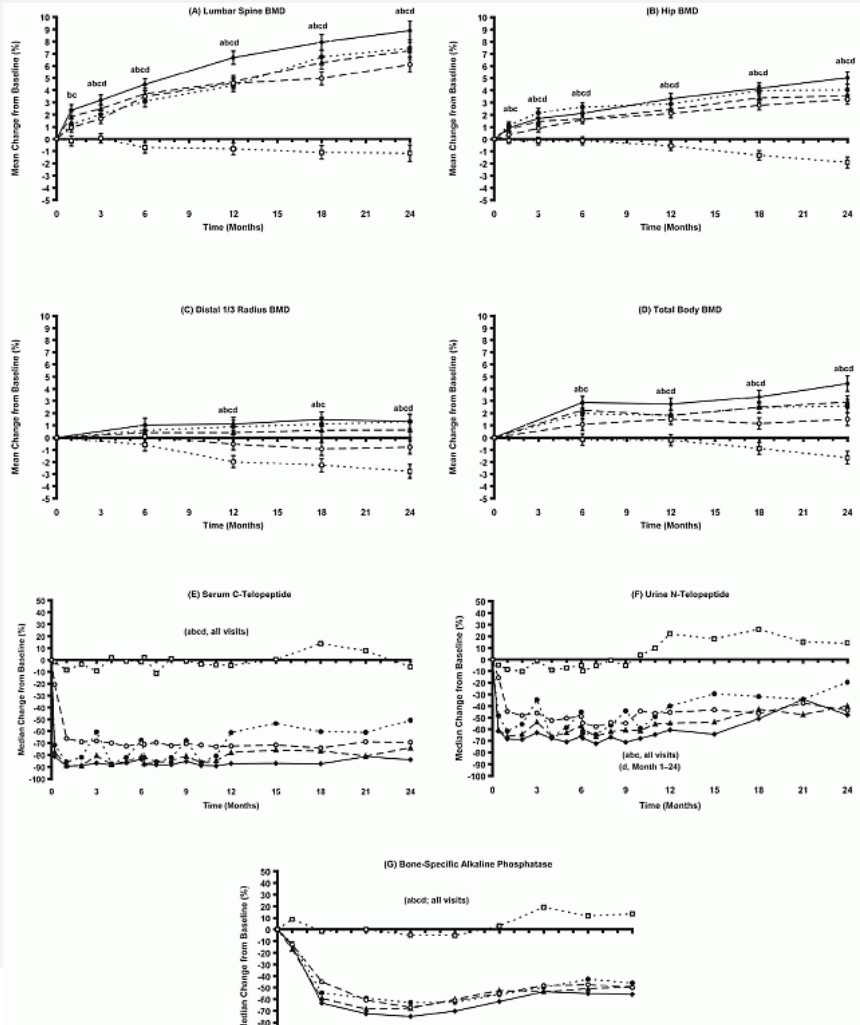
A 5-year randomised controlled double-blind trial of 120 community-dwelling women aged 70-80 years given Calcium 1200 mg/d (Ca group) or 1000 IU/d vitamin D2 (CaD group), double placebo (control). Hip BMD was preserved in CaD (-0.17%) and Ca (0.19%) groups. not controls (-1.27%) at year one and maintained in the CaD group at years 3 and 5. The benefits were in those with baseline 25OHD levels below the median (68 nmol/L). At year one, Ca and CaD groups had 6.8% and 11.3% lower plasma alkaline phosphatase, respectively (P≤0.02), and 28.7% and 34.5% lower urinary DPD/Cr ratio, respectively (P≤0.05). At 5 years, this suppression was only maintained in the CaD group. CaD reduced PTH at 3 and 5 years (27.8 and 31.3%, P≤0.005) in those with baseline PTH above the median (3.6 pmol/L). Addition of vitamin D to calcium has long term beneficial effects on bone density in elderly women living in a sunny climate, probably mediated by a long term reduction in bone turnover rate.

9.2.211 Alfacalcidol-stimulated focal bone formation on the cancellous surface and increased bone formation on the periosteal surface of the lumbar vertebrae of adult female rats
Chen H, Tian X, Liu X, Setterberg RB, Li M, Jee WS
Calcif Tissue Int 2008;82:127-36

Seventy-four 8.5-month-old rats were administered 0, 0.005, 0.025, 0.05 or 0.1 μg/kg of alfacalcidol for 12 weeks, alone or in combination with exercise. At 0.05 and 0.1 μg/kg, alfacalcidol increasd cancellous bone volume. Percent eroded surface, bone resorption and formation were suppressed by alfacalcidol. However, mineral apposition rate was increased. A positive balance between bone formation and resorption was observed in the rats treated with the highest dose of alfacalcidol. Alfacalcidol induced a unique bone formation site ("bouton") on the cancellous surface. These boutons connected adjacent trabeculae and increased trabecular thickness. They exhibited both smooth and scalloped cement lines, suggesting that they were formed by minimodeling- and remodeling-based bone formation. Furthermore, alfacalcidol at 0.1 mug/kg increased periosteal bone formation of the lumbar transverse processes. Bipedal stance exercise alone did not have an effect on bone balance and bone turnover. There were no interactions between alfacalcidol and bipedal stance exercise. Alfacalcidol exhibited both anti-catabolic and anabolic effects on bone in intact female rats. The effect of combined treatment with alfacalcidol and bipedal stance exercise was no better than that of alfacalcidol alone.

9.2.212 Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD
Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, Wang A, Siddhanti S, Fitzpatrick LA
J Bone Miner Res 2007;22:1832-41

Denosumab is a fully human monoclonal antibody that inhibits RANKL. Four hundred twelve postmenopausal women with lumbar spine BMD T-scores of -1.8 to -4.0 or femoral neck/total hip T-scores of -1.8 to -3.5 were randomly assigned to subcutaneous placebo; denosumab 6, 14, or 30 mg every 3 mo; denosumab 14, 60, 100, or 210 mg every 6 mo; or open-label oral alendronate 70 mg once weekly. Denosumab increased BMD at all measured skeletal sites and decreased turnover markers at 24 mo. At the lumbar spine, BMD increases with denosumab ranged from 4.13% to 8.89%. BMD changes with denosumab 30 mg every 3 mo and ≥60 mg every 6 mo were similar to, or in some cases greater than, with alendronate. The incidence of adverse events was similar in the placebo, denosumab, and alendronate treatment groups.



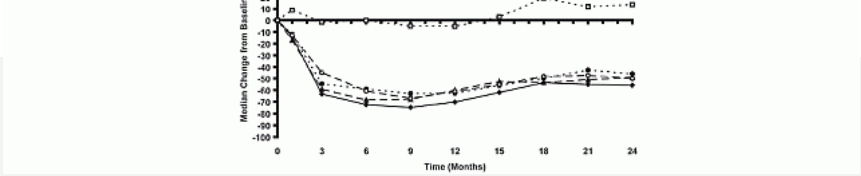


Fig. 9.2.212a Comparison of percentage change in BMD and laboratory parameters with denosumab 3-mo regimens, alendronate, and placebo (□, placebo; ●, denosumab 6 mg; ▲, denosumab 14 mg; ◆, denosumab 30 mg; O, alendronate 70 mg weekly). Between-group differences at p<0.05 were observed based on ANCOVA model adjusting for treatment group, geographical location, and baseline value as follows: (a) denosumab 6 mg vs. placebo; (b) denosumab 14 mg vs. placebo; (c) denosumab 30 mg vs. placebo; (d) alendronate vs. placebo. Error bars denote SE. Reproduced from J Bone Miner Res 2007;22:1832-41 with permission of the American Society for Bone and Mineral Research.

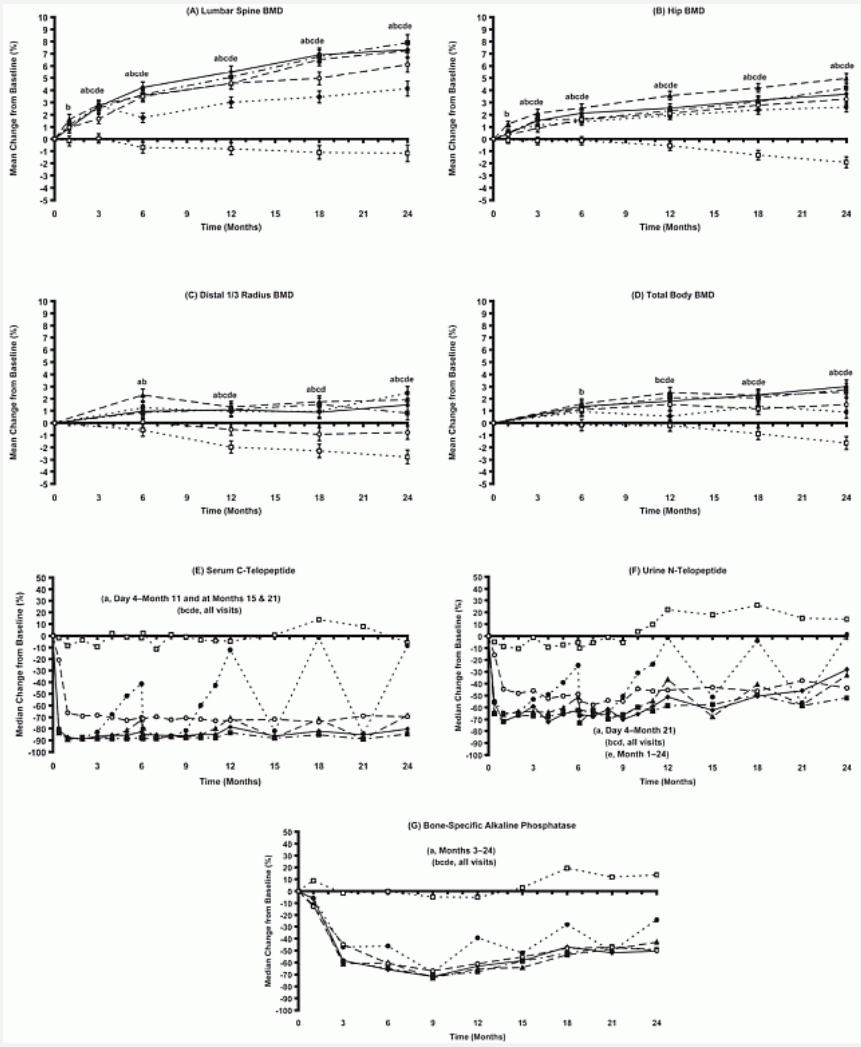


Fig. 9.2.212b Comparison of percentage change in BMD and laboratory parameters with denosumab 6-mo regimens, alendronate, and placebo (□, placebo; ●, denosumab 14 mg; ▲, denosumab 60 mg; ◆, denosumab 100 mg; ■, denosumab 210 mg; O, alendronate 70 mg weekly). Between-group differences at p<0.05 were observed based on ANCOVA model adjusting for treatment group, geographical location, and baseline value as follows: (a) denosumab 14 mg vs. placebo; (b) denosumab 60 mg vs. placebo; (c) denosumab 100 mg vs. placebo; (d) denosumab 210 mg vs. placebo; (e) alendronate vs. placebo. Error bars denote SE. Reproduced from J Bone Miner Res 2007;22:1832-41 with permission of the American Society for Bone and Mineral Research.

9.2.213 Cathepsin K inhibitors prevent matrix-derived growth factor degradation by human osteoclasts
Fuller K, Lawrence KM, Ross JL, Grabowska UB, Shiroo M, Samuelsson B, Chambers TJ
Bone 2008;42:200-11

CathK-inhibitors suppress degradation of the organic matrix of bone while allowing demineralization. CathK-inhibitors increased the concentrations of matrix-derived proteins in supernatants of osteoclasts on bone, most likely through protection against intracellular degradation. Protons are necessary and sufficient for the release of IGF-I from bone matrix, and that recombinant CathK can degrade both marker proteins. In the presence of a CathK-inhibitor, the amount of IGF-I released from matrix exceeded the amount secreted by osteoclasts. CathK-inhibition augmented bone morphogenetic protein (BMP)-2 release. Lastly, MC3T3-E1 numbers were greater after co-culture with osteoclasts on bone with versus without CathK-inhibitor, showing that, in the presence of CathK-inhibitor, osteoclasts release biologically-significant quantities of biologically-active matrix-derived growth factors. These results support a model in which osteoclastic secretion of protons demineralizes bone, causing release of growth factors from bone matrix. Normally these are largely degraded, with collagen, in the resorptive hemivacuole and during transcytosis to the basal surface of the osteoclast, but in the presence of CathK inhibitor they are released intact, and so might augment bone formation.

9.2.214 Estradiol rapidly inhibits osteoclastogenesis and RANKL expression in bone marrow cultures in postmenopausal women: A pilot study
Taxel P, Kaneko H, Lee SK, Aguila HL, Raisz LG, Lorenzo JA
Osteoporos Int 2008;19:193-9

Estrogen (E(2)) deficiency at menopause increases osteoclast (OCL) formation and bone resorption, predisposing women to osteoporosis. We examined receptor activator of NF-kappa B-ligand (RANKL) expression and in vitro OCL formation in cultured bone marrow cells from eight postmenopausal women before and after 3 weeks of E(2) and three untreated premenopausal women. RANKL (3-100 ng/ml) produced a dose-dependent increase in in vitro OC formation and E(2) ($p<0.01$) inhibited OCL formation by 33-50%. A small proportion of marrow cells bound anti- RANKL Ab (0.2-4.3%). There was no effect of E(2) on the percentage of cells binding the anti-RANKL Ab in the R1 fraction. In the R2 fraction E(2) decreased the percentage of cells binding anti-RANKL Ab by 68±9% ($p<0.01$). Three weeks of E(2) had a dual action. It inhibited the ability of hematopoietic cells to form OCLs in response to RANKL, and decreased the production of RANKL in cells of the bone marrow.

9.2.215 Effects of treatment with fluoride on bone mineral density and fracture risk: A meta-analysis
Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L
Osteoporos Int 2008;19:257-68

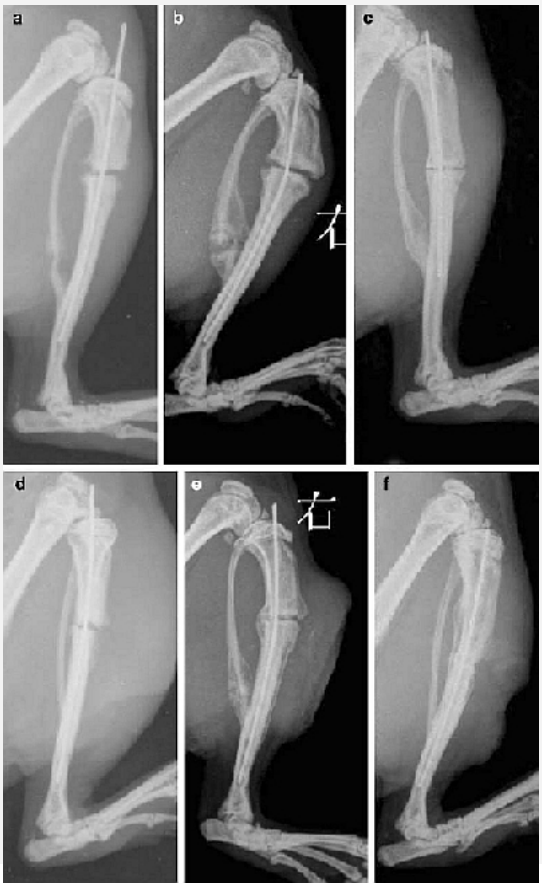
Twenty-five eligible studies were identified. Spine BMD increased 7.9%, 95% CI: 5.4-10.5%, and hip BMD 2.1%, 95% CI: 0.9-3.4%. A meta-regression showed increasing spine BMD with increasing treatment duration (5.04±2.16%/year of treatment). Overall there was no significant effect on the risk of vertebral (OR=0.8, 95% CI: 0.5-1.5) or non-vertebral fracture (OR=0.8, 95% CI: 0.5-1.4). With a daily dose of ≤20 mg fluoride equivalents (152 mg monofluorophosphate/44 mg sodium fluoride), there was a significant reduction in vertebral (OR=0.3, 95% CI: 0.1-0.9) and non-vertebral (OR=0.5, 95% CI: 0.3-0.8) fracture risk. With a daily dose >20 mg fluoride equivalents, there was no reduction in vertebral (OR=1.3, 95% CI: 0.8-2.0) and non-vertebral (OR=1.5, 95% CI: 0.8-2.8) fracture risk. Fluoride increases spine and hip BMD, depending on treatment duration. Overall there was no effect on hip or spine fracture risk. However, in subgroup analyses a low fluoride dose (≤20 mg/day of fluoride equivalents) was associated with a significant reduction in fracture risk.

9.2.216 Effect of vitamin K supplementation on bone loss in elderly men and women
Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B
J Clin Endocrinol Metab 2008;[Epub ahead of print]

To determine the effect of three-year phylloquinone supplementation 452 men and women (60-80 y) were randomized to 500 µg/d or no phylloquinone, plus a daily calcium (600 mg elemental calcium) and vitamin D (400 IU) supplement. Intent-to-treat analysis was used to compare change in measures in 401 participants who completed the trial. There were no differences in changes in bone mineral density at any site between the two groups. The group that received the phylloquinone had higher phylloquinone and lower % undercarboxylated osteocalcin concentrations. No other biochemical measures differed between the two groups. Phylloquinone supplementation does not confer any additional benefit for bone health at the spine or hip when taken with recommended amounts of calcium and vitamin D.

9.2.217 Locally applied simvastatin promotes fracture healing in ovariectomized rat
Wang JW, Xu SW, Yang DS, Lv RK
Osteoporos Int 2007;18:1641-50

Simvastatin (10 mg/kg/day) was injected subcutaneously to tissue overlying the site of fractured tibiae of ovariectomized rats for a treatment period of 5 days. Vehicle reagent was used as a control. Healing quality was evaluated at 1, 2 and 4 weeks after fracture. Compared with that in the vehicle group, the callus cross-section area in simvastatin-treated rats was enlarged by 21.3% ($p<0.05$) at 1 week and by 21.5% ($p<0.05$) at 2 weeks; new woven bone was relatively substantive and arranged more tightly and regularly at 2 and 4 weeks; and maximal load was increased by 57.5% ($p<0.05$) at 2 weeks and by 31.4% ($p<0.05$) at 4 weeks. Histomorphometrically, simvastatin was associated with a significant ($p<0.05$) increase of mineralization width (MLW), mineralization volume (MLV) and mineral apposition rate (MAR). The current study suggests that local application of simvastatin could promote fracture healing in ovariectomized rats.



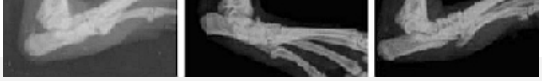


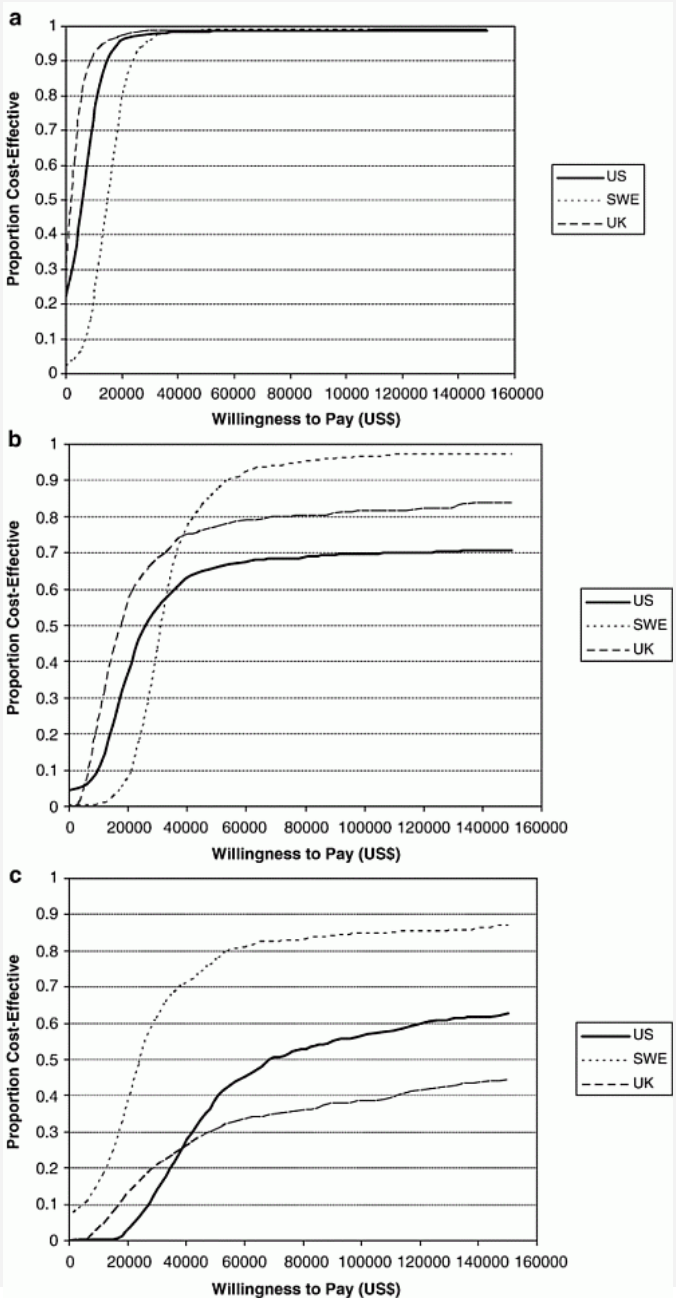
Fig. 9.2.217 Radiographs of tibiae of Sprague-Dawley rats at 1 (a, d), 2 (b, e) and 4 (c, f) weeks after fracture. The progressed consolidation of the fracture gap in OVX+SVS (e, f) groups is clearly recognizable compared with the OVX+vehicle (b, c) group at 2 and 4 weeks. Reproduced from Osteoporos Int 2007; 18:1641-50 wih permission from Springer.

9.2.218 The impact of expressions of treatment efficacy and out-of-pocket expenses on patient and physician interest in osteoporosis treatment: implications for pay-for-performance programs
Sinsky CA, Foreman-Hoffman V, Cram P
J Gen Intern Med 2008;23:164-8

To assess how patient and provider compliance with osteoporosis CPGs varies when efficacy is presented as relative risk reduction (RRR) vs. absolute risk reduction (ARR). Patient and provider acceptance of pharmacotherapy when treatment efficacy (reduction in hip fractures) was expressed in relative terms (35% RRR) vs. absolute terms (1% ARR); acceptance of pharmacotherapy as patient drug copayment increased from 0% to 100% of the total drug costs. Compliance with CPGs fell when the expression of treatment benefit was switched from RRR to ARR for both patients (86% vs. 57% compliance; P<0.001) and physicians (97% vs. 56% compliance; P<0.001). Increasing drug copayment from 0% to 10% of total drug cost decreased patient compliance with CPGs from 80% to 57% (P<0.001) but did not impact physician compliance.

9.2.219 Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK: Results based on the Women's Health Initiative randomised controlled trial
Lekander I, Borgstrom F, Strom O, Zethraeus N, Kanis JA
Bone 2008;42:294-306

The cost effectiveness of 50 year old women was assessed based on a societal perspective and the medical evidence found in the Women Health Initiative (WHI) trials. The model had a lifetime horizon divided into cycle lengths of 1 year and comprised the following disease states: hip fracture, vertebral fracture, wrist fracture, breast cancer, colorectal cancer, coronary heart disease, stroke and venous thromboembolic events. An intervention was modelled by its impact on the disease risks during and after the cessation of treatment. HT compared to no treatment was cost-effective for most subgroups of hysterectomised women, whereas for women with an intact uterus without a previous fracture, HT was commonly dominated by no treatment. Fracture risks were the single most important determinant of the cost effectiveness results.



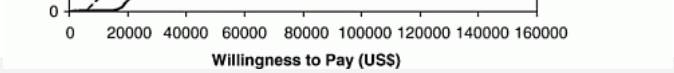


Fig. 9.2.219 Acceptability curves for 60 year old osteoporotic (T-score = −2.5 SD) women. (a) Hysterectomised women with a previous fracture. (b) Hysterectomised women without a previous fracture. (c) Women with intact uterus and a previous fracture. Note: These figures illustrate the results from the probabilistic analyses. The results represent the proportion of ICERs that fall below different values of willingness to pay (WTP). The WTP sets the threshold value for when an intervention is deemed cost-effective. The results illustrated in panel (a) have, for example, a higher probability of falling below smaller values of WTP than the results in panel (c). Reproduced from Bone, 42:294-306, Copyright (2008), with permission from Elsevier.

9.2.220 Successful direct intervention for osteoporosis in patients with minimal trauma fractures
Kuo I, Ong C, Simmons L, Bliuc D, Eisman J, Center J
Osteoporos Int 2007;18:1633-9

From March 2004 to March 2006, 155 consecutive minimal-trauma fracture subjects (mean age 64.0±17.6) attending fracture clinics had a medical assessment, following which they were recommended BMD and laboratory testing. Treatment recommendations were given after review of investigations with follow-up at a median of 8.6 months. Comparison of outcomes was made with a similar group of patients given written information 2 years prior. At baseline, 47% of patients had prior fractures, but only 26% had had BMD screening. Twenty-one percent were on anti-resorptive therapy, and 15% were on calcium/vitamin D. Following intervention, 83% had a BMD and of these, 68% had a T-score < -1.0. Of treatment naive patients, 44% were recommended anti-resorptive therapy and 56% were recommended calcium/vitamin D. Compliance was 80% for anti-resorptive and 76% for calcium/vitamin D. Female gender and lower BMD were predictors of compliance. Compared with information-based intervention, direct intervention improved management two to fivefold, maintaining long-term treatment in 90% of osteoporotic and 73% of osteopenic subjects requiring therapy.

9.2.221 Microstimulation at the bone-implant interface upregulates osteoclast activation pathways
Stadelmann VA, Terrier A, Pioletti DP
Bone 2008;42:358-64

So far no data exists directly quantifying the effect of micromotion and compression on human bone. Gene expression of RANKL, OPG, TGFB2, IFNG and CSF-1 was analyzed after no mechanical stimulation (control), exposure to compression or exposure to micromotions. We observed an 8-fold upregulation of RANKL after exposure to micromotions, and downregulation of OPG, IFNG and TGFB2. The RANKL:OPG ratio was upregulated 24-fold after micromotions. This suggests that the micromotions arising at the bone-implant interface during normal gait cycles induce a bone resorption response after only 1 h, which occurs before any wear debris particles enter the system.

9.2.222 Pharmacologic targeting of a stem/progenitor population in vivo is associated with enhanced bone regeneration in mice
Mukherjee S, Raje N, Schoonmaker JA, Liu JC, Hideshima T, Wein MN, Jones DC, Vallet S, Bouxsein ML, Pozzi S, Chhetri S, Seo YD, Aronson JP, Patel C, Fulciniti M, Purton LE, Glimcher LH, Lian JB, Stein G, Anderson KC, Scadden DT
J Clin Invest 2008;118:491-504

Bortezomib (Bzb) is a proteasome inhibitor used in multiple myeloma. Bzb induces MSCs to undergo osteoblastic differentiation, in part by modulation of the bone-specifying transcription factor Runx-2 in mice. Mice implanted with MSCs showed increased ectopic ossicle and bone formation when recipients received low doses of Bzb. Furthermore, this treatment increased bone formation and rescued bone loss in a mouse model of osteoporosis. Thus, we show that a tissue-resident adult stem cell population in vivo can be pharmacologically modified to promote a regenerative function in adult animals.

9.2.223 Continuous local infusion of fibroblast growth factor-2 enhances consolidation of the bone segment lengthened by distraction osteogenesis in rabbit experiment
Abbaspour A, Takata S, Sairyo K, Katoh S, Yukata K, Yasui N
Bone 2008;42:98-106

Experimental tibial lengthening was achieved in 61 rabbits to examine the effect of continuous local infusion of recombinant human fibroblast growth factor-2 (rhFGF-2) on bone healing of the lengthened segment. The tibial diaphysis was separated by osteotomy and was subjected to slow progressive distraction (rate: 0.35 mm/12 h). At various stages of distraction, rhFGF-2 was infused continuously for 2 weeks into the lengthened segment (rate: 14.28 μg/60 mul/day). Bone healing was significantly accelerated when rhFGF-2 was infused in the beginning of consolidation phase, but not in the distraction phase or in the lag phase. rhFGF-2-treated tibia had increased bone mineral density (BMD), bone mineral content (BMC) and cortical bone thickness (CBT). Three-point bending test demonstrated that rhFGF-2-treated bone had stronger mechanical properties than N/S-treated bone. rhFGF-2 into the lengthened segment can shorten the consolidation phase of limb lengthening and the method is applicable to the clinical treatment.

9.2.224 Recommendations for the clinical evaluation of agents for treatment of osteoporosis: Consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF)
Silverman SL, Cummings SR, Watts NB
J Bone Miner Res 2008;23:159-65

9.2.225 The care gap in diagnosis and treatment of women with a fragility fracture
Bessette L, Ste-Marie LG, Jean S, Davison KS, Beaulieu M, Baranci M, Bessant J, Brown JP
Osteoporos Int 2008;19:79-86

9.2.226 Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA Study
Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanauskaite D, Reid DM, Delmas PD, Recker RR
J Rheumatol 2008;35:488-97

9.2.227 Bisphosphonates reduce local recurrence in extremity giant cell tumor of bone: A case-control study
Tse LF, Wong KC, Kumta SM, Huang L, Chow TC, Griffith JF
Bone 2008;42:68-73

9.2.228 Bisphosphonate-associated osteonecrosis can hide jaw metastases
Bedogni A, Saia G, Ragazzo M, Bettini G, Capelli P, D'Alessandro E, Nocini PF, Russo LL, Lo Muzio L, Blandamura S
Bone 2007;41:942-5

9.2.229 Zoledronate-related osteonecrosis of the mandible
Ho L, Quan V, Henderson R
Clin Nucl Med 2008;33:68-70

9.2.230 The effects of bone remodeling inhibition by alendronate on three-dimensional microarchitecture of subchondral bone tissues in guinea pig primary osteoarthrosis
Ding M, Danielsen CC, Hvid I
Calcif Tissue Int 2008;82:77-86

9.2.231 Characteristics of patients initiating teriparatide for the treatment of osteoporosis
Foster SA, Foley KA, Meadows ES, Johnston JA, Wang S, Pohl GM, Long SR
Osteoporos Int 2008;19:373-7

9.2.232 Control of the SOST bone enhancer by PTH using MEF2 transcription factors
Leupin O, Kramer I, Collette NM, Loots GG, Natt F, Kneissel M, Keller H
J Bone Miner Res 2007;22:1957-67

9.2.233 Genetic background influences fluoride's effects on osteoclastogenesis
Yan D, Gurumurthy A, Wright M, Pfeiler TW, Loboa EG, Everett ET
Bone 2007;41:1036-44

9.2.234 Autologous stem cell regeneration in craniosynostosis
Moioli EK, Clark PA, Sumner DR, Mao JJ
Bone 2008;42:332-40

9.2.235 Uptake and adherence with soft- and hard-shelled hip protectors in Norwegian nursing homes: A cluster randomised trial
Bentzen H, Forsen L, Becker C, Bergland A
Osteoporos Int 2008;19:101-11

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

Volume 9, Issue 2, 2008

Exercise

9.2.236 Physical training preserves bone mineral density in postmenopausal women with forearm fractures and low bone mineral density
Bergstrom I, Landgren B, Brinck J, Freyschuss B
Osteoporos Int 2008;19:177-83

One hundred and twelve postmenopausal women 45-65 years with forearm fractures and T-scores from -1.0 to -3.0 were randomized to either a physical training or control group. Training included three fast 30-minute walks and two sessions of one-hour training per week. A per protocol analysis was performed, including 48 subjects in the training group and 44 subjects in the control group. The total hip BMD increased in the training group +0.005 g/cm2 (±0.018), +0.58%, while it decreased -0.003 g/cm2 (±0.019), -0.36%, (p=0.041) in the control group. No significant effects of physical training were seen in the lumbar spine. A sensitivity intention to treat analysis, including all randomized subjects, showed no significant effect of physical training on BMD at any site. Despite this the authors infer a small but positive effect of physical exercise on hip BMD in postmenopausal women with low BMD.

9.2.237 Interaction between playing golf and HRT on vertebral bone properties in post-menopausal women measured by QCT
Eser P, Cook J, Black J, Iles R, Daly RM, Ptasznik R, Bass SL
Osteoporos Int 2008;19:311-9

Forty-seven postmenopausal women who played golf regularly were compared to 25 controls. Bone parameters at the mid-vertebral body were determined by QCT at spinal levels T3, T7, T12 and L2 (cross-sectional area (CSA), total volumetric BMD (vBMD), trabecular vBMD of the central 50% of total CSA, BMC and cortical rim thickness). At T7 and L2, CSA of trunk muscles was determined. There was a positive interaction between golf and HRT for vertebral CSA and BMC at T12 and L2, but not at T3 or T7 (p ranging <0.02 to 0.07). Current HRT use was associated with a 10-15% greater total and trabecular vBMD. Vertebral CSA was the bone parameter significantly related to muscle CSA. These findings provide preliminary evidence that playing golf may improve lower spine bone strength in postmenopausal women who are using HRT.

9.2.238 WISE-2005: Supine treadmill exercise within lower body negative pressure and flywheel resistive exercise as a countermeasure to bed rest-induced bone loss in women during 60-day simulated microgravity
Smith SM, Zwart SR, Heer M, Lee SM, Baecker N, Meuche S, Macias BR, Shackelford LC, Schneider S, Hargens AR
Bone 2008;42:572-81

After a 20-day ambulatory adaptation to controlled confinement and diet, 16 women participated in a 60-day, 6 degrees head-down-tilt BR and were assigned randomly to one of the two groups. Control subjects (CON, n=8) performed no countermeasure. Exercise subjects (EX, n=8) participated in an exercise program during BR, alternating between supine treadmill exercise within lower body negative pressure (3-4 d wk(-1)) and flywheel resistive exercise (2-3 d wk(-1)). By the last week of BR, excretion of helical peptide (CON, 79%±44 increase; EX, 64%±50, mean±SD) and N-terminal cross-linking telopeptide (CON, 51%±34; EX, 43%±56), markers of bone resorption, were greater than they were before BR in both groups (P<0.05). However, serum concentrations of the bone formation marker procollagen type I N propeptide were greater in EX than CON throughout and after bed rest (P<0.05), while concentrations of the bone formation marker bone alkaline phosphatase tended to be greater in EX than CON. Exercise attenuated loss of hip and leg bone mineral density in EX compared to CON. The combination of resistive and aerobic exercise did not prevent bone resorption but did promote bone formation, and helped mitigate the net bone loss associated with simulated microgravity.

9.2.239 Effects of different types of weight-bearing loading on bone mass and size in young males: A longitudinal study
Nordstrom A, Hogstrom M, Nordstrom P
Bone 2008;42:565-71

9.2.240 Compressive forces induce osteogenic gene expression in calvarial osteoblasts
Rath B, Nam J, Knobloch TJ, Lannutti JJ, Agarwal S
J Biomech 2008;41:1095-103

9.2.241 Responses of intramembranous bone and sutures upon in vivo cyclic tensile and compressive loading
Peptan AI, Lopez A, Kopher RA, Mao JJ
Bone 2008;42:432-8

9.2.242 The lipogenic gene Spot 14 is activated in bone by disuse yet remains unaffected by a mechanical signal anabolic to the skeleton
Zhi J, Xu G, Rubin CT, Hadjiargyrou M
Calcif Tissue Int 2008;82:148-54

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

Volume 9, Issue 2, 2008

Men

9.2.243 An association between socioeconomic, health and health behavioural indicators and fractures in young adult males
Mattila VM, Jormanainen V, Sahi T, Pihlajamaki H
Osteoporos Int 2007;18:1609-15

In 7,378 conscript males (median age 19), of which 7,083 (96%) answered. 2,456 (34.7%) participants reported fracture(s). The most common anatomical locations of fracture were the forearm, the hand and the ankle. The strongest risk indicators for fractures were frequent drunkenness (OR 1.7; 95% CI: 1.3-2.0), regular sports training (OR 1.6; 95% CI: 1.3-1.9), frequent use of health care services (OR 1.5; 95% CI: 1.3-1.8) and obesity (OR 1.5; 95% CI: 1.2-1.9).

9.2.244 Outdoor air pollution and bone mineral density in elderly men: The Oslo Health Study
Alvaer K, Meyer HE, Falch JA, Nafstad P, Sogaard AJ
Osteoporos Int 2007;18:1669-74

In an osteoporosis sub-study of the population-based Oslo Health Study (2000-2001) BMD of total body and total hip (mg/cm(2)) was measured by DXA in 590 men 75-76 years old. Exposure to air pollution (particulate matter (PM(10) and PM(2.5)) and nitrogen dioxide (NO(2))) at each participant's home address was estimated from 1992 to 2001. Air pollution was inversely associated with total body BMD, whereas no association was found for total hip BMD. The adjusted odds ratio (OR) [95% CI] for low total body BMD (Z-score ≤-1) was per standard deviation increase 1.33 [1.05-1.70] for PM(2.5), 1.28 [1.00-1.63] for PM(10), and 1.24 [0.97-1.59] for NO(2). Stratified by smoking status the adjusted OR for PM(2.5) was 1.73 [1.02-2.95] in current smokers, 1.40 [1.03-1.90] in former smokers and 0.83 [0.43-1.58] in non-smokers. There was a weak but statistically significant inverse association between indicators of air pollution and total body BMD. Further investigations are warranted.

9.2.245 Endogenous sex hormones and incident fracture risk in older men: The Dubbo Osteoporosis Epidemiology Study
Meier C, Nguyen TV, Handelsman DJ, Schindler C, Kushnir MM, Rockwood AL, Meikle AW, Center JR, Eisman JA, Seibel MJ
Arch Intern Med 2008;168:47-54

609 men older than 60 years observed between January 1989 and December 2005, with the median duration being 5.8 years (up to 13 years). During follow-up, 113 men had at least 1 low-trauma fracture. The risk of fracture was increased in men with reduced testosterone (hazard ratio [HR], 1.33; 1.09-1.62). After adjustment for sex hormone-binding globulin, serum testosterone (HR, 1.48; 95% CI, 1.22-1.78) and serum estradiol (HR, 1.21; 95% CI, 1.00-1.47) were associated with overall fracture risk. After further adjustment for major risk factors testosterone was still associated with risk of fracture, particularly with hip (HR, 1.88; 95% CI, 1.24-2.82) and nonvertebral (HR, 1.32; 95% CI, 1.03-1.68) fractures.

9.2.246 Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: A randomized controlled trial
Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, Grobbee DE, van der Schouw YT
Jama 2008;299:39-52

In a double-blind, randomized, placebo-controlled trial of 237 healthy men between the ages of 60 and 80 years with a testosterone below 13.7 nmol/L randomly assigned to 80 mg of testosterone undecenoate or placebo twice daily for 6 months. 207 men completed the study. Lean mass increased and fat mass decreased without an increase of mobility or muscle strength. Cognitive function and BMD did not change. Insulin sensitivity improved but HDL cholesterol decreased; by the end of the study, 47.8% in the testosterone group vs 35.5% in the placebo had the metabolic syndrome (P=0.07). Quality-of-life was no different except for one hormone-related quality-of-life measure. No negative effects on prostate were detected. Testosterone during 6 months to older men with a low normal testosterone did not affect functional status or cognition.

9.2.247 Adherence to alendronate in male veterans
Hansen KE, Swenson ED, Baltz B, Schuna AA, Jones AN, Elliott ME
Osteoporos Int 2008;19:349-56

Adherence in the first 12 and 24 months of therapy was 59% and 54%, respectively. In multivariate analyses, non-adherence was more likely in men using tobacco (OR 2.08, 95% CI 1.13, 3.84, p=0.02) and reporting side effects (OR 2.06, 95% CI 1.14, 3.73, p=0.02) and less likely in men undergoing bone density during therapy (OR 0.49, 95% CI 0.26, 0.90, p=0.02). Alendronate non-adherence is more likely in male veterans who smoke or report side effects, and less likely in men having bone densitometry during therapy.

9.2.248 The effect of combined androgen blockade on bone turnover and bone mineral density in men with prostate cancer
Yamada Y, Takahashi S, Fujimura T, Nishimatsu H, Ishikawa A, Kume H, Tomita K, Takeuchi T, Kitamura T
Osteoporos Int 2008;19:321-7

Bicalutamide (BL) maintains BMD. 204 men were evaluated (control group: n=56, castration group: n=102, 'CAB with BL' group: n=22, 'CAB with estramustine phosphate (EMP)' group: n=24). The BMD % Z-score of the castration group was lower than that of the control group or the 'CAB with EMP' group (90.6% vs. 95.5%, 98.6%; p<0.042, p<0.044, respectively). Levels of u-NTx, u-DPD, OC of the castration group were the highest followed by the control group, then the 'CAB with BL' group and the 'CAB with EMP' group.

9.2.249 Characteristics of males over 50 years who present with a fracture: Epidemiology and underlying risk factors
Sharma S, Fraser M, Lovell F, Reece A, McLellan AR

J Bone Joint Surg Br 2008;90:72-7

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

Volume 9, Issue 2, 2008

Reviews

General

9.2.250 A reference standard for the description of osteoporosis
Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, 3rd, Khaltaev N
Bone 2008;42:467-75

9.2.251 Bone mineralization density distribution in health and disease
Roschger P, Paschalis EP, Fratzl P, Klaushofer K
Bone 2008;42:456-66

9.2.252 Interaction of bone morphogenetic proteins with cells of the osteoclast lineage: Review of the existing evidence
Giannoudis PV, Kanakaris NK, Einhorn TA
Osteoporos Int 2007;18:1565-81

9.2.253 A unified theory for osteonal and hemi-osteonal remodeling
van Oers RFM, Ruimerman R, Tanck E, Hilbers PAJ, Huiskes R
Bone 2008;42:250-9

9.2.254 Genetics, pathogenesis and complications of osteopetrosis
Del Fattore A, Cappariello A, Teti A
Bone 2008;42:19-29

Risk Factors

9.2.255 Correlation of obesity and osteoporosis: Effect of fat mass on the determination of osteoporosis
Zhao LJ, Jiang H, Papasian CJ, Maulik D, Drees B, Hamilton J, Deng HW
J Bone Miner Res 2008;23:17-29

9.2.256 Depression and osteoporosis: Epidemiology and potential mediating pathways
Mezuk B, Eaton WW, Golden SH
Osteoporos Int 2008;19:1-12

9.2.257 Skeletal consequences of thiazolidinedione therapy
Grey A
Osteoporos Int 2008;19:129-37

Falls

9.2.258 Shifting the focus in fracture prevention from osteoporosis to falls
Jarvinen TL, Sievanen H, Khan KM, Heinonen A, Kannus P
Bmj 2008;336:124-6

Treatment

9.2.259 The role of calcium and vitamin D in the management of osteoporosis
Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY
Bone 2008;42:246-9

The role of calcium and vitamin D supplementation in the treatment of osteoporosis has been extensively studied. The aim of this paper was to reach, where possible, consensus views on five key questions relating to calcium and vitamin D supplementation in the management of osteoporosis. Whereas global strategies that target supplementation to the general population could not be justified in terms of efficacy and health economics, there is a clearer rationale for supplementing patients who are at increased risk of osteoporosis and those who have developed osteoporosis, including those already taking other treatments for osteoporosis. The combination of vitamin D with calcium may be beneficial in terms of efficacy and, perhaps, for optimising adherence.

9.2.260 Meta-analysis: Vitamin D compounds in chronic kidney disease
Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GF
Ann Intern Med 2007;147:840-53

To determine whether vitamin D therapy improves biochemical markers of mineral metabolism and cardiovascular and mortality outcomes in chronic kidney disease randomized, controlled trials of vitamin D compounds in chronic kidney disease were identified. Seventy-six trials were identified; 3667 participants. Vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification, or parathyroidectomy. Compared with placebo, vitamin D sterols were associated with an increased risk for hypercalcemia (relative risk, 2.37 [95% CI, 1.16-4.85]) and hyperphosphatemia (relative risk, 1.77 [CI, 1.15-2.74]) but did not show a consistent reduction in PTH. Compared with placebo, more recently developed vitamin D analogues were associated with hypercalcemia (relative risk, 5.15 [CI, 1.06-24.97]) but not hyperphosphatemia, and levels of PTH were reduced (weighted mean difference, -10.77 pmol/L [CI, -20.51 to -1.03 pmol/L]). For suppression of PTH, intravenous administration was superior to oral vitamin D, but higher intravenous doses were used. Vitamin D compounds do not consistently reduce PTH levels, and beneficial effects on patient-level outcomes are unproven. The value of vitamin D treatment for people with chronic kidney disease remains uncertain.

9.2.261 Systematic review: Comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis
MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J
Ann Intern Med 2008;148:197-213

9.2.262 Positive effects of intravenous zoledronic acid on bone remodeling and structure: Are different effects on osteoblast activity to other oral bisphosphonates responsible?
Ebeling PR, Burr DB
J Bone Miner Res 2008;23:2-5

Exercise

9.2.263 Tai chi for osteoporosis: A systematic review
Lee MS, Pittler MH, Shin BC, Ernst E
Osteoporos Int 2008;19:139-46

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

Volume 9, Issue 2, 2008

Invest in Your Bones Campaign

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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Managing Editor: Fina Liu

International Osteoporosis Foundation

Progress In Osteoporosis Volume 9, Issue 3, 2008

- PDF version
- Prof. Pierre D. Delmas, Foundation President of the IOF
- Overview

Literature Review

- Epidemiology
- Morbidity/Mortality
- Genetics
- Measurement of Bone Mass
- Bone Material
- Bone Structure
- Biomechanics
- Growth
- Remodelling Markers
- Bone Formation
- Bone Resorption
- Osteocytes
- Systemic Factors
- Local Factors
- Risk Factors
- Corticosteroid Therapy
- Falls
- Treatment
- Exercise
- Men
- Reviews

Invest In Your Bones Campaign

- Campaign vision
- About the Campaign

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IOF World Congress on Osteoporosis in Bangkok, Thailand, December 3-7, 2008
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Diagnosis of fracture risk becomes much easier, bringing benefits to those at risk and cost savings...
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Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
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Volume 9, Issue 3, 2008

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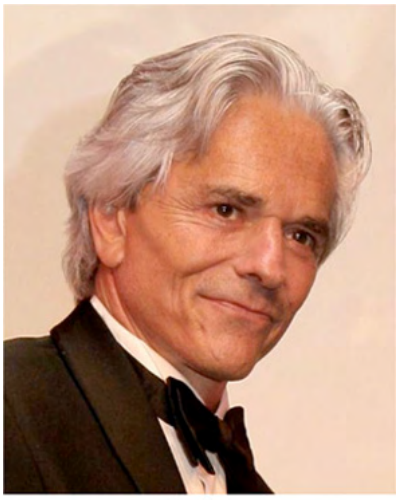
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Great leaders are rare because the combination of qualities essential to great leadership and great statesmanship are uncommon in a single individual. We have been fortunate to have Pierre, whose vision, imagination, relentless energy, talent and courage has created a great society. His effortless, or seemingly effortless, ability to inspire and to earn the loyalty of his peers has brought together an effective administrative body that has selflessly defined a global need for disease prevention and has reasoned a measured pathway to its solution.

Pierre created the IOF, a worldwide network now of 183 member societies from 89 locations, strong after successfully overseeing the merger of the European Foundation for Osteoporosis and the International Federation of Societies for Skeletal Disease. His vision has enfranchised orphan countries by giving them a voice, access to funding, educational resources and opportunities to share in the great debates of the scientific method. He realized support of these national societies in the fight against osteoporosis, increased awareness of the problem of fractures in the aging population and motivated others to work towards reducing this burden.

Pierre and his effective executive have supervised training courses, organized scientific meetings including world congresses, regional conferences in Asia-Pacific, Latin America and the Middle East, regional training courses, initiated the quarterly journal (Progress in Osteoporosis), World Osteoporosis Day, worldwide conferences of patient societies and creation of numerous grants for young investigators.

The Executive Committee, Board of the IOF, members of the Committe of National Socities, Committee of Scientific Advisors and Committee of Corporate Advisors join to express their thanks, admiration and respect for Professor Pierre Delmas on the occasion of his retirement as Foundation President of the IOF during the past 10 years and look forward to his continued support as a Board Member of the IOF and Advisor to the Executive Committee.


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Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
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Volume 9, Issue 3, 2008

Between the idea
And the reality
Between the motion
And the act
Falls the Shadow

Between the conception
And the creation
Between the emotion
And the response
Falls the Shadow

Between the desire
And the spasm
Between the potency
And the existence
Between the essence
And the descent
Falls the Shadow

From *The Hollow Men*
T.S. Eliot

Overview

Arrthymias and osteoporosis treatment – cause or coincidence?

Arrthymias and osteoporosis occur in elderly persons so the possibility that the association between atrial fibrillation and bisphosphonate use, particular using zolendronic acid is the result of coincidence of aging of bone and heart. **Heckbert et al** reported a population-based case-control study and identified 719 women with AF and 966 controls without AF, selected at random, matched on age and blood pressure. More cases with AF than controls had ever used alendronate (6.5% [n=47] vs. 4.1% [n=40]; P=0.03) producing an odds ratio of 1.86 (95% CI 1.09-3.15) after adjustment. **Arch Intern Med 2008;168:826-31**

This data is difficult to interpret give that case control methodology is not a high level of evidence based medicine. Compare this study with the data reported by Sorenson et al (2008) who report no greater exposure to etidronate or alendronate among 13586 cases with AF then 68054 controls. Where does truth lie?

Microdamage and bisphosphonate, a challenge to understand

Bone toughness, a tissues capacity to absorb energy is reduced using bisphosphonates. **Allen et al** studied beagle rib morphology. Three years alendronate 0.2 or 1.0 mg/kg reduced toughness with the higher dose (above that used in osteoporosis in women/kg basis) (**Calcif Tissue Int 2008 [Epub ahead of print]**). Neither ultimate stress nor modulus differed relative to controls. There was no difference in overall microdamage accumulation. The data support a dose related effect on bone quality. Microdamage occurrence might be region specific, depending on loadings circumstances. These drugs are pretty safe, but not always, and the effects are likely to depend on dose, duration of therapy, region, features in the species treated such as bone remodeling rate, level and duration of suppression.

Bisphosphonate action

There are not many beautifully written works of art in the scientific literature. If you are interested to see what can be achieved if time is taken to construct a work of art then read this by **Russell and his colleagues: Osteoporos Int 2008;19:733-59**.

Mineral binding affinities differ among the BPs and may influence their differential distribution within bone, their potency, and duration of action. The nitrogen-containing BPs inhibit farnesyl pyrophosphate synthase in osteoclasts, an enzyme in the mevalonate pathway that generates isoprenoid lipids used for modification of GTP-binding proteins needed for osteoclast function. Each BP has a unique profile that may help to explain clinical differences in speed and duration of action, and effects on fracture reduction.

Are all bisphosphonates the same – of course not

Fuchs et al gave alendronate (ALN) and risedronate (RIS) to 6-month old OVX rats. Turnover were similarly to a similar extent – not more greatly with alendronate, but 16 weeks after withdrawal, trabecular BFR/BS in the proximal tibia was reestablished post-RIS, not post-ALN, relative to controls (but not clearly differently relative to each other). BMD of the 5th lumbar vertebra remained higher than controls post-ALN, not post-RIS. **J Bone Miner Res 2008 [Epub ahead of print]**

The notion that ALN suppresses remodeling more than RIS is not at all well founded but is widely accepted as such, mainly based on the FACT trial (Rosen et al, 2005), a study that is difficult to interpret for a range of reasons. However, the evidence of persistent suppression with ALN over RIS following cessation of treatment has a better evidence base – is this a good thing or bad thing?

Anti-resorptives – new opportunities for dissociating resorption and formation

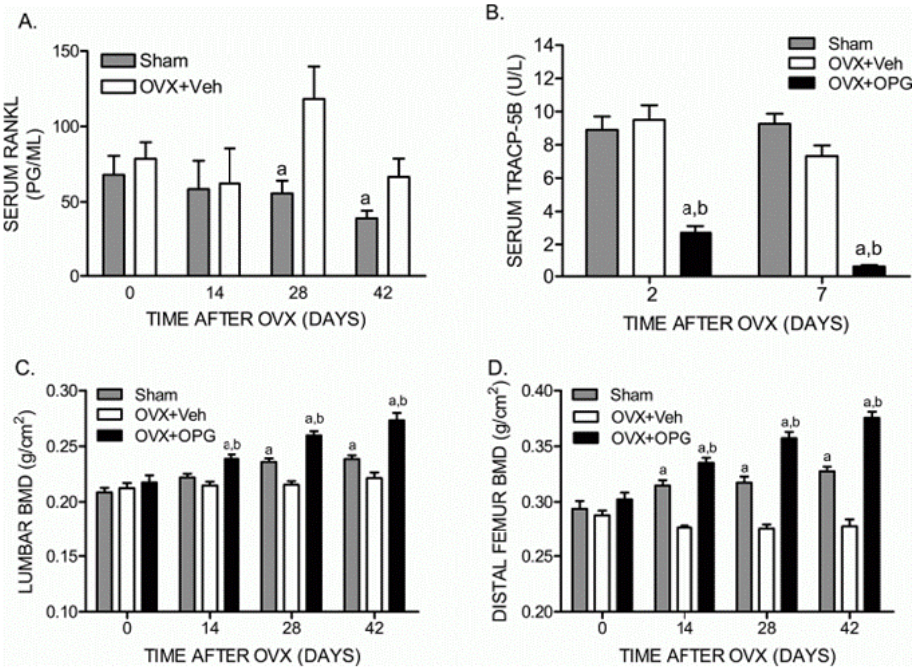
Estrogen deficiency is mediated by cytokines such as TNFalpha and IL-1. The p38 pathway mediates cytokines effects so the selective p38alpha inhibitor, SD-282, was assessed during 8 weeks by **Caverzasio et al** and found to blunt increase in DPD/Cr induced by OVX in adult rats. SD-282 enhanced by two-fold the rise in serum osteocalcin, blocked vertebral bone loss, reduced trabecular bone loss in long bones, and enhanced cross sectional area rise of the diaphysis. Whether this opens doors to differing action of drugs on bone formation and resorption is difficult to say, markers of ‘formation’ and ‘resorption’ are not the same as histological evidence of resorption at the tissue and cellular (BMU) levels. **J Bone Miner Res 2008 [Epub ahead of print]**

PTH and raloxifene

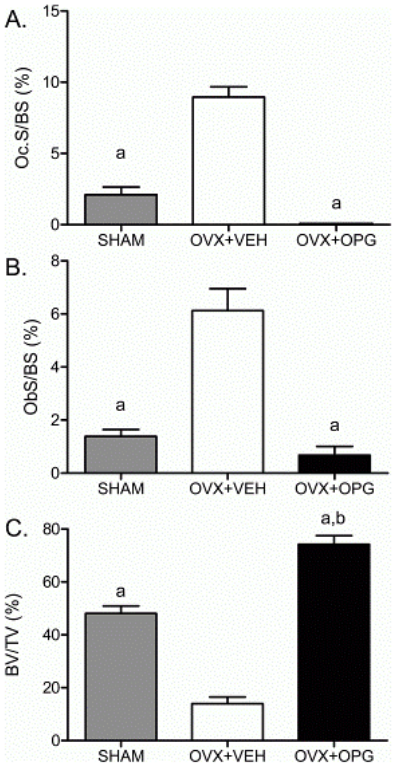
Cosman et al report that 42 women receiving raloxifene either continued it or one group had 1-34PTH daily added for 12 months and then were followed for 12 months on raloxifene alone. Biochemical indices and BMD increased during PTH, except BMD declined in the radius. From this design it is not possible to conclude whether blunting of the PTH has occurred by raloxifene as there is no PTH-alone group. After PTH withdrawal, BMD declined but increased at femoral neck. At 24 months, spine and femoral neck BMD remained higher than baseline, while radius BMD remained lower. Gains in BMD of the spine and hip, and loss at the radius, are seen with PTH. While the authors conclude raloxifene partially maintains PTH gains, this is difficult to infer without a group receiving PTH alone, then stopping the PTH. **Osteoporos Int 2008;19:529-35**

RANKL inhibition with osteoprotegerin

Ominsky et al report that OVX rats treated with human OPG-Fc had reduced osteoclast surface and serum TRACP5b with prevention OVX-associated bone loss. Vertebrae had increased dry and ash weight, with no differences in tissue mineralization. Micro-CT showed higher trabecular bone volume fraction, vBMD, bone area, trabecular thickness, and number; whereas their cortical compartments had greater bone area. OPG improved cortical area in L(5) and the femur neck to levels that were greater than sham controls. L(5) and femur necks showed greater maximum load versus OVX. **J Bone Miner Res 2008;23:672-82**



Biochemical markers of bone turnover and areal BMD. Serum RANKL (A) and serum TRACP5b (B) were measured by ELISAs at the time points indicated. Areal BMD was measured at L1-L5 (C) and distal femur (D) by DXA. Data represent means and SEs for 6-11 rats per group. [a]Significantly different from OVX+Veh, $p<0.05$; [b]significantly different from sham control, $p<0.05$. *Reproduced from J Bone Miner Res 2008;23:672-82 with permission of the American Society of Bone and Mineral Research.*



Bone histomorphometry parameters at the distal femoral metaphysis. (A) Osteoclast surface (% bone surface), (B) osteoblast surface (% bone surface), and (C) cancellous bone volume (% total volume) were assessed in the distal femur. Data represent means and SEs for 4-11 rats per group. [a]Significantly different from OVX-Veh, $p<0.05$; [b]significantly different from sham control, $p<0.05$. *Reproduced from J Bone Miner Res 2008;23:672-82 with permission of the American Society of Bone and Mineral Research.*

Osteopenia and fracture prevention with risedronate

Siris et al report that 620 postmenopausal women with osteopenia and no prevalent vertebral fractures were identified from BMD Multinational, BMD North America, VERT Multinational and VERT North America trials. 309 received placebo, 311 received risedronate 5 mg. Risedronate reduced the risk of fragility fractures by 73% over 3 years vs. placebo (p=0.023); cumulative fragility fracture incidence was 6.9% in placebo-treated vs. 2.2% in risedronate-treated patients. While this may be the case, selection according to osteopenia at the proximal femur leaves the possibility that a proportion of these patients had osteoporosis at the spine. **Osteoporos Int 2008;19:681-6**

Calcium and vitamin D, the dynamic duo?

Nieves et al report that in 76,507 postmenopausal Caucasian women, vitamin D intake was calculated from milk, fish, supplements and sunlight exposure. Three years later, 36,209 participants returned a questionnaire about new fractures. Women reported 2,205 new osteoporosis-related fractures. The 3-year risk of fracture was not associated with intake of calcium or vitamin D. **Osteoporos Int 2008;19:673-9**

Osteoblast death and aminobisphosphates

It is not commonly appreciated that the main effect of anti-resorptive agents is through the inhibition of the birthrate of new remodeling units. This effect is responsible for the reduction in the surface extent of bone resorption and later surface extent of bone formation. **Idris et al** report that pamidronate and alendronate inhibited osteoblast growth, caused osteoblast apoptosis, and inhibited protein prenylation in osteoblasts. Alendronate inhibited protein prenylation in calvarial osteoblasts in vivo. Interestingly, pamidronate and alendronate inhibited nodule formation at low concentrations without affecting osteoblast growth, apoptosis or differentiation. **Calcif Tissue Int 2008;82:191-201**

SERM on basedoxifene

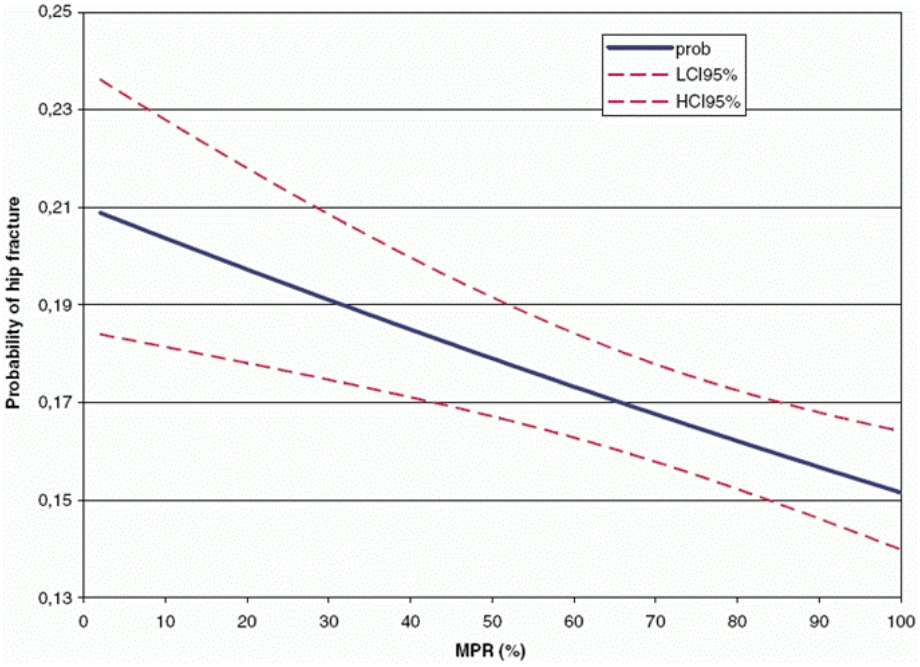
Miller et al report that bazedoxifene 10, 20, or 40 mg/d and raloxifene 60 mg/d studied in 1434 women (mean age, 58 yr) prevented bone loss, decreased serum osteocalcin and C-telopeptide. Bazedoxifene prevented bone loss and reduced turnover as well as raloxifene and was well tolerated. The outstanding issue with SERMs is whether they can reduce nonvertebral fractures. **J Bone Miner Res 2008;23:525-35**

Zoledronic acid versus alendronate in rats

Gasser et al compared single intravenous doses of ZOL 0.8, 4, 20, 100, 500 µg/kg, alendronate 200 µg/kg before OVX for 32 wk. OVX-associated BMD loss was attenuated by ZOL. Alendronate 200 µg/kg was of equivalent to ZOL 20 µg/kg. OVX-associated decreases in trabecular architectural parameters were attenuated by ZOL. Alendronate 200 µg/kg was equivalent to ZOL 20 µg/kg. Bone formation parameters were reduced by ZOL 100-500 µg/kg. Alendronate 200 µg/kg was equivalent to ZOL 100 µg/kg. Alendronate 200 ug/kg was of similar potency to ZOL 20 µg/kg. Compared with alendronate, ZOL shows 10-fold higher potency in preventing bone loss. **J Bone Miner Res 2008;23:544-51**

Adhere, persist, comply or fracture

Rabenda et al report the serious consequences of poor compliance at 12 months. The medication possession ratio (MPR) at 12 months was higher among patients receiving weekly (n=15,021, 70.5%) compared to daily alendronate (n=14,136, 58.6%;). At 12 months, persistence was 39.45%. For each decrease of the MPR by 1%, the risk of hip fracture increased by 0.4%. The relative risk reduction for hip fracture was 60% (HR: 0.404; 0.357-0.457) for persistent compared to nonpersistent patients. **Osteoporos Int 2008;19: 811-8**



Probability of hip fracture according to the full range of MPR. *Reproduced from Osteoporosis Int 2008;19:811-8 with permission from Springer.*

Genetics

The great benefit of genetic research is the discovery of pathways in bone biology, rewriting the text books. In terms of identifying individuals at risk for fracture or specific treatment approaches there is little if any contribution because the proportion

of trait variance attributable to a single of genetic polymorphism is small.

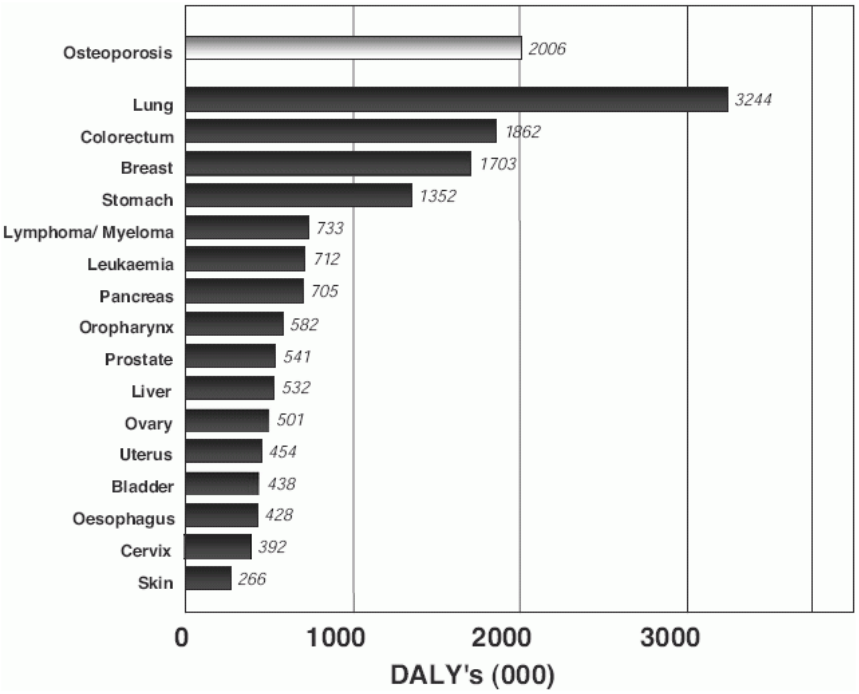
Richards et al report an association between a SNP in the LRP5 gene was associated with decreased BMD for femoral neck and an increased risk of fractures (OR 1.3, 1.09-1.52) and osteoporosis (OR 1.3, 1.08-1.63, p=0.008). 314,075 SNPs were identified in 2094 women and tested for replication in 6463 people for association with fractures. SNPs rs4355801 on chromosome 8, near to the osteoprotegerin gene, and rs3736228, on chromosome 11 in the LRP5 gene were found. Three SNPs near the TNFRSF11B gene were associated with decreased BMD and risk of osteoporosis (OR 1.2, 1.01-1.42). The presence of both increased the risk of fractures (OR 1.3, 1.08-1.63, p=0.006). **Lancet 2008; 371:1505-12**

Styrkarsdottir et al tested 5861 subjects for 301,019 SNPs and BMD. Association between 74 SNPs at 32 loci in Icelandic, Danish and Australian subjects showed associations. Three regions close to (RANKL) (chromosomal location, 13q14), the osteoprotegerin gene (OPG) (8q24), and the estrogen receptor 1 gene (ESR1) (6q25). Two regions close to the zinc finger and BTB domain containing 40 gene (ZBTB40) (1p36) and the major histocompatibility complex region (6p21). The 1p36, 8q24, and 6p21 loci were associated with fractures, as were loci at 18q21, close to the RANK gene and loci at 2p16 and 11p11. **N Engl J Med 2008 [Epub ahead of print]**

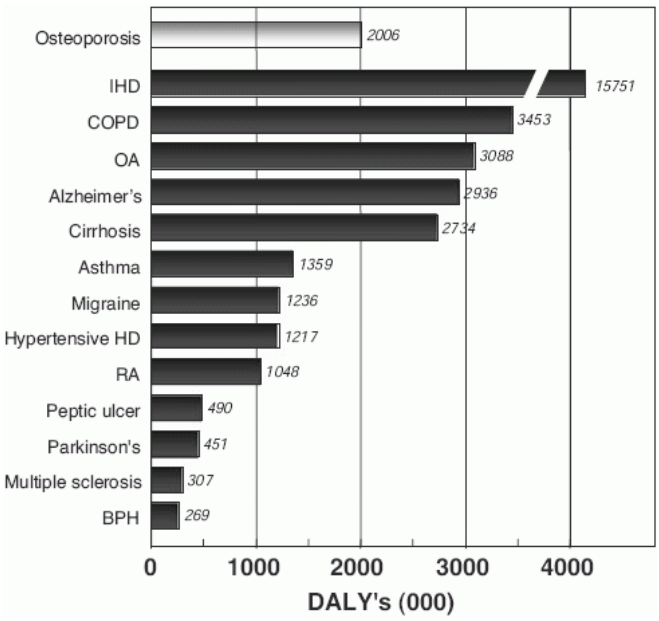
FRAX….ing lyrical

FRAX has arrived. It may appear to be salvation, the answer to uncertainty, but that is unlikely because the decision to treat or not to treat will always be difficult in some situations. There will be no magic formula to tell us what is high risk or low risk – and so when to and not to treat. Is a 1% in 10 years high or low risk? Is 10% in 10 high – i.e., 1 in 100 people in your office will fracture – which one will it be? Sounds like pretty low odds but in medicine a 1-3% per year risk is the sort of risk present in clinical trials. **Kanis et al** construct 4 models comprising the 10-year probability of hip fracture, with and without femoral neck BMD, and the 10-year probability of a major osteoporotic fracture, with and without BMD. In the absence of BMD, hip fracture probability in women with a fixed BMI (25 kg/m2) ranged from 0.2% at 50 years for women without risk factors to 22% at 80 years with a parental history of hip fracture (~100-fold range). In men, the probabilities were lower, as was the range (0.1-11% in the examples above). For a major osteoporotic fracture the probabilities ranged from 3.5-31% in women, and from 2.8-15% in men in the example above. **Osteoporos Int 2008;19:385-97**

Kanis et al provide a comprehensive set of guidelines in a European setting on the assessment and treatment of postmenopausal women with or at risk from osteoporosis reviewing the role of BMD measurement for the diagnosis of osteoporosis and assessment of fracture risk, management of osteoporosis, monitoring of treatment, assessment of fracture risk, case finding strategies investigation and health economics of treatment. **Osteoporos Int 2008;19:399-428**



Burden of diseases estimated as disability-adjusted life-years (DALYs) lost due to a selection of non-communicable diseases in Europe. IHD ischaemic heart disease, COPD chronic obstructive pulmonary disease, OA osteoarthritis, RA rheumatoid arthritis, BPH benign prostatic hyperplasia. *Reproduced from Osteoporosis Int 2008;19:399-428 with permission from Springer.*



Burden of diseases estimated as disability-adjusted life-years (DALYs) lost due to a selection of neoplastic diseases in Europe. *Reproduced from Osteoporosis Int 2008;19:399-428 with permission from Springer.*

Osteocyte – the first among equals

The first event in bone remodeling is not known. The growing awareness of the osteocyte as the likely conductor of the orchestral concert of bone remodeling is an exciting advance in our understanding and Dr. Noble has made important contributions in this area. **Kogianni et al** report that osteocyte apoptosis precedes osteoclastic bone resorption, apoptotic osteocytes support osteoclastogenesis and osteoclastic bone resorption in vivo and in vitro and increase osteoclastic resorption. indicating that the site-specific apoptotic death of osteocytes underlies the mechanism by which targeted remodeling is initiated in bone. **J Bone Miner Res 2008 [Epub ahead of print]**

Remodeling balance and bone gain and loss

There are excellent lessons here. **Tian et al** gave 6-month-old female rats PGE(2). Continuous or intermittent PGE(2). Both routes stimulated bone remodeling, but continuous PGE(2) produced a negative BMU balance causing cancellous bone loss and shortened the formation period and cortical bone loss because the negative endocortical bone balance and increased intracortical porosity bone loss was greater than periosteal bone gain. Intermittent PGE(2) increased cancellous bone by positive balance from stimulated bone formation and shortened resorption period; while cortical bone gain occurred from endocortical bone gain exceeding the decrease in periosteal bone and increased intracortical bone loss. **Bone 2008;42:914-20**

Men and fractures, uncommon, hard to identify

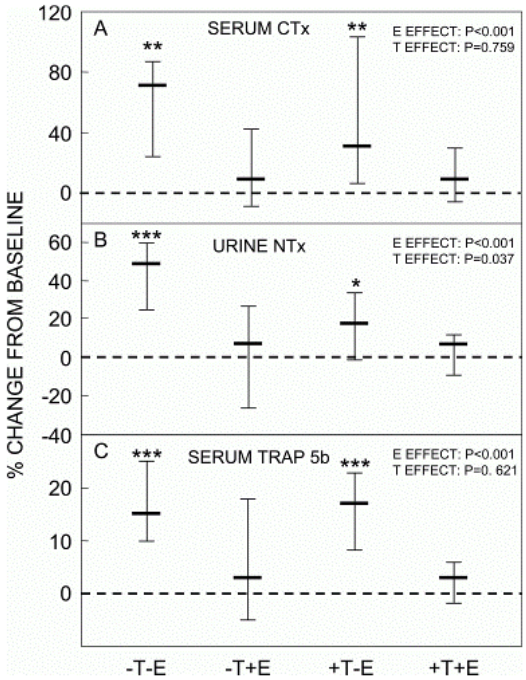
Freitas et al report some challenges in fracture prevention in men. 5995 men were followed for about 5 years. Only 1% sustained incident clinical vertebral fractures (2.2/1,000 person-years; 0.7% in men 65-69 years and 5% ≥85 years. Most with incident fractures did not have osteoporosis. **Osteoporos Int 2008;19:615-23**

Men neglected

Men with osteoporosis are still not treated. One legal case will solve this problem. **Papaioannou et al** followed 2187 men and report diagnosis and treatment at baseline and year five was 2.3% and 10.3% of men with a clinical fracture. At year five, 90% of men with a fracture were untreated. Hip fractures were the most commonly treated (37.5% by year five). A diagnosis of osteoporosis resulted in greater treatment: 67% of participants with diagnosed osteoporosis were treated with a bisphosphonate and 87% were taking calcium and/or vitamin D (year five). **Osteoporos Int 2008;19:581-7**

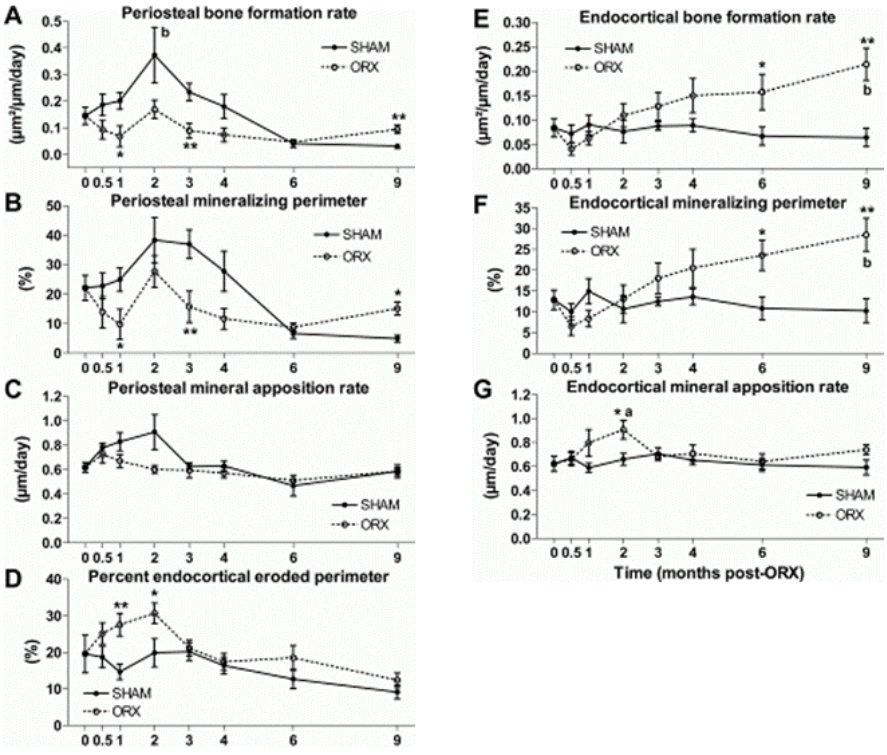
Osteoporosis in the male

Lovely design in this study by **Sanyal et al** who suppressed sex hormones in 59 men using a GnRH agonist and aromatase blockade and then randomized to sex steroid deficiency (-T, -E), E alone (-T, +E), T alone (+T, -E), or both (+T, +E). Serum CTX and TRACP5b increased in the -T, -E despite suppression of FSH. E (not T) prevented increases in serum CTX and TRACP. E suppresses RANKL mRNA in marrow osteoblasts. E suppresses resorption more than T and increased bone resorption after sex steroid deficiency occur independently of FSH. E effects may be mediated by regulation of RANKL production by osteoblastic cells. **J Bone Miner Res 2008;23:705-14**

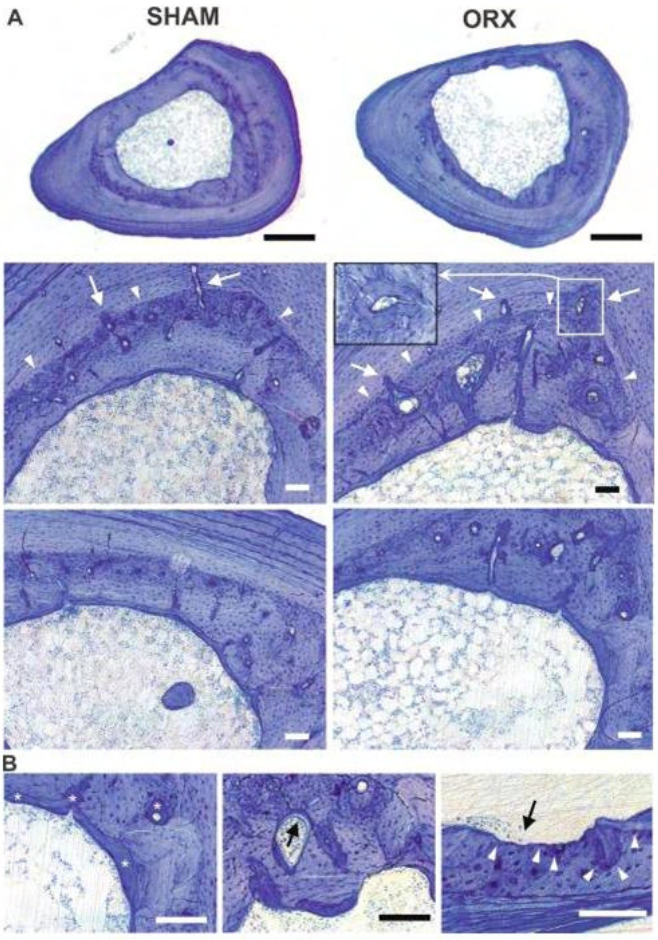


Percent change from baseline in (A) serum CTX, (B) urine NTX, and (C) serum TRACP5b levels in the four study groups between the baseline and final visits. *p<0.05, **p<0.01, and ***p<0.001 for change from baseline. The overall effect of E and T on the bone markers was analyzed using the two-factor ANOVA model described in the Materials and Methods section. Shown are the medians and interquartile ranges. *Reproduced from J Bone Miner Res 2008;23:705-14 with permission of the American Society of Bone and Mineral Research.*

Reim et al gonadectomized 13-mo-old male Fischer-344 rats. 9-mo-old ORX rats were supplemented with testosterone undecanoate. Androgen deficiency induced a sustained decrease in periosteal bone formation. The major mechanism for cortical bone loss was an expansion of the marrow cavity with increase in endocortical eroded perimeter followed by a sustained increase in endocortical bone formation. All these changes were prevented by testosterone in an insulin-like growth factor system-independent fashion. **J Bone Miner Res 2008;23:694-704**



Periosteal bone formation rate (BFR/B.Pm) (A), periosteal mineralizing perimeter (B), periosteal mineral apposition rate (MAR) (C), percent endocortical eroded perimeter (E.Pm/B.Pm) (D), endocortical BFR/B.Pm (E), endocortical mineralizing perimeter (F), and endocortical MAR (G) measured by histomorphometry in the tibial shaft of SHAM and ORX rats and plotted as a function of time after surgery. Each data point is the mean±SE of 8-15 animals. *p<0.05, **p<0.01, ***p<0.001 vs. SHAM group by t-test. ^{a}p<0.05, ^{b}p<0.01, ^{c}p<0.001 vs. Baseline group by ANOVA followed by Dunnett's test. *Reproduced from J Bone Miner Res 2008;23:694-704 with permission of the American Society of Bone and Mineral Research.*



Representative crossections of the tibial shaft from SHAM and ORX rats at the end of the trial (i.e., 9 mo after surgery). Low power views are shown in A, top panel. Increased endocortical and intracortical bone remodeling is evident in the ORX relative to SHAM rats by an increased amount of newly formed, darker stained, bone packages (A, middle and bottom panels). Note that the intracortical bone remodeling units originate from the endocortical bone surface (A, middle and bottom panels). Intracortical remodeling units crossing the tide mark (arrowheads) between endocortical and periosteal bone are marked by arrows (A, middle panel). Inset in A (middle panel) shows a high power view of an intracortical remodeling unit. (B) Higher-power views of endocortical bone surfaces in ORX rats. The scalloped cement lines of the darker stained packages of newly formed bone are indicative of remodeling activity (asterisks, left). Osteoid seams and osteoblasts (arrow, middle) show active bone formation in an intracortical bone remodeling site. Active bone resorption activity is indicated by eroded surfaces with osteoclasts (arrow) resorbing older remodeling units as indicated by underlying scalloped cements lines (arrowheads, right). Fine-ground, 20-m-thick sections. Toluidine blue stain. Bar 500 m in A, top panel; bar 100 m in A, middle and bottom panels, and B. *Reproduced from J Bone Miner Res 2008;23:694-704 with permission of the American Society of Bone and Mineral Research.*

'This is indeed a mystery', I remarked. 'What do you imagine that it means?'
'I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.'

From 'A Scandal in Bohemia' in *The Adventures of Sherlock Holmes*
Sir Arthur Conan Doyle

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 9, Issue 3, 2008

Epidemiology

9.3.1 Epidemiology of distal forearm fractures in Oslo, Norway
Lofthus CM, Frihagen F, Meyer HE, Nordsletten L, Melhuus K, Falch JA
Osteoporos Int 2008;19:781-6

Patients aged ≥20 years resident in Oslo sustaining a distal forearm fracture in a one-year period in 1998/99 were identified. The age-adjusted fracture rates per 10,000 for the age group ≥50 years were 109.8 and 25.4 in 1998/99 compared with 108.3 and 23.5 in 1979 for women and men, respectively (n.s.). The relative risk of fracture in Asians was 0.72 (95% CI 0.53-1.00) compared with ethnic Norwegians. The overall incidence of distal forearm fractures in Oslo is higher than in other countries and has not changed.

Progress in
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Morbidity/Mortality

9.3.2 Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy: The Observational Study of Severe Osteoporosis (OSSO)
Cooper C, Jakob F, Chinn C, Martin-Mola E, Fardellone P, Adami S, Thalassinos NC, Melo-Gomes J, Torgerson D, Gibson A, Marin F
Osteoporos Int 2008;19:493-501

To assess the fracture incidence and health-related quality of life (HRQoL) in women with an inadequate clinical outcome to osteoporosis therapy, 1,885 women with osteoporosis and an inadequate response to therapy (a) fragility fracture despite therapy for one year (N=988), or (b) discontinued drug therapy due to adverse effects and/or noncompliance (N=897), were assessed during one year for HRQoL using the EQ-5D and the QUALEFFO questionnaires. 166 (8.8%) women had 209 fractures (1,139 fractures/10,000 women-years). Women with an index fracture were more likely to sustain an incident fracture (hazard ratio 1.91; 95% CI 1.37-2.66; p<0.001). Comorbidities or antidepressant use at baseline also increased the risk of incident fracture. Median total EQ-5D Health State Values and QUALEFFO scores were worse in women with an incident fracture regardless of index fracture status. The worst scores were reported in the EQ-5D subdomains of selfcare, usual activities and pain/discomfort.

9.3.3 Utility values associated with osteoporotic fracture: A systematic review of the literature
Hiligsmann M, Ethgen O, Richy F, Reginster JY
Calcif Tissue Int 2008;82:288-92

From the 152 studies, 16 were retained. Ten investigated utility values for hip fractures, eleven for vertebral fractures, five for distal forearm fractures, and four for other osteoporotic fractures and fracture interactions. Utility values differed between studies, partly due to the valuation technique used, the severity of fractures, and the sample size. There is no meaningful average value across different studies, different samples, different countries, or different instruments.

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

Volume 9, Issue 3, 2008

Genetics

9.3.4 Multiple genetic loci for bone mineral density and fractures
Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, Jonsdottir T, Saemundsdottir J, Center JR, Nguyen TV, Bagger Y, Gulcher JR, Eisman JA, Christiansen C, Sigurdsson G, Kong A, Thorsteinsdottir U, Stefansson K
N Engl J Med 2008;[Epub ahead of print]

5861 Icelandic subjects tested for an association between 301,019 SNPs and BMD were studied. Association between 74 SNPs at 32 loci in replication sets of Icelandic, Danish and Australian subjects (4165, 2269 and 1491 subjects, respectively) showed associations with BMD. Three regions close to or within genes shown to be important for bone; (RANKL) (chromosomal location, 13q14), the osteoprotegerin gene (OPG) (8q24), and the estrogen receptor 1 gene (ESR1) (6q25). The two other regions close to the zinc finger and BTB domain containing 40 gene (ZBTB40) (1p36) and the major histocompatibility complex region (6p21). The 1p36, 8q24, and 6p21 loci were also associated with osteoporotic fractures, as were loci at 18q21, close to the RANK gene, and loci at 2p16 and 11p11.

9.3.5 Bone mineral density, osteoporosis, and osteoporotic fractures: A genome-wide association study
Richards JB, Rivadeneira F, Inouye M, Pastinen TM, Soranzo N, Wilson SG, Andrew T, Falchi M, Gwilliam R, Ahmadi KR, Valdes AM, Arp P, Whittaker P, Verlaan DJ, Jhamai M, Kumanduri V, Moorhouse M, van Meurs JB, Hofman A, Pols HA, Hart D, Zhai G, Kato BS, Mu
Lancet 2008;371:1505-12

314,075 single nucleotide polymorphisms (SNPs) were identified in 2,094 women and tested for replication in 6,463 people for association with fractures. SNPs rs4355801, on chromosome 8 near to the osteoprotegerin gene, and rs3736228, on chromosome 11 in the LRP5 gene, were found. A nonsynonymous SNP in the LRP5 gene was associated with decreased BMD for femoral neck and an increased risk of fractures (OR 1.3, 1.09-1.52) and osteoporosis (OR 1.3, 1.08-1.63, p=0.008). Three SNPs near the TNFRSF11B gene were associated with decreased BMD for spine and femoral neck and increased risk of osteoporosis (OR 1.2, 1.01-1.42). 1,883 (22%) of 8,557 people were heterozygous for these risk alleles, and these alleles had a cumulative association with BMD. The presence of both increased the risk of fractures (OR 1.3, 1.08-1.63, p=0.006) independent of BMD. The combined effect of these risk alleles on fractures is similar to environmental risk factors, and they are present in more than one in five white people.

9.3.6 Large-scale analysis of association between polymorphisms in the transforming growth factor beta 1 gene (TGFβ1) and osteoporosis: The GENOMOS study
Langdahl BL, Uitterlinden AG, Ralston SH, Trikalinos TA, Balcells S, Brandi ML, Scollen S, Lips P, Lorenc R, Obermayer-Pietsch B, Reid DM, Armas JB, Arp PP, Bassiti A, Bustamante M, Husted LB, Carey AH, Perez Cano R, Dobnig H, Dunning AM, Fahrleitner-Pamm
Bone 2008;42:969-81

Associations between TGFβ1 polymorphisms and BMD and fracture in 28,924 participants using TGFβ1 polymorphic sites: G(-1639)-A (G(-800)-A, rs1800468), C(-1348)-T (C(-509)-T, rs1800469), T(29)-C (Leu10Pro, rs1982073), G(74)-C (Arg25Pro, rs1800471) and C(788)-T (Thr263Ile, rs1800472). There were no differences in women or men for any polymorphisms with the exception of a weak association with reduced BMD (-12 mg/cm^2) in men with the T(-1348) allele ($p<0.05$). None of the haplotypes was associated with BMD and none of the polymorphisms or haplotypes affected overall risk of fractures; however, the odds ratio for incident vertebral fracture in carriers of the rare T(788) allele was 1.64 (95% CI 1.09-2.64), $p<0.05$.

9.3.7 Estrogen receptor alpha CA dinucleotide repeat polymorphism is associated with rate of bone loss in perimenopausal women and bone mineral density and risk of osteoporotic fractures in postmenopausal women
Lai BM, Cheung CL, Luk KD, Kung AW
Osteoporos Int 2008;19:571-9

D6S440 is an intronic CA repeat polymorphism downstream of the 5'-splicing site of exon 5 of ESR1. The associations of D6S440 with BMD, rate of bone loss and fracture risk were evaluated in 452 pre-, 110 peri- and 622 postmenopausal southern Chinese women. Post- but not premenopausal women with less CA repeats had lower spine and hip BMD. The number of CA repeats was related to hip BMD in postmenopausal women (beta=0.008; p=0.004). Postmenopausal women with CA repeats <18 had higher risks of having osteoporosis (spine OR 2.46, 95% CI 1.30-4.65; hip: OR 3.79 (1.64-8.74)) and low trauma fractures (OR 2.31 (1.29-4.14)) than those with ≥18 repeats. Perimenopausal women with <18 CA repeats had greater bone loss in 18 months at the hip than those with ≥18 repeats (-1.96% vs. -1.61%, p=0.029). ESR1 CA repeat polymorphism is associated with BMD variation, rate of bone loss and fracture risk, and this may be a useful genetic marker for fracture risk assessment.

9.3.8 Osteoprotegerin Lys3Asn polymorphism and the risk of fracture in older women
Moffett SP, Oakley JI, Cauley JA, Lui LY, Ensrud KE, Taylor BC, Hillier TA, Hochberg MC, Li J, Cayabyab S, Lee JM, Peltz G, Cummings SR, Zmuda JM
J Clin Endocrinol Metab 2008;93:2002-8

Lys3Asn polymorphism was assessed in the OPG gene with BMD and the risk of fracture in 6695 women aged 65 years and older. Women homozygous for the minor G (Lys) allele had lower BMD at the intertrochanter, distal radius, lumbar spine and calcaneus than those with the C (Asn) allele. There were 701 incident hip fractures during 13.6 years including 362 femoral neck and 333 intertrochanteric hip fractures. Women with the C/C (Asn-Asn) genotype had a 51% higher risk of femoral neck fracture (95%CI 1.13-2.02) and 26% higher risk of hip fracture (95%CI 1.02-1.54) than those with the G/G (Lys-Lys) genotype independent of BMD. Intertrochanteric fractures were not associated with the Lys3Asn polymorphism.

9.3.9 Large-scale association study between two coding LRP5 gene polymorphisms and bone phenotypes and fractures in men

Grundberg E, Lau EM, Lorentzson M, Karlsson M, Holmberg A, Groop L, Mellstrom D, Orwoll E, Mallmin H, Ohlsson C, Ljunggren O, Akesson K

Osteoporos Int 2008;19:829-37

The low-density lipoprotein receptor-related protein 5 (LRP5)-Wnt signalling system is of importance for regulating osteoblastic activity, which became clear after findings that inactivating mutations in LRP5 cause osteoporosis. The overall aim of this study was to investigate the association between polymorphisms in the LRP5 gene and BMD in MrOS Sweden (n=3014, aged 69-81 years) and MrOs Hong Kong (n=2000, aged >65 years) and the Swedish GOOD study (n=1068, aged 18-20 years). When combining the data from the Swedish cohorts in a meta-analysis (n=3800), men carrying the 667Met-allele had 3% lower BMD at lumbar spine compared with non-carriers ($p<0.05$). The Val667Met SNP was not polymorphic in the Hong Kong population. There were no associations between the Ala1330Val SNP and bone phenotypes in the study populations. No associations between the LRP5 polymorphisms and self-reported fractures were seen in MrOs Sweden. The Val667Met polymorphism but not the Ala1330Val contributes to the observed variability in BMD in the Swedish populations.

9.3.10 Association studies of ALOX5 and bone mineral density in healthy adults

Foroud T, Ichikawa S, Koller D, Lai D, Curry L, Xuei X, Edenberg HJ, Hui S, Peacock M, Econs MJ

Osteoporos Int 2008;19:637-43

ALOX5 encodes arachidonate 5-lipoxygenase contributes factor to aBMD in rats. SNPs distributed throughout ALOX5 were genotyped in 1688 European American, premenopausal sisters, 512 African American premenopausal sisters and 715 European American brothers. Significant ($p \leq 0.05$) evidence of association was observed with three of the SNPs. However, despite the linkage disequilibrium between SNPs, adjacent SNPs did not provide evidence of association in any of the three study groups.

9.3.11 Genetic and environmental influence on structural strength of weight-bearing and non-weight-bearing bone: A twin study

Mikkola TM, Sipila S, Rantanen T, Sievanen H, Suominen H, Kaprio J, Koskenvuo M, Kauppinen M, Heinonen A

J Bone Miner Res 2008;23:492-8

pQCT of 103 monozygotic (MZ) and 114 dizygotic (DZ) 63- to 76-yr-old female twin pairs to estimate the compressive strength of the distal tibia and distal radius. The MZ and DZ twins did not differ in mean age, height, weight, or bone structural strength. The age-adjusted Cholesky model showed that additive genetic factors accounted for 83% (95% CI, 77-88%) of the variance in radial strength and 61% (95% CI, 52-69%) of the variance in tibial strength, and these were fully correlated. A shared environmental factor accounted for 15% (95% CI, 10-20%) of tibial strength. An individual environmental factor accounted for 17% (95% CI, 12-23%) of the variance in radial strength and 10% (95% CI 5-17%) of the variance in tibial strength. The relative contribution of an individual environmental factor specific to tibial strength was 14% (95% CI 11-18%). The results suggest that, in older women, the majority of the individual differences in the compressive structural strength of the forearm and leg are regulated by genetic and environmental factors that are common to both bone sites. However, the relative importance of environmental factors was greater for the weight-bearing tibia than for the non-weight-bearing radius.

9.3.12 Genetic analyses in a sample of individuals with high or low BMD shows association with multiple Wnt pathway genes

Sims AM, Shephard N, Carter K, Doan T, Dowling A, Duncan EL, Eisman J, Jones G, Nicholson G, Prince R, Seeman E, Thomas G, Wass JA, Brown MA

J Bone Miner Res 2008;23:499-506

96 tag-single nucleotide polymorphism (SNPs) lying in 13 Wnt signaling pathway genes were selected to tag common genetic variation (minor allele frequency [MAF]>5% with an $r^2>0.8$) within 5 kb of all exons of 13 Wnt signaling pathway genes. The genes studied included LRP1, LRP5, LRP6, Wnt3a, Wnt7b, Wnt10b, SFRP1, SFRP2, DKK1, DKK2, FZD7, WISP3, and SOST. 344 cases with either high or low BMD were genotyped by Illumina Goldengate microarray SNP genotyping methods. Strong association was shown with LRP5, polymorphisms (minimum p=0.0006). In addition, polymorphisms of the Wnt antagonist, SFRP1, were associated with BMD and BMC (minimum p=0.00042). Previously reported associations of LRP1, LRP6, and SOST with BMD were confirmed. Two other Wnt pathway genes, Wnt3a and DKK2, also showed nominal association with BMD. Polymorphisms of multiple members of the Wnt pathway are associated with BMD variation.

9.3.13 Association of bone morphogenetic proteins with otosclerosis

Schrauwen I, Thys M, Vanderstraeten K, Fransen E, Dieltjens N, Huyghe JR, Ealy M, Claustres M, Cremers CR, Dhooge I, Declau F, Van de Heyning P, Vincent R, Somers T, Offeciers E, Smith RJ, Van Camp G

J Bone Miner Res 2008;23:507-16

To identify major genetic factors in otosclerosis, tag single nucleotide polymorphisms (SNPs) in 13 candidate susceptibility genes were studied in a stepwise strategy. Two SNPs were identified that showed the same effect in both populations. The first SNP, rs3178250, is located in the 3' untranslated region of BMP2. Individuals homozygote for the C allele are protected against otosclerosis (combined populations: p=2.2 x 10(-4); OR=2.027; 95% CI 1.380-2.979). The second SNP, rs17563, is an amino acid changing (p.Ala152Val) SNP located in BMP4. The G allele, coding for the amino acid alanine, confers susceptibility in both populations (combined populations: p=0.002; OR=1.209; 95% CI 1.070-1.370). Polymorphisms in the BMP2 and BMP4 genes, both members of the TGFβ superfamily, contribute to the susceptibility to otosclerosis and further strengthen the results from the recently reported association of TGFβ1 with this disease.

9.3.14 Large-scale analysis of association between LRP5 and LRP6 variants and osteoporosis

van Meurs JB, Trikalinos TA, Ralston SH, Balcells S, Brandi ML, Brixen K, Kiel DP, Langdahl BL, Lips P, Ljunggren O, Lorenc R, Obermayer-Pietsch B, Ohlsson C, Pettersson U, Reid DM, Rousseau F, Scollen S, Van Hul W, Agueda L, Akesson K, Benevolenskaya LI,

Jama 2008;299:1277-90

9.3.15 In vivo genome-wide expression study on human circulating B cells suggests a novel ESR1 and MAPK3 network for postmenopausal osteoporosis

Xiao P, Chen Y, Jiang H, Liu YZ, Pan F, Yang TL, Tang ZH, Larsen JA, Lappe JM, Recker RR, Deng HW

J Bone Miner Res 2008;23:644-54

9.3.16 Influence of factors regulating bone formation and remodeling on bone quality in osteonecrosis of the femoral head
Tingart M, Beckmann J, Opolka A, Matsuura M, Wiech O, Grifka J, Grassel S
Calcif Tissue Int 2008;82:300-8

9.3.17 A Pro253Arg mutation in fibroblast growth factor receptor 2 (Fgfr2) causes skeleton malformation mimicking human Apert syndrome by affecting both chondrogenesis and osteogenesis
Yin L, Du X, Li C, Xu X, Chen Z, Su N, Zhao L, Qi H, Li F, Xue J, Yang J, Jin M, Deng C, Chen L
Bone 2008;42:631-43

9.3.18 Role of genetic background in determining phenotypic severity throughout postnatal development and at peak bone mass in Col1a2 deficient mice (oim)
Carleton SM, McBride DJ, Carson WL, Huntington CE, Twenter KL, Rolwes KM, Winkelmann CT, Morris JS, Taylor JF, Phillips CL
Bone 2008;42:681-94

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

Volume 9, Issue 3, 2008

Measurement of Bone Mass

9.3.19 In vivo determination of bone structure in postmenopausal women: A comparison of HR-pQCT and high-field MR imaging
Kazakia GJ, Hyun B, Burghardt AJ, Krug R, Newitt DC, de Papp AE, Link TM, Majumdar S
J Bone Miner Res 2008;23:463-74

Postmenopausal osteopenic women (n=52) showed correlations between HR-pQCT and MRI ($p<0.0001$) and were strongest for Tb.N ($r^2=0.52$), Ct.Th ($r^2=0.59$), and site-specific Tb.Sp ($r^2=0.54$-0.60). MRI and HR-pQCT provided different values of structure parameters ($p<0.0001$), with BV/TV and Tb.Th exhibiting the largest discrepancies (MR/HR-pQCT=3-4). Although differences in the Tb.N values were significant, the mean differences were on the order of our reproducibility measurements. Systematic differences between MRI and HR-pQCT analysis procedures leading to discrepancies in cortical thickness values were observed, with MRI values higher. Minimal correlations were found between MRI or HR-pQCT parameters and DXA BMD or T-score, except between HR-pQCT measures at the radius and the ultradistal radius T-scores, where moderate correlations were found ($r^2=0.19$-0.58).

9.3.20 Fate of untreated asymptomatic osteonecrosis of the femoral head
Nam KW, Kim YL, Yoo JJ, Koo KH, Yoon KS, Kim HJ
J Bone Joint Surg Am 2008;90:477-84

One hundred and five asymptomatic hips of patients with bilateral nontraumatic osteonecrosis of the femoral head followed without any treatment for at least 5 years were enrolled in this study. Sixty-two hips became symptomatic, 43 hips remained asymptomatic for more than 5 years. Of the 21 hips with a small necrotic lesion (<30% of the area of the femoral head), one became painful; of the 24 hips with a medium-sized necrotic lesion (30-50% of the area of the femoral head), 11 became painful; and of the 60 hips with a large necrotic lesion (>50% of the area of the femoral head), 50 became painful. Forty-six of the 62 hips that became symptomatic required surgery. Pain developed within 5 years after the diagnosis in 58 (94%) of the 62 symptomatic hips. No treatment appears to be necessary for asymptomatic necrotic lesions with an area smaller than 30% of the femoral head, as the vast majority of these lesions will remain asymptomatic for more than 5 years.

9.3.21 How important are BMD accuracy errors for the clinical interpretation of DXA scans?
Blake GM, Fogelman I
J Bone Miner Res 2008;23:457-62

9.3.22 Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: Applications in the study of human trabecular bone microarchitecture
Pothuaud L, Carceller P, Hans D
Bone 2008;42:775-87

9.3.23 Assessment of trabecular bone structure comparing magnetic resonance imaging at 3 Tesla with high-resolution peripheral quantitative computed tomography ex vivo and in vivo
Krug R, Carballido-Gamio J, Burghardt AJ, Kazakia G, Hyun BH, Jobke B, Banerjee S, Huber M, Link TM, Majumdar S
Osteoporos Int 2008;19:653-61

9.3.24 Resolution dependence of the non-metric trabecular structure indices
Sode M, Burghardt AJ, Nissenson RA, Majumdar S
Bone 2008;42:728-36

9.3.25 Bone ultrasonography at phalanxes in patients with Rett syndrome: A 3-year longitudinal study
Gonnelli S, Caffarelli C, Hayek J, Montagnani A, Cadirni A, Franci B, Lucani B, Rossi S, Nuti R
Bone 2008;42:737-42

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

Volume 9, Issue 3, 2008

Bone Material

9.3.26 Disturbed synthesis of type II collagen interferes with rate of bone formation and growth and increases bone resorption in transgenic mice

Nieminen J, Sahlman J, Hirvonen T, Lapvetelainen T, Miettinen M, Arnala I, Malluche HH, Helminen HJ

Calcif Tissue Int 2008;82:229-37

Transgenic mice carrying a deleted human type II collagen gene (COL2A1) were smaller compared with controls. Bone mass remained unchanged in transgenic mice after 1 month of age, leading to differences of 47% in trabecular bone volume (P=0.012) and 40% in trabecular thickness (P<0.01) at the age of 3 months. At the age of 3 months the eroded surface per bone volume was 31% greater (P<0.05). Trabecular thickness correlated with weight (R=0.71, P<0.001) and weight correlated with bone volume in control mice (R=0.27, P<0.01), not in transgenic mice. The disturbed synthesis of cartilage-specific type II collagen in growing transgenic mice retarded bone development, increased bone resorption, and altered tissue properties. Altered synthesis of cartilage-specific molecule(s) can disturb postnatal bone development and growth.

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

Volume 9, Issue 3, 2008

Bone Structure

9.3.27 Experimental hip fracture load can be predicted from plain radiography by combined analysis of trabecular bone structure and bone geometry
Pulkkinen P, Jamsa T, Lochmuller EM, Kuhn V, Nieminen MT, Eckstein F
Osteoporos Int 2008;19:547-58

Sixty-two cadaver femurs (34 females, 28 males) were mechanically tested in side impact configuration. Fracture patterns were classified as being cervical or trochanteric. Computerized image analysis was applied to obtain structure-related trabecular measurements. In cervical fracture cases, trabecular bone area and femoral neck axis length explained 64% of the variability in failure loads, while femoral neck BMD also explained 64%. In trochanteric fracture cases, Euler number and femoral cortex thickness explained 66% of the variability in failure load, while trochanteric BMD explained 72%.

9.3.28 Does thoracic or lumbar spine bone architecture predict vertebral failure strength more accurately than density?
Lochmuller EM, Poschl K, Wurstlin L, Matsuura M, Muller R, Link TM, Eckstein F
Osteoporos Int 2008;19:537-45

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

Volume 9, Issue 3, 2008

Biomechanics

9.3.29 Percolation theory relates corticocancellous architecture to mechanical function in vertebrae of inbred mouse strains
Tommasini SM, Wearne SL, Hof PR, Jepsen KJ
Bone 2008;42:743-50

Different combinations of cortical, trabecular, and compositional traits lead to different load transfer pathways within the vertebral bodies. Two-dimensional coronal sections were converted to network graphs with the cortical shell considered as one highly connected node. Percolation parameters including correlation length (average number of connected nodes between superior and inferior surfaces), chemical length (minimum number of connected nodes between surfaces), and backbone mass (strut number) were measured. A and B6 mice transfer load through trabecular pathways in the middle of the vertebral body and the cortical shell. C3H mice transfer load primarily through the cortical shell. Thus, the measures provided by percolation theory provide a quantitative approach to study how different combinations of cortical and trabecular traits lead to mechanically functional structures. A network approach to study corticocancellous architecture during growth should further understanding of the biological basis of skeletal fragility.

9.3.30 Subject-specific hip geometry affects predicted hip joint contact forces during gait
Lenaerts G, De Groote F, Demeulenaere B, Mulier M, Van der Perre G, Spaepen A, Jonkers I
J Biomech 2008;41:1243-52

9.3.31 In vivo static creep loading of the rat forelimb reduces ulnar structural properties at time-zero and induces damage-dependent woven bone formation
Lynch JA, Silva MJ
Bone 2008;42:942-9

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

Volume 9, Issue 3, 2008

Growth

9.3.32 Influence of age at menarche on forearm bone microstructure in healthy young women
Chevalley T, Bonjour JP, Ferrari S, Rizzoli R
J Clin Endocrinol Metab 2008;[Epub ahead of print]

In 124 healthy women aged 20.4±0.6 (SD) yrs, aBMD inversely correlated with MENA for total radius (R=-0.21, p=0.018), diaphysis (R=-0.18, p=0.043) and metaphysis (R=-0.19, p=0.031). Subjects with MENA>median (LATER: 14.0±0.7 (±SD) yrs) had lower aBMD than those with MENA

9.3.33 Relationship of total body fat mass to bone area in New Zealand five-year-olds
Goulding A, Taylor RW, Grant AM, Murdoch L, Williams SM, Taylor BJ
Calcif Tissue Int 2008;82:293-9

In 194 preschool children (81 girls, 113 boys), relationships of total-body fat mass and lean mass to total-body-less-head (TBLH) bone area and TBLH bone mineral content (BMC) were evaluated. Girls had higher mean fat mass (3.9 vs. 3.2 kg) and lower lean mass (14.5 vs. 15.2 kg) than boys (P<0.001), but their heights, weights, and TBLH bone area were similar. Although a given weight of lean tissue was associated with greater increases in TBLH area than a given weight of fat tissue, fat mass was an independent predictor of TBLH bone area (R^2=0.79, P<0.001) and TBLH BMC (R^2=0.74, P<0.001). The authors infer that increased fat mass is associated with outward expansion of the TBLH skeletal envelope (wider bones) independently of height and lean mass in very young children.

9.3.34 Evidence that abnormal high bone mineralization in growing children with osteogenesis imperfecta is not associated with specific collagen mutations
Roschger P, Fratzl-Zelman N, Misof BM, Glorieux FH, Klaushofer K, Rauch F
Calcif Tissue Int 2008;82:263-70

Transiliac bone biopsies from 19 young OI patients (age range 2.0-14.1 years) and 19 age-matched controls were used to assess histomorphometric parameters and bone mineralization density distribution. Compared to age-matched controls, iliac bone samples in the OI group were smaller and had thinner cortices and less trabecular bone. Resorption parameters were similar between groups, whereas surface-based parameters of bone formation were higher in OI patients with the exception of bone formation rate per osteoblast surface, which was reduced in OI. Backscattered electron imaging revealed a higher mean mineralization density (+7%, P<0.001) in OI patients, which was accompanied by a reduced heterogeneity of mineralization (-13%, P<0.001). However, the increase of mean degree of mineralization in OI did not exceed the average level of normal adult bone. No differences were found between the two mutation types.

9.3.35 Sex-specific developmental changes in muscle size and bone geometry at the femoral shaft
Hogler W, Blimkie CJ, Cowell CT, Inglis D, Rauch F, Kemp AF, Wiebe P, Duncan CS, Farpour-Lambert N, Woodhead HJ
Bone 2008;42:982-9

In 145 healthy subjects (6-25 years, 94 females). MRI and DXA were used to determine femur length, bone mineral content, cortical bone mineral density, bone diameter; cortical thickness; total, cortical and medullary areas; cross-sectional and polar moments of area; bone strength index and muscle area at the proximal one-third site of the femur. Results were dimensionally scaled by raising two-, three- and four-dimensional variables to the power of 1/2, 1/3 and 1/4, respectively. In prepubertal children, unscaled results expressed as percentages of adult values were lowest for variables with the highest dimensions (e.g., moments of area < bone mineral content < cross-sectional areas < femur length). However, when dimensionally scaled, results in children represented similar percentages of the respective average adult values. Before puberty, there was no sex difference in adjusted bone or muscle variables. After puberty, males had greater total and cortical bone area, bone diameter, moments of area, bone strength index and muscle area than women, both in absolute terms as well as adjusted for femur length and weight. The largest sex difference was found for muscle area. When compared relative to muscle size, young adult women attained greater total and cortical bone area than men. Postpubertal females have narrower femora, less bone strength and muscle size than males. However, when muscle size is taken into account, females have a larger femoral bone cross-section and more cortical bone.

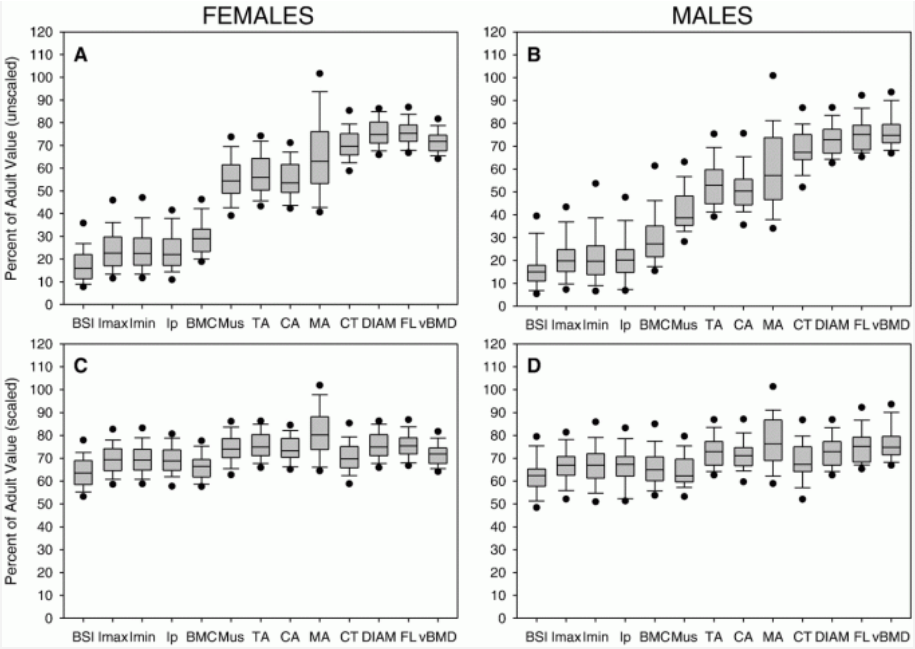


Fig. 9.3.35a Results in prepubertal children expressed as percentages of the average result in young adults of the same sex. Panels A and B represent unscaled results, panels C and D show dimensionally scaled results. Shown are boxplots which indicate the median, interquartile range and 10th and 90th centiles. Dots represent the 5th and 95th centiles. Abbreviations of variables (with decreasing geometrical dimensions from left to right): BSI, Bone strength index; Imax, maximum moment of area; Imin, minimum moment of area; Ip, polar moment of area; BMC, bone mineral content; Mus, total muscle area; TA, total bone area; CA, cortical bone area; MA, marrow area; CT, cortical thickness; DIAM, external bone diameter; FL, femur length; and vBMD, cortical bone mineral density. Reproduced from Bone, 42:982-9, Copyright (2008), with permission from Elsevier.

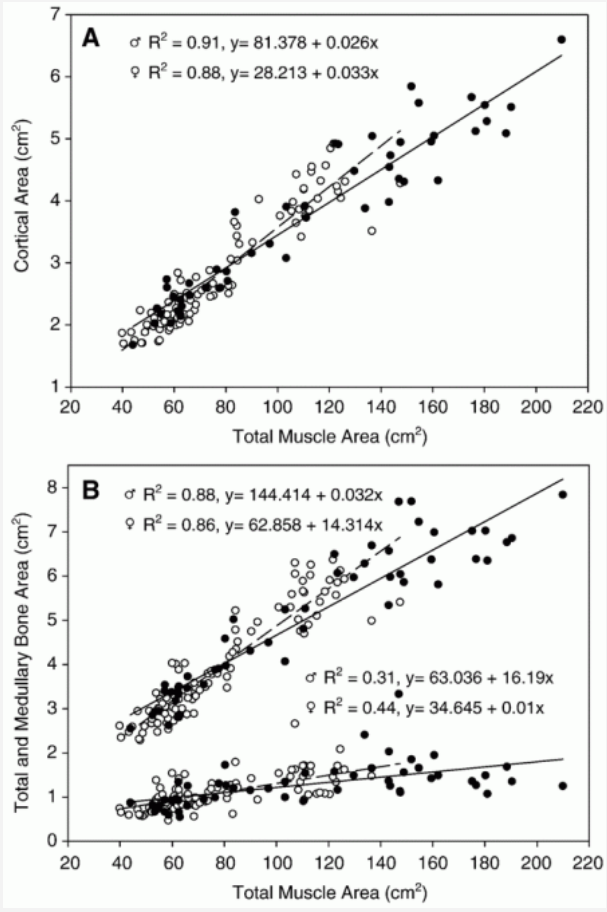


Fig. 9.3.35b Cortical area (A), as well as total and medullary area (B) in relation to muscle area in females (open circles, dotted regression lines) and males (filled circles, straight regression lines). Intercepts and slopes of the regression lines for total and cortical area were greater in females than males relative to muscle area ($p<0.05$). 95% CI of Intercepts (IC) and slopes: Cortical area vs. muscle area: Females IC 7.971-48.454, slope 0.030-0.035; males IC 51.505-111.251, slope 0.024-0.029 ($p<0.001$). Total area vs. muscle area: Females IC 34.429-91.287, slope 0.039-0.046; males IC 102.08-186.748, slope 0.029-0.036 ($p<0.001$). Marrow area vs. muscle area: Females IC 16.283-53.008, slope 0.007-0.012; males IC 32.536-93.535, slope 0.003-0.008 (p=n.s.). Reproduced from Bone, 42:982-9, Copyright (2008), with permission from Elsevier.

9.3.36 Parathyroid hormone mediates bone growth through the regulation of osteoblast proliferation and differentiation
Pettway GJ, Meganck JA, Koh AJ, Keller ET, Goldstein SA, McCauley LK
Bone 2008;42:806-18

Ossicles were generated from bone marrow stromal cells (BMSCs) implanted in immunocompromised mice. Three weeks of PTH

(40 µg/kg/day) resulted in an anabolic response in PTH-treated implants. A novel in vivo tracking strategy with luciferase tagged BMSCs and weekly bioluminescent imaging of ossicles revealed increased donor cell proliferation in PTH-treated ossicles. The greatest increase occurred during the first week, and the activity remained elevated in PTH-treated implants over time. Zoledronic acid (ZA) with PTH reduced the PTH-mediated increase in luciferase BMSC activity, serum osteocalcin, and serum tartrate resistant acid phosphotase-5b (TRAP-5b), but ZA did not reduce the PTH-induced increase in total bone.

9.3.37 Jump starting skeletal health: A 4-year longitudinal study assessing the effects of jumping on skeletal development in pre and circum pubertal children
Gunter K, Baxter-Jones AD, Mirwald RL, Almstedt H, Fuller A, Durski S, Snow C
Bone 2008;42:710-8

9.3.38 Overexpression of Smurf2 stimulates endochondral ossification through upregulation of β-catenin
Wu Q, Chen D, Zuscik MJ, O'Keefe RJ, Rosier RN
J Bone Miner Res 2008;23:552-63

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

Volume 9, Issue 3, 2008

Remodelling Markers

9.3.39 Serial assessment of serum bone metabolism markers identifies women with the highest rate of bone loss and osteoporosis risk
Ivaska KK, Lenora J, Gerdhem P, Akesson K, Vaananen HK, Obrant KJ
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Baseline, 1, 3 and 5 years followup of 573 of 1044 women all 75 years old at baseline showed baseline markers correlated weakly to change in total body aBMD. Women with constantly high turnover lost more bone at total body (-2.6%) than women with intermediate (-1.6%) or low turnover (-0.2%, p for trend <0.001). They also had a greater decrease in hip BMD (-8.3%, -6.0% and -5.1%, respectively, p=0.010).

9.3.40 Establishing a reference range for bone turnover markers in young, healthy women
Glover SJ, Garnero P, Naylor K, Rogers A, Eastell R
Bone 2008;42:623-30

Biochemical markers of bone turnover (BTMs) were measured in peripheral blood and second morning void urine collected from 200 healthy premenopausal women ages 30-45 years. BTMs were higher before the age of 35 years than after it. BTMs were higher in women with low BMI (βCTX and OC), low alcohol consumption (PINP), current smoking habit (bone ALP and NTX), and around time of ovulation (NTX).

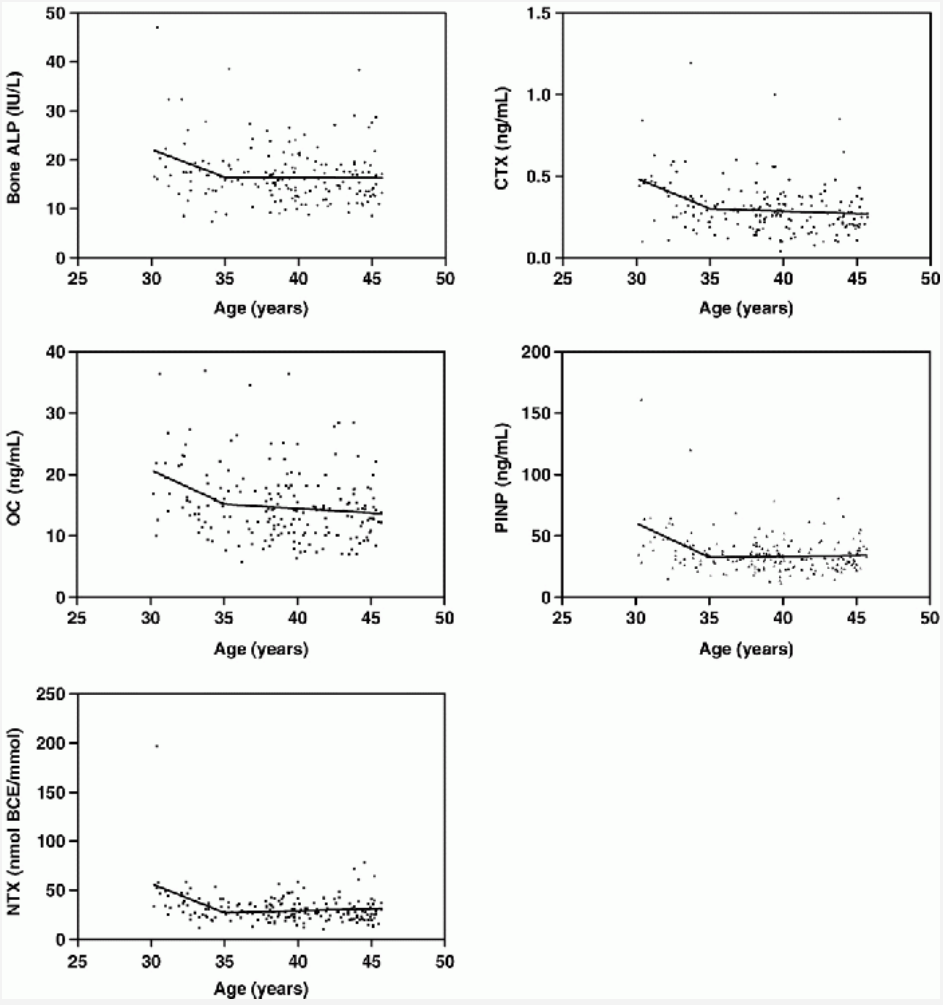


Fig. 9.3.40 Scatter plots showing segmental regression, of age and bone ALP, βCTX, OC, PINP and NTX (n=193). Reproduced from Bone, 42:623-30, Copyright (2008), with permission from Elsevier.

9.3.41 Serum levels of TRAP5b, a new bone resorption marker unaffected by renal dysfunction, as a useful marker of cortical bone loss in hemodialysis patients
Shidara K, Inaba M, Okuno S, Yamada S, Kumeda Y, Imanishi Y, Yamakawa T, Ishimura E, Nishizawa Y
Calcif Tissue Int 2008;82:278-87

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

Volume 9, Issue 3, 2008

Bone Formation

9.3.42 Comparison of osteogenic ability of rat mesenchymal stem cells from bone marrow, periosteum, and adipose tissue
Hayashi O, Katsube Y, Hirose M, Ohgushi H, Ito H
Calcif Tissue Int 2008;82:238-47

Mesenchymal stem cells (MSCs) are able to differentiate into various functional cells including osteoblasts. Recently, adipose tissue-derived MSCs (AMSCs) differentiate into many lineages, and. The purpose of this study was to compare the osteogenic differentiation capability of MSCs from bone marrow (BMSCs), MSCs from periosteum (PMSCs), and AMSCs using in vitro culture and in vivo implantation experiments. MSCs from 7-week-old rats were seeded and cultured for 7 days in primary culture to assay a colony-forming unit. The frequency of the unit was the smallest in the BMSCs ($P<0.001$). After primary culture, subculture was performed under osteogenic differentiation conditions for 1 and 2 weeks to detect mineralization as well as the bone-specific proteins of alkaline phosphatase and osteocalcin as osteogenic markers. BMSCs and PMSCs showed distinct osteogenic differentiation capability in comparison with other MSCs ($P<0.001$). For the in vivo assay, composites of these cells and hydroxyapatite ceramics were subcutaneously implanted into syngeneic rats and harvested after 6 weeks. New bone formation was detected in the composites using BMSCs and PMSCs, although it was hard to detect in other composites. Bone volume of BMSC composites was more than that of AMSC composites ($P<0.001$). These results indicate that BMSCs and PMSCs could be ideal candidates for utilization in practical bone tissue regeneration.

9.3.43 Mobilization of endothelial progenitor cells in fracture healing and distraction osteogenesis
Lee DY, Cho TJ, Kim JA, Lee HR, Yoo WJ, Chung CY, Choi IH
Bone 2008;42:932-41

9.3.44 Bone formation during distraction osteogenesis is dependent on both VEGFR1 and VEGFR2 signaling
Jacobsen KA, Al-Aql ZS, Wan C, Fitch JL, Stapleton SN, Mason ZD, Cole RM, Gilbert SR, Clemens TL, Morgan EF, Einhorn TA, Gerstenfeld LC
J Bone Miner Res 2008;23:596-609

9.3.45 Trigeminal nitric oxide synthase expression correlates with new bone formation during distraction osteogenesis
de Albuquerque RF, Jr., Aparecida Del Bel E, Brentegani LG, Moura de Oliveira MT, Mardegan Issa JP
Calcif Tissue Int 2008;82:309-15

9.3.46 Cell viability, osteoblast differentiation, and gene expression are altered in human osteoblasts from hypertrophic fracture non-unions
Hofmann A, Ritz U, Hessmann MH, Schmid C, Tresch A, Rompe JD, Meurer A, Rommens PM
Bone 2008;42:894-906

9.3.47 Influence of age and mechanical stability on bone defect healing: Age reverses mechanical effects
Strube P, Sentuerk U, Riha T, Kaspar K, Mueller M, Kasper G, Matziolis G, Duda GN, Perka C
Bone 2008;42:758-64

9.3.48 Influence of short-term adenoviral vector and prolonged lentiviral vector mediated bone morphogenetic protein-2 expression on the quality of bone repair in a rat femoral defect model
Virk MS, Conduah A, Park SH, Liu N, Sugiyama O, Cuomo A, Kang C, Lieberman JR
Bone 2008;42:921-31

9.3.49 Bim, Bak, and Bax regulate osteoblast survival
Liang M, Russell G, Hulley PA
J Bone Miner Res 2008;23:610-20

9.3.50 Molecular requirements for induction of CTGF expression by TGFβ1 in primary osteoblasts
Arnott JA, Zhang X, Sanjay A, Owen TA, Smock SL, Rehman S, Delong WG, Safadi FF, Popoff SN
Bone 2008;42:871-85

9.3.51 Ubc9 promotes the stability of Smad4 and the nuclear accumulation of Smad1 in osteoblast-like Saos-2 cells
Shimada K, Suzuki N, Ono Y, Tanaka K, Maeno M, Ito K
Bone 2008;42:886-93

9.3.52 Dkk1-induced inhibition of Wnt signaling in osteoblast differentiation is an underlying mechanism of bone loss in multiple myeloma
Qiang YW, Barlogie B, Rudikoff S, Shaughnessy JD, Jr.
Bone 2008;42:669-80

9.3.53 Doubly truncated FosB isoform (Delta2DeltaFosB) induces osteosclerosis in transgenic mice and modulates expression and phosphorylation of Smads in osteoblasts independent of intrinsic AP-1 activity
Sabatakos G, Rowe GC, Kveiborg M, Wu M, Neff L, Chiusaroli R, Philbrick WM, Baron R
J Bone Miner Res 2008;23:584-95

9.3.54 Circadian mechanisms in murine and human bone marrow mesenchymal stem cells following dexamethasone exposure
Wu X, Yu G, Parks H, Hebert T, Goh BC, Dietrich MA, Pelled G, Izadpanah R, Gazit D, Bunnell BA, Gimble JM
Bone 2008;42:861-70

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

Volume 9, Issue 3, 2008

Bone Resorption

9.3.55 Osteoprotegerin decreases human osteoclast apoptosis by inhibiting the TRAIL pathway
Chamoux E, Houde N, L'Eriger K, Roux S
J Cell Physiol 2008;[Epub ahead of print]

Osteoprotegerin (OPG) is a secreted decoy receptor that recognizes RANKL, and blocks the interaction between RANK and RANKL, leading to the inhibition of osteoclast differentiation and activation. Osteoclast apoptosis was evaluated by adding various doses of OPG to human osteoclast cultures obtained from cord blood monocytes. Apoptosis decreased after adding the OPG. Osteoclasts expressed TRAIL, and that TRAIL levels in the culture medium dose-dependently decreased in presence of OPG, as did the level of activated caspase-8 in osteoclasts. In addition, the expression of TRAIL by osteoclasts was not affected in the presence of OPG. OPG inhibits osteoclast apoptosis by binding and thus inhibiting endogenously produced TRAIL in human osteoclast cultures. TRAIL could be an autocrine factor for the regulation of osteoclast survival/apoptosis.

9.3.56 Skeletal deterioration induced by RANKL infusion: A model for high-turnover bone disease
Yuan YY, Kostenuik PJ, Ominsky MS, Morony S, Adamu S, Simionescu DT, Basalyga DM, Asuncion FJ, Bateman TA
Osteoporos Int 2008;19:625-35

RANKL was administered continuously for 28 days to 6 mo old Sprague-Dawley (SD); n=12 receiving continuous saline (VEH) or human RANKL (35 µg/kg/day, LOW or 175 µg/kg/day, HI). High dose RANKL stimulated serum osteocalcin and TRAP-5b levels and reduced femur cortical bone volume (-7.6%) and trabecular volume fraction (BV/TV) at the proximal tibia (-64% vs. VEH). Bone quality was degraded in HI, as evidenced by decreased femoral percent mineralization, trabecular connectivity, and increased endocortical bone resorption perimeters. Both cortical and trabecular bone mechanical properties were reduced.

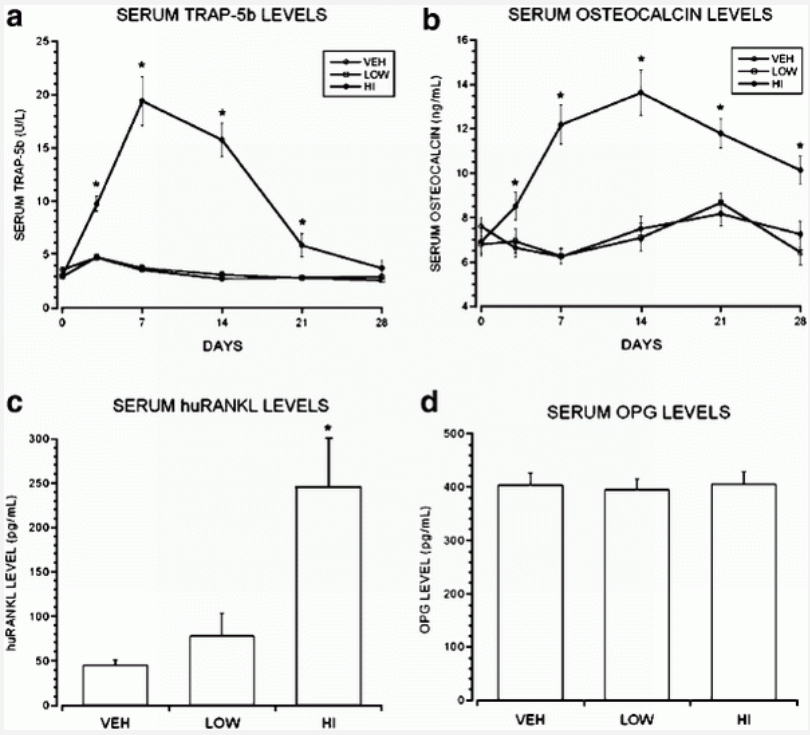


*Fig. 9.3.56a Serum was collected on day 0, 3, 7, 14, 21 and 28 of this study to examine bone turnover marker levels. There were no significant differences in serum marker levels of LOW during the entire course of the study were observed. However, bone turnover markers were greatly enhanced in the rats treated with high-dose RANKL. (a) TRAP-5b (bone resorption marker) levels in HI increased steeply during the first week of the study, peaking on day 7 with a fivefold increase, and gradually declined to baseline at sacrifice. (b) Serum osteocalcin (bone formation marker) levels in HI gradually increased and peaked at day 14 with an 82% higher than the VEH, then decreased and ending at 40% higher than VEH. (c) huRANKL levels at sacrifice were fivefold higher in HI than in VEH. (d) Differences were not observed in serum rat OPG levels at sacrifice between groups. Data are presented as the mean±SE. *: p<0.001 vs. VEH. Reproduced from Osteoporosis Int 2008;19:625-35 with permission from Springer.*

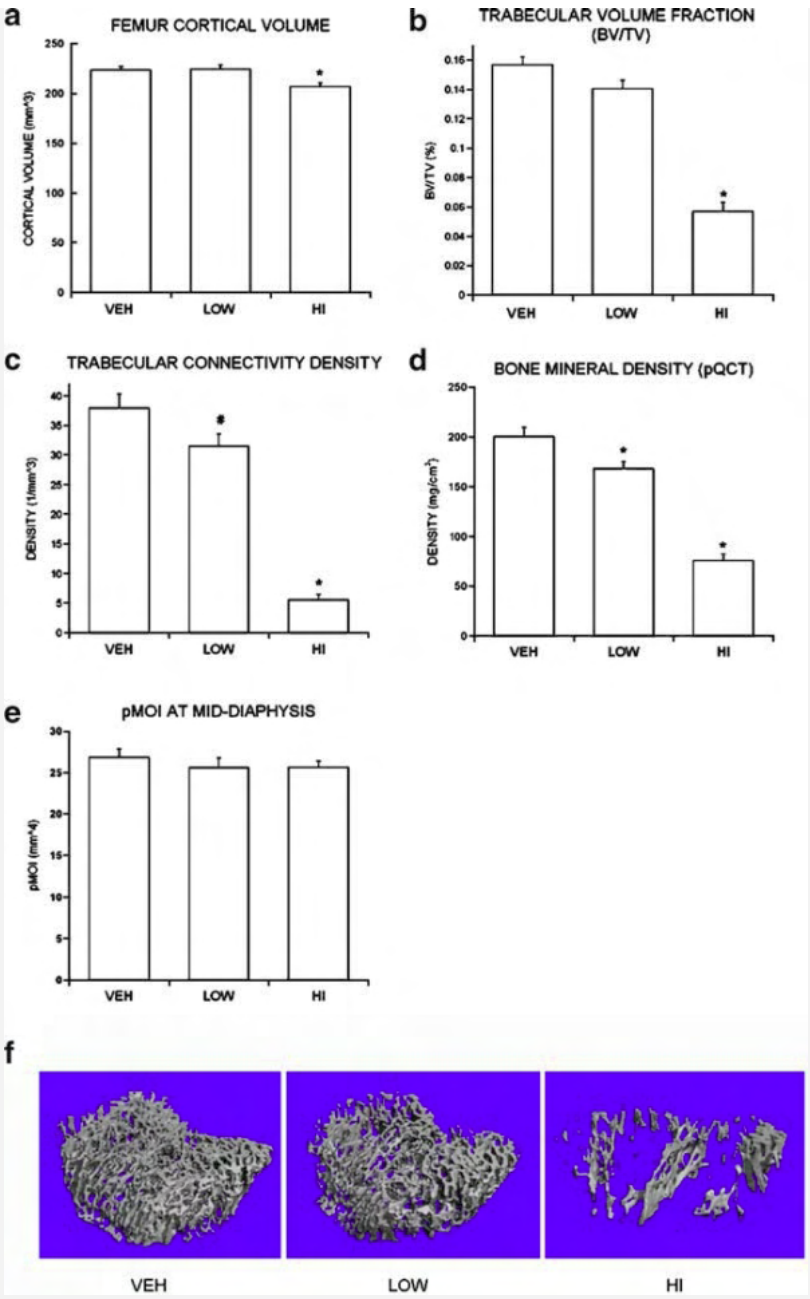


*Fig. 9.3.56b Cortical and trabecular bone properties were obtained via MicroCT (a, b, c, e, f) and pQCT (d) analysis from the femoral diaphyses and proximal tibias. (a) Cortical volume reduced by 7.6% in the HI group ($p<0.05$ vs. VEH), no change was observed in the LOW. (b) Trabecular volume fraction (BV/TV) decreased by 64% in HI ($p<0.001$ vs. VEH). (c) Connectivity density (Conn-Dens.) decreased by 86% ($p<0.001$) in HI, trend of decrease by 17% was observed in LOW ($p=0.054$). (d) Bone mineral density data obtained from the trabecular bone at proximal tibia showed 16% and 62% decrease in LOWand HI compared to VEH ($p<0.05$), respectively. (e) No significant differences were observed in Polar Moment of Inertia (pMOI) at mid-femoral diaphyses. (f) 3D microCT pictures of trabecular bone at proximal tibia. Data are presented as the mean±SE. *: Significant different vs. VEH. #: Trend of difference ($p=0.054$) vs. VEH. Reproduced from Osteoporosis Int 2008;19:625-35 with permission from Springer.*

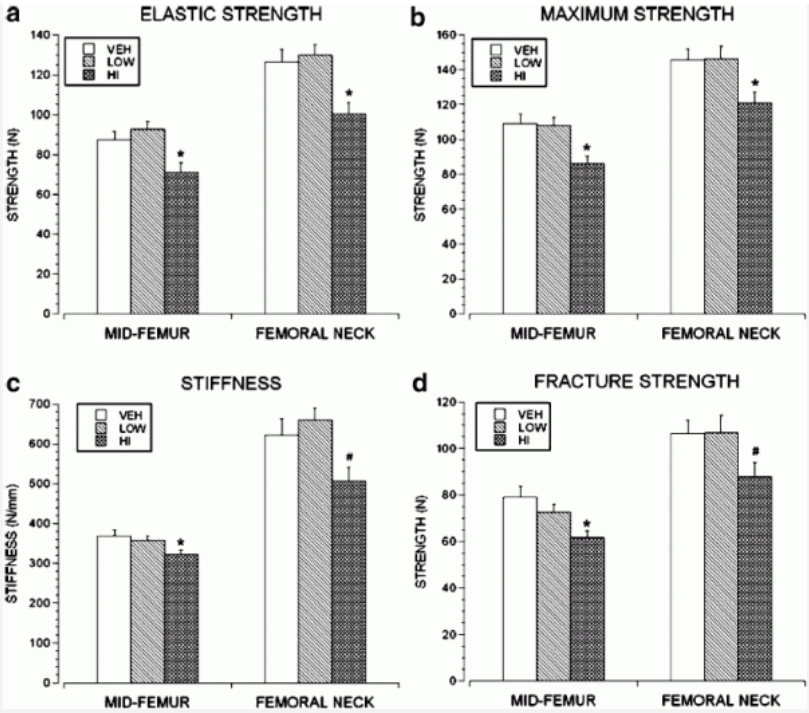


*Fig. 9.3.56c Mechanical properties were determined at the femur diaphysis and neck. High-dose RANKL infusion degraded femur mechanical properties in both diaphyses and necks with a similar manner (a-d). Decreased mechanical parameters were observed from elastic strength (a, 18%), maximum strength (b, 21%), fracture strength (c, 22%) and elastic stiffness (d, 13%, vs. VEH) at femoral diaphyses through three-point bending tests. Similarly, at the femoral neck region, high-dose RANKL treatment significantly decreased elastic strength by 20% (a, p<0.05) and maximum strength by 17% (b, p<0.05), and caused trend of decreases in fracture strength by 17% (c, p=0.105) and elastic stiffness by18% (d, p=0.061) compared to VEH, respectively. No differences were observed in the rats treated with low-dose RANKL. Data are presented as the mean±SE. *: p<0.05 vs. VEH. #: Trend of decrease vs. VEH. Reproduced from Osteoporosis Int 2008;19:625-35 with permission from Springer.*

9.3.57 Role of Bcl2 in osteoclastogenesis and PTH anabolic actions in bone
Yamashita J, Datta NS, Chun YH, Yang DY, Carey AA, Kreider JM, Goldstein SA, McCauley LK
J Bone Miner Res 2008;23:621-32

9.3.58 Poly(adp-ribose) polymerase-1 regulates Tracp gene promoter activity during RANKL-induced osteoclastogenesis
Beranger GE, Momier D, Rochet N, Carle GF, Scimeca JC
J Bone Miner Res 2008;23:564-71

9.3.59 Activation of peroxisome proliferator-activated receptor gamma inhibits TNFα-mediated osteoclast differentiation in human peripheral monocytes in part via suppression of monocyte chemoattractant protein-1 expression
Hounoki H, Sugiyama E, Mohamed SG, Shinoda K, Taki H, Abdel-Aziz HO, Maruyama M, Kobayashi M, Miyahara T
Bone 2008;42:765-74

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

Volume 9, Issue 3, 2008

Osteocytes

9.3.60 Osteocyte-derived sclerostin inhibits bone formation: Its role in bone morphogenetic protein and Wnt signaling
ten Dijke P, Krause C, de Gorter DJ, Lowik CW, van Bezooijen RL
J Bone Joint Surg Am 2008;90 Suppl 1:31-5

Sclerosteosis and Van Buchem disease are rare, high bone mass disorders linked to deficiency in the SOST gene, encoding sclerostin. Sclerostin a glycoprotein antagonizing BMP and/or Wnt activity. Sclerostin is expressed by osteocytes and inhibits BMP-induced osteoblast differentiation. Sclerostin binds weakly to BMPs and does not inhibit direct BMP-induced responses. Instead, sclerostin antagonizes canonical Wnt signaling by binding to Wnt coreceptors, low density lipoprotein receptor related protein 5 and 6. Several lipoprotein receptor related protein 5 mutants that cause the high bone mass trait are defective in sclerostin binding. Thus, high bone mass in sclerosteosis and Van Buchem disease may result from increased Wnt signaling due to the absence of or insensitivity to sclerostin.

9.3.61 Quantitative associations between osteocyte density and biomechanics, microcrack and microstructure in OVX rats vertebral trabeculae
Ma YL, Dai RC, Sheng ZF, Jin Y, Zhang YH, Fang LN, Fan HJ, Liao EY
J Biomech 2008;41:1324-32

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

Volume 9, Issue 3, 2008

Systemic Factors

9.3.62 Impact of glucose-dependent insulinotropic peptide on age-induced bone loss
Ding KH, Shi XM, Zhong Q, Kang B, Xie D, Bollag WB, Bollag RJ, Hill W, Washington W, Mi QS, Insogna K, Chutkan N, Hamrick M, Isales CM
J Bone Miner Res 2008;23:536-43

Glucose-dependent insulinotropic peptide (GIP) is an enteric hormone whose receptors are present in osteoblasts, and GIP is known to stimulate osteoblastic activity in vitro. In vivo, GIP-overexpressing C57BL/6 transgenic (GIP Tg(+)) mice have increased bone mass compared with controls. Bone histomorphometric data suggest that GIP increases osteoblast number, possibly by preventing osteoblastic apoptosis. Changes in BMD, biomechanics, biomarkers of bone turnover, and bone histology were assessed in C57BL/6 GIP Tg(+) versus Tg(-) (littermate) mice between the ages of 1 and 24 mo of age. In addition, age-related changes in GIP receptor (GIPR) expression and GIP effects on differentiation of BMSCs were also assessed as potential causal factors in aging-induced bone loss. Bone mass and strength in GIP Tg(+) mice did not drop in a similar age-dependent fashion as in controls. GIP Tg(+) mice had increased osteoblastic activity compared with wildtype control mice. BMSCs express GIPR, that the expression decreases in an age-dependent manner, and that stimulation of BMSCs with GIP led to increased osteoblastic differentiation. Elevated GIP levels prevent age-related loss of bone mass and bone strength and suggest that age-related decreases in GIP receptor expression in BMSCs may play a role in this bone loss. Elevations in GIP may be an effective countermeasure to age-induced bone loss.

9.3.63 Genetic variation in the PTH pathway and bone phenotypes in elderly women: Evaluation of PTH, PTHLH, PTHR1 and PTHR2 genes
Tenne M, McGuigan F, Jansson L, Gerdhem P, Obrant KJ, Luthman H, Akesson K
Bone 2008;42:719-27

In 1044 women, all 75 years old, SNPs from 4 genes and derived haplotypes in the PTH signaling pathway were analysed in 745-1005 women. Six SNPs in the PTH gene and 3 SNPs each in the PTHLH, PTHR1 and PTHR2 genes were investigated in relation to BMD (assessed at baseline), fracture (434 prevalent fractures of all types over lifetime, self-reported and 174 incident fractures up to 7 years, X-ray verified) and serum PTH. Individually, SNPs in the 4 loci did not show any association with BMD. Three of 5 common haplotypes, accounting for >98% of alleles at the PTH locus, were identified as independent predictors of fracture. Haplotype 9 (19%) was suggestive of an association with fractures of any type sustained during lifetime (p=0.018), with carriers of one or more copies of the haplotype having the lowest incidence (p=0.006). Haplotypes 1 (13%) and 5 (37%) and 9 were suggestive of an association with fractures sustained between 50 and 75 years (p=0.02, p=0.013 and p=0.034). Carriers of haplotypes 1 and 5 were more likely to suffer a fracture (haplotype 1, p=0.045; haplotype 5, p=0.008). Polymorphisms in PTH may contribute to the risk of fracture through mechanisms that are independent of BMD.

9.3.64 FGF23 is elevated in Gambian children with rickets
Prentice A, Ceesay M, Nigdikar S, Allen SJ, Pettifor JM
Bone 2008;42:788-97

Fibroblast growth factor 23 (FGF23) is a phosphaturic factor that is elevated in several diseases associated with hypophosphatemia and rickets. Rickets in the absence of vitamin D deficiency has been reported in African and Asian populations with a low calcium intake, but the definition of risk factors has proved elusive. The 46 patients (30 males, 16 females) had bone deformities typical of rickets and were 1.1-16.4 years old (geometric mean, 3.4 years). Active rickets was present in 28%. Plasma 25-hydroxyvitamin D was above 20 nmol/l in all patients. The rickets patients had lower plasma phosphate, lower 25-hydroxyvitamin D, higher 1,25-dihydroxyvitamin D and elevated total alkaline phosphatase than local children. Those with active rickets had raised parathyroid hormone concentration. The patients had significantly higher FGF23 than local children (geometric mean (-1SD, +1SD, range) RU/ml: 367 (87, 1552, 46-7052, n=39) vs. 51 (23, 112, 3-130, n=30), p≤0.001). At presentation, the majority (74%) had an FGF23 that was above the range seen in local children, some grossly so (upto 50-fold). There was no difference in FGF23 between those with active rickets and the other patients. Plasma phosphate was significantly and inversely correlated with FGF23 concentration. Some clinical improvements were noted after 6-12 months, during which time calcium and vitamin D had been prescribed, but FGF23 remained elevated in many patients. Perturbations of phosphate and FGF23 regulation may be implicated in the pathogenesis of calcium-deficiency rickets in Africa and Asia.

9.3.65 Increased plasma osteoprotegerin concentrations are associated with indices of bone strength of the hip
Samelson EJ, Broe KE, Demissie S, Beck TJ, Karasik D, Kathiresan S, Kiel DP
J Clin Endocrinol Metab 2008;93:1789-95

9.3.66 OPG and sRANKL serum concentrations in osteopenic, postmenopausal women after 2-year genistein administration
Marini H, Minutoli L, Polito F, Bitto A, Altavilla D, Atteritano M, Gaudio A, Mazzaferro S, Frisina A, Frisina N, Lubrano C, Bonaiuto M, D'Anna R, Cannata ML, Corrado F, Cancellieri F, Faraci M, Marini R, Adamo EB, Wilson S, Squadrito F
J Bone Miner Res 2008;23:715-20

9.3.67 Association of increased active PTH(1-84) fraction with decreased GFR and serum Ca in predialysis CRF patients: modulation by serum 25-OH-D
Kurajoh M, Inaba M, Yamada S, Imanishi Y, Tsuchida T, Ishimura E, Nishizawa Y
Osteoporos Int 2008;19:709-16

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

Volume 9, Issue 3, 2008

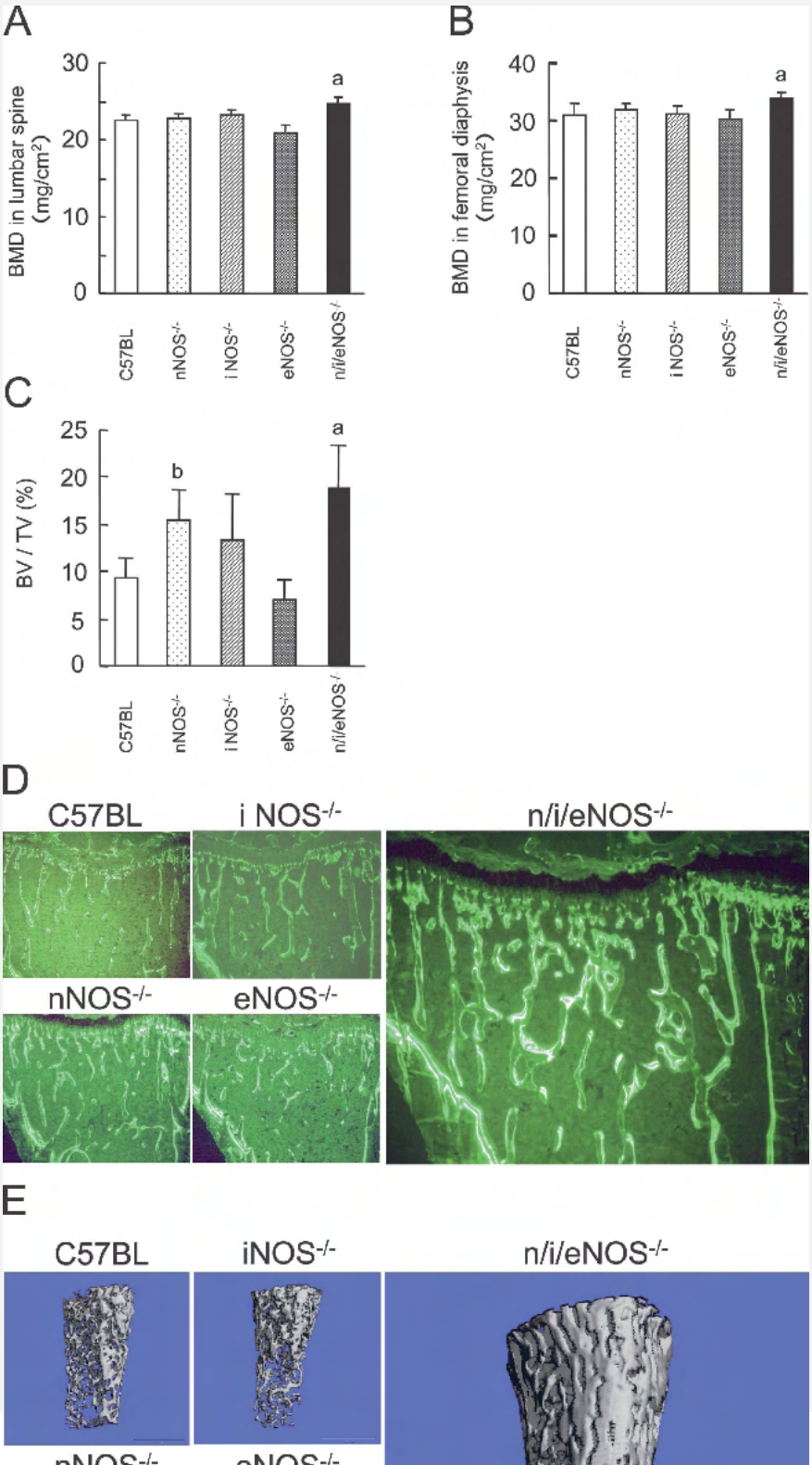
Local Factors

9.3.68 Genetic disruption of all NO synthase isoforms enhances BMD and bone turnover in mice in vivo: Involvement of the renin-angiotensin system

Sabanai K, Tsutsui M, Sakai A, Hirasawa H, Tanaka S, Nakamura E, Tanimoto A, Sasaguri Y, Ito M, Shimokawa H, Nakamura T, Yanagihara N

J Bone Miner Res 2008;23:633-43

NO is synthesized by NO synthase (NOS) isoforms, neuronal (nNOS), inducible (iNOS) and endothelial NOS (eNOS). Mice with three NOS genes are disrupted. nNOS(-/-), iNOS(-/-), and eNOS(-/-) and triply n/i/eNOS(-/-) mice. BMD was higher only in the triply NOS(-/-) mice. Markers of osteoblastic bone formation were also larger only in the triply NOS(-/-) mice. Markers of osteoclastic bone resorption were greater only in the triply NOS(-/-) mice. Renin-angiotensin system in bone was activated in the triply NOS(-/-) mice, and long-term angiotensin II type 1 (AT(1)) receptor blocker normalized this pathological bone remodeling in those mice.



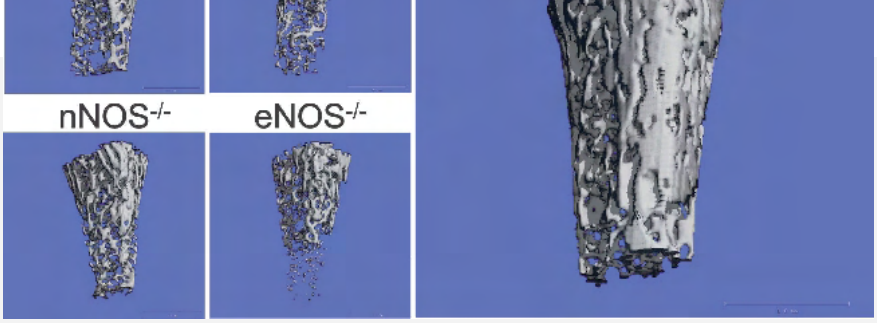


Fig. 9.3.68 Increased BMD, enhanced trabecular bone volume (BV/TV), and abnormal trabecular bone microstructure in the triply n/i/eNOS-/- mice. All experiments were performed in 12-wk-old male mice. (A and B) BMD values in the lumbar spine and femoral diaphysis (as assessed by DXA; n=7-10). (C) Trabecular BV/TV (n=6-8). (D and E) Calcein double labeling in the proximal tibia and 3D μCT of the femur. In both analyses, trabecular bone thickness and density were increased in the triply n/i/eNOS-/- mice. [a]p<0.01, [b]p<0.05 vs. wildtype C57BL. Reproduced from J Bone Miner Res 2008;23:633-43 with permission of the American Society of Bone and Mineral Research.

9.3.69 Interleukin-4 and interleukin-13 stimulate the osteoclast inhibitor osteoprotegerin by human endothelial cells through the STAT6 pathway

Stein NC, Kreutzmann C, Zimmermann SP, Niebergall U, Hellmeyer L, Goettsch C, Schoppet M, Hofbauer LC

J Bone Miner Res 2008;23:750-8

9.3.70 Impact of pregnancy-associated plasma protein-a deletion on the adult murine skeleton

Tanner SJ, Hefferan TE, Rosen CJ, Conover CA

J Bone Miner Res 2008;23:655-62

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

Volume 9, Issue 3, 2008

Risk Factors

9.3.71 FRAX™ and the assessment of fracture probability in men and women from the UK
Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E
Osteoporos Int 2008;19:385-97

To apply an assessment tool for fracture prediction with clinical risk factors (CRFs) (BMI, a prior fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other causes of osteoporosis, current smoking, and alcohol intake ≥3 units daily) with and without BMD. Four models were constructed comprising the 10-year probability of hip fracture, with and without femoral neck BMD, and the 10-year probability of a major osteoporotic fracture, with and without BMD. In the absence of BMD, hip fracture probability in women with a fixed BMI (25 kg/m^2) ranged from 0.2% at the age of 50 years for women without CRFs to 22% at the age of 80 years with a parental history of hip fracture (approximately 100-fold range). In men, the probabilities were lower, as was the range (0.1-11% in the examples above). For a major osteoporotic fracture the probabilities ranged from 3.5-31% in women, and from 2.8-15% in men in the example above.

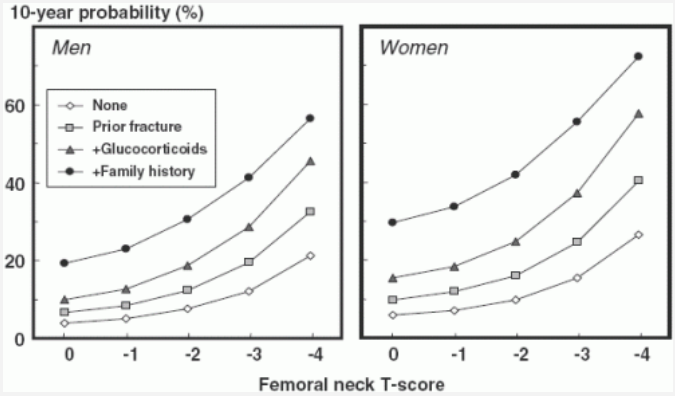


Fig. 9.3.71 10-year probability of a major osteoporotic fracture in men and women aged 65 years according to T-score and clinical risk factors. Body mass index is set at 25 kg/m^2. Reproduced from Osteoporos Int 2008;19:385-97 with permission from Springer.

9.3.72 Development and application of a Japanese model of the WHO fracture risk assessment tool (FRAX™)
Fujiwara S, Nakamura T, Orimo H, Hosoi T, Gorai I, Oden A, Johansson H, Kanis JA
Osteoporos Int 2008;19:429-35

To evaluate a Japanese version of FRAX, fracture probabilities were computed from published data on the fracture and death hazards in Japan. Probabilities took account of age, sex, the presence of clinical risk factors and femoral neck BMD. The 10-year probabilities of a major osteoporosis related fracture that corresponded to current intervention thresholds ranged from approximately 5% at the age of 50 years to more than 20% at the age of 80 years. The use of femoral neck BMD predicts fracture as well as or better than BMD tests at the lumbar spine.

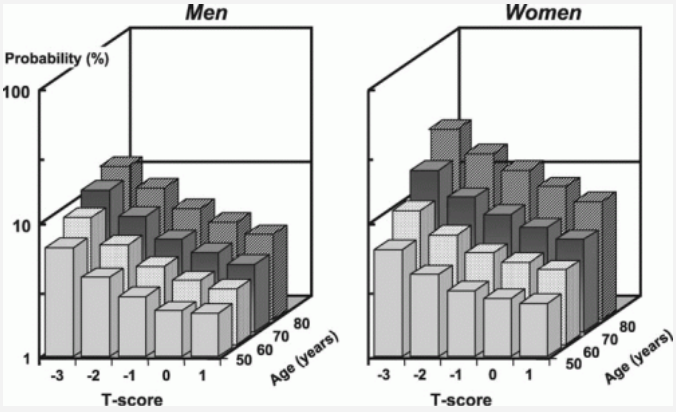


Fig. 9.3.72a Ten-year probability (%) of osteoporotic fracture (hip, clinical spine, humerus, forearm) in Japanese men and women without clinical risk factors according to age and T-score for BMD at the femoral neck. Reproduced from Osteoporosis Int 2008;19:429-35 with permission from Springer.

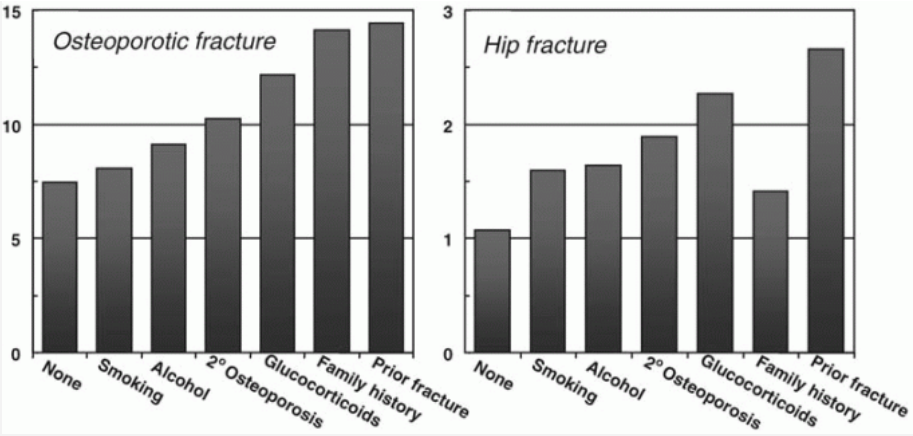


Fig. 9.3.72b Ten-year probability for osteoporotic (hip, clinical spine, humerus, forearm) and hip fracture (%) according to the presence of a clinical risk factor, in women at the age of 65 years and with a BMI of 23.4 kg/m^2. Reproduced from Osteoporosis Int 2008;19:429-35 with permission from Springer.

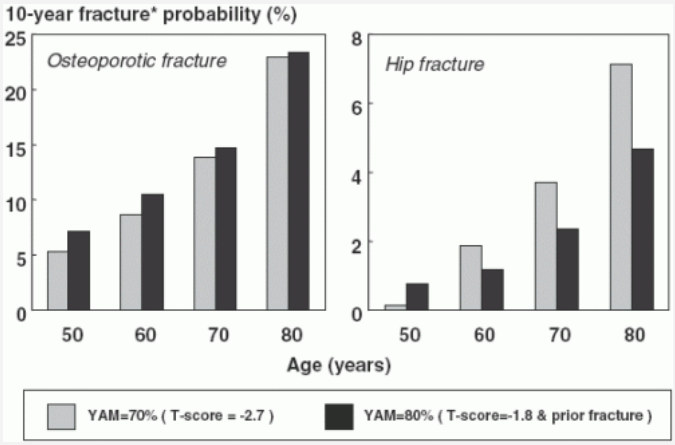
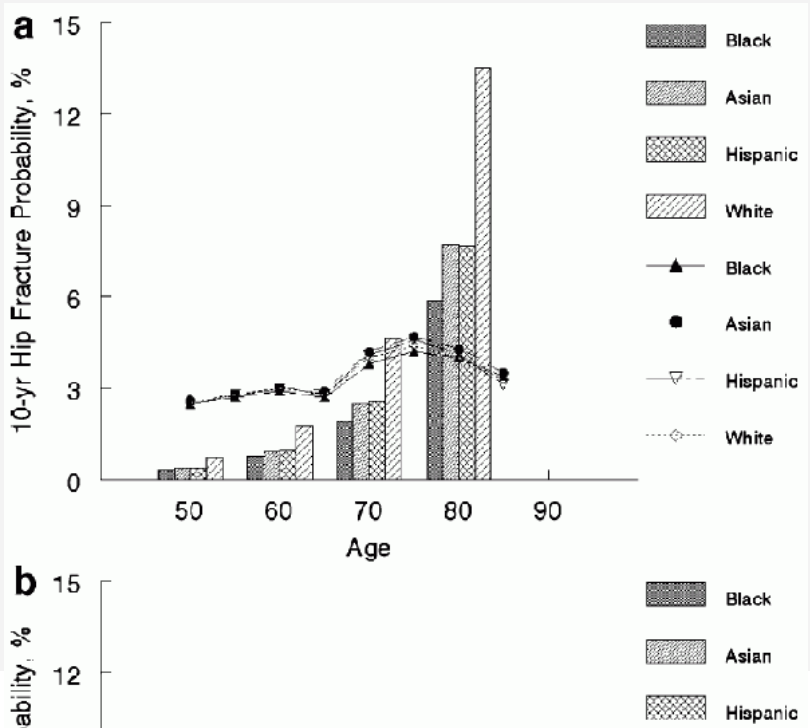


Fig. 9.3.72c Ten-year probability of osteoporotic (hip, clinical spine, humerus, forearm) and hip fracture based on women at the threshold for the diagnosis of osteoporosis using the criteria of the Japanese Bone Mineral Metabolism Association. Reproduced from Osteoporosis Int 2008;19:429-35 with permission from Springer.

9.3.73 Cost-effective osteoporosis treatment thresholds: The United States perspective
Tosteson AN, Melton LJ, 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, Lindsay RL
Osteoporos Int 2008;19:437-47

A Markov-cohort model of annual United States age-specific incidence of clinical hip, spine, forearm, shoulder, rib, pelvis and lower leg fractures, costs (2,005 USD), and quality-adjusted life years (QALYs) was used to assess the cost-effectiveness of osteoporosis treatment ($600/yr drug cost for 5 years with 35% fracture reduction) by gender and race/ethnicity groups. To determine the 10-year hip fracture probability at which treatment became cost-effective, average annual age-specific probabilities for all fractures were multiplied by a relative risk that was systematically varied from 0-10 until a cost of $60,000 per QALY gained was observed for treatment relative to no intervention. Osteoporosis treatment was cost-effective when the 10-year hip fracture probability reached ~3%.



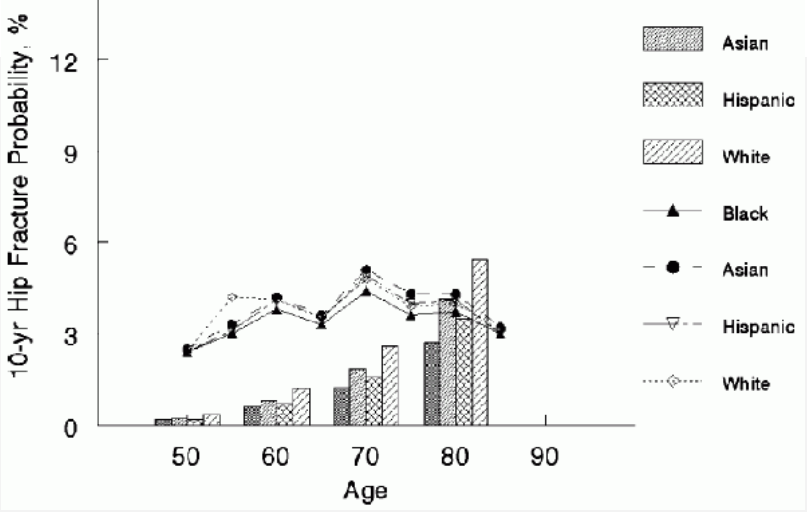


Fig. 9.3.73 Absolute 10-year hip fracture risk by age and race at which it is cost-effective to treat (shown by lines) and average 10-year hip fracture risk by age and race (shown by vertical bars) for a) women and b) men in the United States. Reproduced from Osteoporosis Int 2008;19:437-47 with permission from Springer.

9.3.74 Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA
Dawson-Hughes B, Tosteson AN, Melton LJ, 3rd, Baim S, Favus MJ, Khosla S, Lindsay RL
Osteoporos Int 2008;19:449-58

The WHO fracture prediction algorithm was calibrated to the US population. It is cost-effective to treat patients with a fragility fracture and those with osteoporosis by WHO criteria, as well as older individuals at average risk and osteopenic patients with additional risk factors. However, the estimated 10-year fracture probability was lower in men and nonwhite women compared to postmenopausal white women.

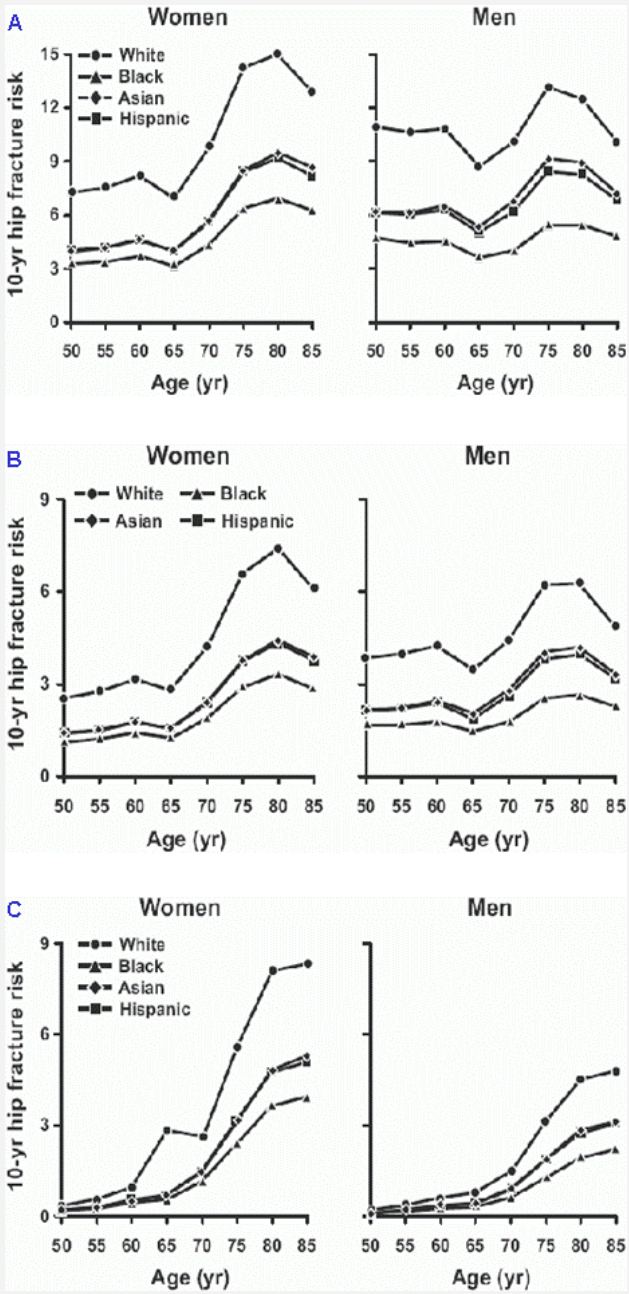


Fig. 9.3.74 (A) Ten-year hip fracture probabilities for patients with prior fracture plus osteopenia (T-score −2.0) who smoke and drink and who are women or men, by age and race. (B) Ten-year hip fracture probabilities for patients with osteoporosis (T-score −2.5) but no clinical risk factors who are women or men, by age and race. (C) Average ten-year hip fracture probabilities for women and men, by age and race. Adapted from Osteoporosis Int 2008;19:449-58 with permission from Springer.

9.3.75 Absolute fracture risk reporting in clinical practice: A physician-centered survey
Leslie WD
Osteoporos Int 2008;19:459-63

When asked whether the report contained the information needed to manage patients, the mean score for the absolute fracture risk report was higher than for the T-score-based report ($p<0.0001$). When asked whether the report was easy to understand, the mean score for the absolute fracture risk report was again higher than for the T-score-based report ($p<0.0001$). Non-specialists gave a higher ranking than specialists to the absolute fracture risk information ($p<0.05$). Absolute fracture risk reporting is well-received by physicians and is strongly preferred to traditional T-score-based reporting. Nonspecialist physicians are particularly supportive of risk-based BMD reporting.

9.3.76 Does a history of non-vertebral fracture identify women without osteoporosis for treatment?
Ryder KM, Cummings SR, Palermo L, Satterfield S, Bauer DC, Feldstein AC, Schousboe JT, Schwartz AV, Ensrud K
J Gen Intern Med 2008;[Epub ahead of print]

From the Fracture Intervention Trial (FIT) of 2,785 postmenopausal women with a femoral neck T-score between -1 and -2.5 and no prevalent vertebral fracture, 880 (31.6%) reported a fracture. Women were randomized to placebo or alendronate and were followed for 4.2±0.5 years. In the placebo arm, a prior fracture identified women with a 1.5-fold increased risk for non-vertebral fracture., There was no evidence that the effect of alendronate differed across subgroups of women with and without prior fracture. Assessing a clinical risk factor, prior non-vertebral fracture, did not identify women with low bone mass for whom alendronate reduced future non-vertebral fracture risk.

9.3.77 Wrist fracture as a predictor of future fractures in younger versus older postmenopausal women: Results from the National Osteoporosis Risk Assessment (NORA)
Barrett-Connor E, Sajjan SG, Siris ES, Miller PD, Chen YT, Markson LE
Osteoporos Int 2008;19:607-13

In the National Osteoporosis Risk Assessment (NORA) study, 158,940 postmenopausal women, aged 50-98 (median 63) years, 8665 reported wrist fracture at baseline; 4,316 women reported at least one new fracture within three years. The RR for any subsequent clinical fracture, adjusted for covariates and baseline BMD T-score, was 2.4 (2.0, 2.9) for younger and 2.1 (1.9, 2.3) for older women. A prior wrist fracture increased the risk of a future wrist fracture about 3-fold and doubled the risk of any osteoporotic fracture.

9.3.78 Association between alcohol consumption and both osteoporotic fracture and bone density
Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA, Jr., Malik R, Arnsten JH
Am J Med 2008;121:406-18

Compared with abstainers, persons consuming from more than 0.5 to 1.0 drinks per day had lower hip fracture risk (relative risk=0.80 [95% CI 0.71-0.91]), and persons consuming more than 2 drinks per day had higher risk (relative risk=1.39 [95% CI 1.08-1.79]). Compared with abstainers and heavier drinkers, persons who consume 0.5 to 1.0 drink per day have a lower risk of hip fracture.

9.3.79 Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D
Macdonald HM, Mavroeidi A, Barr RJ, Black AJ, Fraser WD, Reid DM
Bone 2008;42:996-1003

In 3113 women (age 54.8 [SD 2.3] years) living at latitude 57 degrees N, BMD was measured at the sampling visit and 6 years before. Seasonal variation in 25(OH)D was not substantial with a peak in the autumn (23.7 [9.9] ng/ml) and a nadir in spring (19.7 [7.6] ng/ml). Daily intake was 4.2 [2.5] μg from food and 5.8 [4.0] μg including vitamin D from cod liver oil and multivitamins. The latter was associated with 25(OH)D at each season whereas vitamin D from food was associated with 25(OH)D in winter and spring only. Sunlight exposure was associated with 25(OH)D in summer and autumn. 25(OH)D was negatively associated with increased resorption and bone loss ($P<0.05$). Using an insufficiency cutoff of <28 ng/ml 25(OH)D, showed lower resorption markers in the upper category (fDPD/Cr 5.1 [1.7] nmol/mmol compared to 5.3 [2.1] nmol/mmol, $P=0.03$) and no difference in BMD or bone loss. 25(OH)D was lower ($P<0.01$) and parathyroid hormone higher ($P<0.01$) in the top quintile of body mass index.

9.3.80 Association of race, body fat, and season with vitamin D status among young women: A cross-sectional study
McKinney K, Breitkopf CR, Berenson AB
Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

A cross-sectional study was conducted on 800 non-Hispanic white, non-Hispanic black, and Hispanic women 16-33 years of age, Serum 25-OHD levels differed among the racial groups (all pairwise differences $P<0.001$), with the lowest value among non-Hispanic blacks (37.7 nmol/L) and the highest value among non-Hispanic whites (71.8 nmol/L). Among Hispanics, mean serum 25-OHD was 47.9 nmol/L. Serum 25-OHD was negatively associated with %TBF ($r=-0.28$), body mass index ($r=-0.36$), and TBF ($r=-0.33$), all $P<0.001$, and positively associated with dietary vitamin D ($r=0.10$) and pack years of smoking ($r=0.11$), both $P<0.01$. In the summer months, serum 25-OHD values were higher (55.4 nmol/L) than in the winter months (48.1 nmol/L), $P<0.001$. The final regression model predicting serum 25-OHD levels included race, %TBF, and season (all $P<0.05$) and explained 36% of the variance in 25-OHD. Favorable environmental conditions do not result in sufficient vitamin D status for young women, especially non-Hispanic blacks, Hispanics, and the obese.

9.3.81 Seasonal variation of serum α- and β-cryptoxanthin and 25-OH-vitamin D(3) in women with osteoporosis
Granado-Lorencio F, Olmedilla-Alonso B, Herrero-Barbudo C, Blanco-Navarro I, Perez-Sacristan B
Osteoporos Int 2008;19:717-20

Dietary intake and serum levels of β-cryptoxanthin have been inversely related to different bone and joint disorders and in vitro and animal studies have shown that β-cryptoxanthin displays a unique anabolic effect on bone calcification. Serum α- and β-cryptoxanthin and 25-OH-vitamin D(3) in women with osteoporosis (N=644) were analyzed. Overall, seasonal variations were found for the three analytes and interindividual variation was also high (60-73%). β-cryptoxanthin and 25-OH-vitamin D(3) exhibited a marked seasonal distribution in serum, with vitamin D displaying the highest values in summer and β-cryptoxanthin in winter.

9.3.82 Mutations in the insulin-like factor 3 receptor are associated with osteoporosis
Ferlin A, Pepe A, Gianesello L, Garolla A, Feng S, Giannini S, Zaccolo M, Facciolli A, Morello R, Agoulnik AI, Foresta C
J Bone Miner Res 2008;23:683-93

Insulin-like factor 3 (INSL3) is produced by testicular Leydig cells, binds to its specific G protein-coupled receptor RXFP2 (relaxin family peptide 2) and is involved in testicular descent during fetal development. In 25 men (age, 27-41 yr) with the well characterized T222P mutation in the RXFP2 gene. Sixteen of 25 (64%) young men with RXFP2 mutations had reduced BMD. Stimulation of these cells with INSL3 produced a dose- and time-dependent increase in cAMP and cell proliferation, confirming the functionality of the RXFP2/INSL3 receptor-ligand complex. Consistent with the human phenotype, bone histomorphometric and muCT analyses of Rxfp2(-/-) mice showed decreased bone mass, mineralizing surface, bone formation, and osteoclast surface compared with wildtype littermates.

9.3.83 Association of aromatase and estrogen receptor gene polymorphisms with hip fractures
Valero C, Perez-Castrillon JL, Zarrabeitia MT, Hernandez JL, Alonso MA, Del Pino-Montes J, Olmos JM, Gonzalez-Macias J, Riancho JA
Osteoporos Int 2008;19:787-92

In 498 women with hip fractures and 356 controls a C/G polymorphism of the aromatase gene and a T/C polymorphism of the estrogen receptor α gene were analyzed. Aromatase gene expression was determined in 43 femoral neck samples by real-time RT-PCR. There were no differences in the distribution of genotypes between the fracture and control groups. However, among women with a TT genotype of the estrogen receptor, the CC aromatase genotype was more frequent in women with fractures than in controls (39 vs. 23%, p=0.009). Thus, women homozygous for T alleles of estrogen receptor and C alleles of aromatase were at increased risk of fracture (odds ratio 2.0; 95% CI 1.2-3.4). The aromatase polymorphism was associated with RNA levels in bone tissue, which were three times lower in samples with a CC genotype (p=0.009).

9.3.84 Body composition and bone density in Canadian White and Aboriginal women: The First Nations bone health study
Leslie WD, Weiler HA, Lix LM, Nyomba BL
Bone 2008;42:990-5

9.3.85 Association between caffeine intake and bone mass among young women: Potential effect modification by depot medroxyprogesterone acetate use
Wetmore CM, Ichikawa L, Lacroix AZ, Ott SM, Scholes D
Osteoporos Int 2008;19:519-27

9.3.86 Vitamin K1 intake is associated with higher bone mineral density and reduced bone resorption in early postmenopausal Scottish women: No evidence of gene-nutrient interaction with apolipoprotein E polymorphisms
Macdonald HM, McGuigan FE, Lanham-New SA, Fraser WD, Ralston SH, Reid DM
Am J Clin Nutr 2008;87:1513-20

9.3.87 Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: A randomized, double-blind, placebo controlled study
Brink E, Coxam V, Robins S, Wahala K, Cassidy A, Branca F
Am J Clin Nutr 2008;87:761-70

9.3.88 Skeletal fluorosis from instant tea
Whyte MP, Totty WG, Lim VT, Whitford GM
J Bone Miner Res 2008;23:759-69

9.3.89 Low-grade metabolic acidosis may be the cause of sodium chloride-induced exaggerated bone resorption
Frings-Meuthen P, Baecker N, Heer M
J Bone Miner Res 2008;23:517-24

9.3.90 Pelvic body composition measurements by quantitative computed tomography: Association with recent hip fracture
Lang T, Koyama A, Li C, Li J, Lu Y, Saeed I, Gazze E, Keyak J, Harris T, Cheng X
Bone 2008;42:798-805

9.3.91 In vivo magnetic resonance detects rapid remodeling changes in the topology of the trabecular bone network after menopause and the protective effect of estradiol
Wehrli FW, Ladinsky GA, Jones C, Benito M, Magland J, Vasilic B, Popescu AM, Zemel B, Cucchiara AJ, Wright AC, Song HK, Saha PK, Peachey H, Snyder PJ
J Bone Miner Res 2008;23:730-40

9.3.92 Plasma osteopontin increases after bariatric surgery and correlates with markers of bone turnover but not with insulin resistance
Riedl M, Vila G, Maier C, Handisurya A, Shakeri-Manesch S, Prager G, Wagner O, Kautzky-Willer A, Ludvik B, Clodi M, Luger A

J Clin Endocrinol Metab 2008;[Epub ahead of print]

9.3.93 Does osteoprotegerin or receptor activator of nuclear factor kappa B ligand mediate the association between bone and coronary artery calcification?
Bakhireva LN, Laughlin GA, Bettencourt R, Barrett-Connor E
J Clin Endocrinol Metab 2008;93:2009-12

9.3.94 The effect of feeding different sugar-sweetened beverages to growing female Sprague-Dawley rats on bone mass and strength
Tsanzi E, Light HR, Tou JC
Bone 2008;42:960-8

9.3.95 Effects of low-dose parathyroid hormone on bone mass, turnover, and ectopic osteoinduction in a rat model for chronic alcohol abuse
Iwaniec UT, Trevisiol CH, Maddalozzo GF, Rosen CJ, Turner RT
Bone 2008;42:695-701

9.3.96 Spinal cord injury causes rapid osteoclastic resorption and growth plate abnormalities in growing rats (SCI-induced bone loss in growing rats)
Morse L, Teng YD, Pham L, Newton K, Yu D, Liao WL, Kohler T, Muller R, Graves D, Stashenko P, Battaglino R
Osteoporos Int 2008;19:645-52

9.3.97 Changes of substance P-immunoreactive nerve fiber innervation density in the sublesional bones in young growing rats at an early stage after spinal cord injury
Liu D, Li H, Zhao CQ, Jiang LS, Dai LY
Osteoporos Int 2008;19:559-69

Volume 9, Issue 3, 2008

Corticosteroid Therapy

9.3.98 Fracture risk associated with different types of oral corticosteroids and effect of termination of corticosteroids on the risk of fractures
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2008;82:249-57

Cases were all subjects with any fracture (n=124,655). For each case, three controls (n=373,962) matched on age and gender were randomly drawn from the population. Oral prednisolone/prednisone was associated with a dose-dependent increase in fracture risk starting from 6.7 mg/day. Oral budesonide was not associated with an increase in fracture risk, but the doses in were low (<3 mg/day). Oral hydrocortisone was not associated with risk of fractures. Oral methylprednisolone was only used intermittently and was not associated with an increase in overall fracture risk at the low doses used. After termination of oral prednisolone/prednisone, it took more than 1 year for fracture risk to return to background.

9.3.99 Glucocorticoid excess affects cortical bone geometry in premenopausal, but not postmenopausal, women
Kaji H, Yamauchi M, Chihara K, Sugimoto T
Calcif Tissue Int 2008;82:182-90

Ninety-six women receiving oral GC and 10 women with Cushing syndrome (CS) were compared to controls using peripheral quantitative computed tomography. Total area, periosteal circumference, and polar strength strain index (SSIp) were lower in patients compared with control subjects in premenopausal women. Moreover, cortical area and thickness as well as periosteal circumference and SSIp were lower in patients with CS compared to controls in premenopausal women. Total area, cortical area, cortical thickness, periosteal circumference, as well as SSIp were lower in GC-treated patients with vertebral fractures compared to those without vertebral fractures in premenopausal women. In conclusion, endogenous or exogenous GC excess affects bone geometry of forearms of premenopausal, but not postmenopausal, women.

9.3.100 Efficacy of intravenous alendronate for the treatment of glucocorticoid-induced osteoporosis in children with autoimmune diseases
Inoue Y, Shimojo N, Suzuki S, Arima T, Tomiita M, Minagawa M, Kohno Y
Clin Rheumatol 2008;[Epub ahead of print]

9.3.101 Effects of alendronate and pamidronate on cultured rat metatarsal bones: Failure to prevent dexamethasone-induced growth retardation
Heino TJ, Chagin AS, Takigawa M, Savendahl L
Bone 2008;42:702-9

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

Volume 9, Issue 3, 2008

Falls

9.3.102 Evaluation of a fall-prevention program in older people after femoral neck fracture: A one-year follow-up
Berggren M, Stenvall M, Olofsson B, Gustafson Y
Osteoporos Int 2008;19:801-9

The randomized, controlled trial with a one-year follow-up at Umeå University Hospital, Sweden, included 199 patients operated on for femoral neck fracture, aged ≥70 years. After one year 44 participants had fallen 138 times in the intervention group compared with 55 participants and 191 falls in the control group. The crude postoperative fall incidence was 4.16/1,000 days in the intervention group vs. 6.43/1,000 days in the control group. The incidence rate ratio was 0.64 (95% CI: 0.40-1.02, p=0.063). Seven new fractures occurred in the intervention group and 11 in the control group.

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

Volume 9, Issue 3, 2008

Treatment

9.3.103 Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture
Cadarette SM, Katz JN, Brookhart MA, Sturmer T, Stedman MR, Solomon DH
Ann Intern Med 2008;148:637-46

This is a seriously flawed document for obvious reasons. Enrollees in 2 statewide pharmaceutical benefit programs identified 43,135 new recipients of bisphosphonates, nasal calcitonin, and raloxifene who began treatment from 2000 to 2005. 1051 nonvertebral fractures were observed within 12 months. No differences in fracture risk were found between risedronate or raloxifene relative to alendronate. Among those with a fracture history, raloxifene users had more nonvertebral fractures (HR, 1.78 [CI, 1.20-2.63]) than alendronate users. Calcitonin users had more nonvertebral fractures than alendronate users (HR, 1.40, [CI, 1.20-1.63]). What inferences can be made about the drug, about the type of recipient about the reasons a doctor might choose one drug over another.

9.3.104 Strontium ranelate prevents quality of life impairment in post-menopausal women with established vertebral osteoporosis
Marquis P, Roux C, de la Loge C, Diaz-Curiel M, Cormier C, Isaia G, Badurski J, Wark J, Meunier PJ
Osteoporos Int 2008;19:503-10

The SOTI study used the SF-36(R) questionnaire and disease-specific QUALIOST(R) module, and demonstrated that treatment improved quality of life. QoL was assessed 6 monthly over 3 years using the QUALIOST(R) and SF-36(R) questionnaires in 1,240 women were included (strontium ranelate: n=618 and placebo: n=622). The QUALIOST(R) total score decreased in the strontium ranelate group, indicating preserved QoL compared with a deterioration in the placebo group (P=0.016). Strontium ranelate patients had reduced QUALIOST(R) emotional and physical dimension scores (P=0.019 and 0.032, respectively, vs. placebo). There was a trend towards better SF-36(R) scores in the strontium ranelate group, although there were no between-group differences. More strontium ranelate patients (+31%) were free from back pain over 3 years vs. placebo (P=0.005), with an effect from the first year of treatment (P=0.023).

9.3.105 Loss of treatment benefit due to low compliance with bisphosphonate therapy
Penning-van Beest FJ, Erkens JA, Olson M, Herings RM
Osteoporos Int 2008;19:511-7

New female users of alendronate or risedronate between 1999-2004, aged ≥45 years were identified and were followed until first hospitalisation for an osteoporotic fracture, death, or end of study period. Compliance with bisphosphonates was measured over 90-day intervals using Medication Possession Ratio (MPR). In 8822 new female bisphosphonate users (22,484 person-years of follow-up), 176 fractures occurred (excluding the first six months). Noncompliant bisphosphonate use was associated with a 45% increased fracture risk compared to compliant use (MPR≥80%). Fracture risk increased with poorer compliance (p-value <0.05 for trend). A MPR <20% was associated with an 80% increased fracture risk compared to a MPR≥90%.

9.3.106 Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women
Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, Deswaef A, Verpooten GA, Reginster JY
Osteoporos Int 2008;19:811-8

Compliance at 12 months was quantified using the medication possession ratio (MPR). Persistence was calculated as the number of days from the initial prescription to a gap of more than 5 weeks after completion of the previous refill. A logistic regression model was used to estimate the impact of compliance on the risk of hip fracture. The impact of persistence on hip fracture risk was analysed using the Cox proportional hazards model. The mean MPR at 12 months was higher among patients receiving weekly (n=15.021) compared to daily alendronate (n=14,136) (daily=58.6%; weekly=70.5%; p<0.001). At 12 months, the rate of persistence was 39.45%. For each decrease of the MPR by 1%, the risk of hip fractures increased by 0.4% (OR: 0.996:0.994-0.998). The relative risk reduction for hip fractures was 60% (HR: 0.404: 0.357-0.457) for persistent compared to nonpersistent patients. These results confirm that adherence to current therapeutic regimens remains suboptimal.

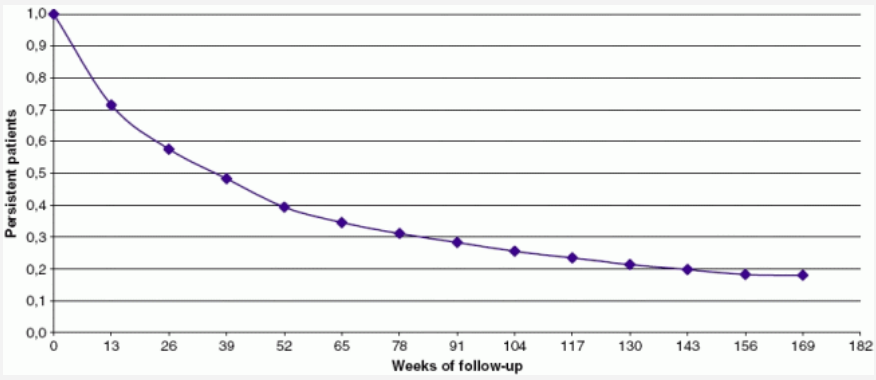


Fig. 9.3.106 Persistence in the total population treated by alendronate (daily group, weekly group and switch group). Reproduced from Osteoporos Int 2008;19:811-8 with permission from Springer.

9.3.107 Use of alendronate and risk of incident atrial fibrillation in women

Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM
Arch Intern Med 2008;168:826-31

The HORIZON (Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly) trial reported a higher risk of serious atrial fibrillation (AF) in zoledronic acid recipients. In this study ever use of alendronate in a clinical practice setting identified 719 women with AF and 966 controls without AF. More AF case patients had ever used alendronate (6.5% [n=47] vs. 4.1% [n=40]; P=0.03), so ever use of alendronate was associated with a higher risk of incident AF (odds ratio, 1.86; 95%CI 1.09-3.15). The authors estimated that 3% of incident AF in this population might be explained by alendronate use.

9.3.108 The effects of zoledronic acid on serum lipids in multiple myeloma patients
Gozzetti A, Gennari L, Merlotti D, Salvadori S, De Paola V, Avanzati A, Franci B, Marchini E, Tozzi M, Campagna MS, Nuti R, Lauria F, Martini G
Calcif Tissue Int 2008;82:258-62

Nitrogen-containing bisphosphonates (N-BPs) inhibit squalene synthase or farnesyl pyrophosphate synthase. Zoledronic acid (ZA) has antitumor activity. Sixteen of 26 patients with myeloma were treated with ZA (4 mg) at baseline and at months 1, 2, 4, and 6. The remaining 10 served as controls. In treated patients, TC decreased by 13% at 6 months. Moreover, LDL-C decreased by 21% at 6 months, no difference was seen in HDL-C and TGs. TC/HDL-C ratio decreased by 17% and HDL-C/LDL-C ratio increased by 36%.

9.3.109 Risedronate prevents bone loss in breast cancer survivors: A 2-year, randomized, double-blind, placebo-controlled clinical trial
Greenspan SL, Brufsky A, Lembersky BC, Bhattacharya R, Vujevich KT, Perera S, Sereika SM, Vogel VG
J Clin Oncol 2008;[Epub ahead of print]

87 postmenopausal women chemotherapy for breast cancer were randomly assigned to weekly risedronate 35 mg or placebo for 2 yrs. 13% received an aromatase inhibitor (AI). After 2 yrs, there were differences of 1.6 to 2.5% (P<0.05) at the spine and hip BMD between groups. At completion, 44% were taking an AI. Adjusting for an AI, placebo plus AI had a decrease in BMD of 4.8% at the spine and 2.8% at the total hip. In women receiving risedronate + AI, spine BMD decreased by 2.4% and was stable at the hip. Women receiving placebo not on an AI, maintained BMD at the spine, and had a 1.2±0.5% loss at the total hip. Women who received risedronate but no AI had the greatest improvement in BMD of 2.2% at the total hip.

9.3.110 Effects of risedronate on fracture risk in postmenopausal women with osteopenia
Siris ES, Simon JA, Barton IP, McClung MR, Grauer A
Osteoporos Int 2008;19:681-6

Postmenopausal women with osteopenia and no prevalent vertebral fractures were identified from BMD Multinational, BMD North America, VERT Multinational and VERT North America). 620 women with osteopenia were included, receiving either placebo (n=309) or risedronate 5 mg (n=311). Risedronate reduced the risk of fragility fractures by 73% over 3 years versus placebo (p=0.023); cumulative fragility fracture incidence was 6.9% in placebo-treated vs. 2.2% in risedronate-treated patients.

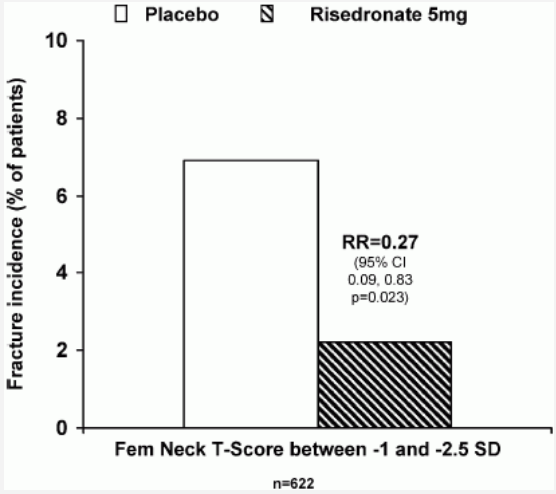


Fig. 9.3.110 Reduction of fragility fracture risk in patients with femoral neck T-score between −1 and −2.5 SD and no prevalent vertebral fractures. Reproduced from Osteoporosis Int 2008;19:681-6 with permission from Springer.

9.3.111 Bisphosphonates can block the deterioration in implant fixation after withdrawal of intermittent doses of parathyroid hormone
Johansson HR, Skripitz R, Aspenberg P
J Bone Joint Surg Br 2008;90:400-4

The stimulatory effect of PTH on fixation was lost after 16 days from withdrawal. Specimens treated with either PTH or saline during the first two weeks showed no difference in the mechanical or histological results (pull-out force 76 N vs. 81 N; bone volume density 19% vs. 20%). Treatment with PTH for two weeks followed by pamidronate almost doubled the pull-out force (152 N; p<0.001) and the bone volume density (37%; ANOVA, p<0.001). Pamidronate alone did not have this effect (89 N and 25%, respectively). Thus, the deterioration can be blocked by bisphosphonates.

9.3.112 Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy
Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R
Osteoporos Int 2008;19:529-35

Forty-two postmenopausal women with osteoporosis on raloxifene were randomized to raloxifene or 1-34PTH daily for 12 months

and continuing raloxifene. Women were then followed for 12 months on raloxifene alone. Biochemical indices increased rapidly during PTH with peak increments of 125-584% for the three markers. After one year of PTH, mean BMD increases were 9.6% for spine, 2.7% for total hip, 3.6% for trochanter (all p<0.005) and 1.2% in femoral neck (NS), while BMD declined 4.3% in the radius (p=0.003). After PTH withdrawal, on continued raloxifene, BMD declined (0.7-2.9% losses; NS) at all sites, except the femoral neck, where BMD increased modestly (p=0.04). At 24 months, spine and femoral neck BMD remained higher than baseline, while radius BMD remained lower (all p<0.04). Gains in BMD of the spine and hip, but not the radius, are seen with one year of PTH in patients on raloxifene. After PTH is discontinued, raloxifene partially maintains PTH-induced BMD gains in the spine and hip.

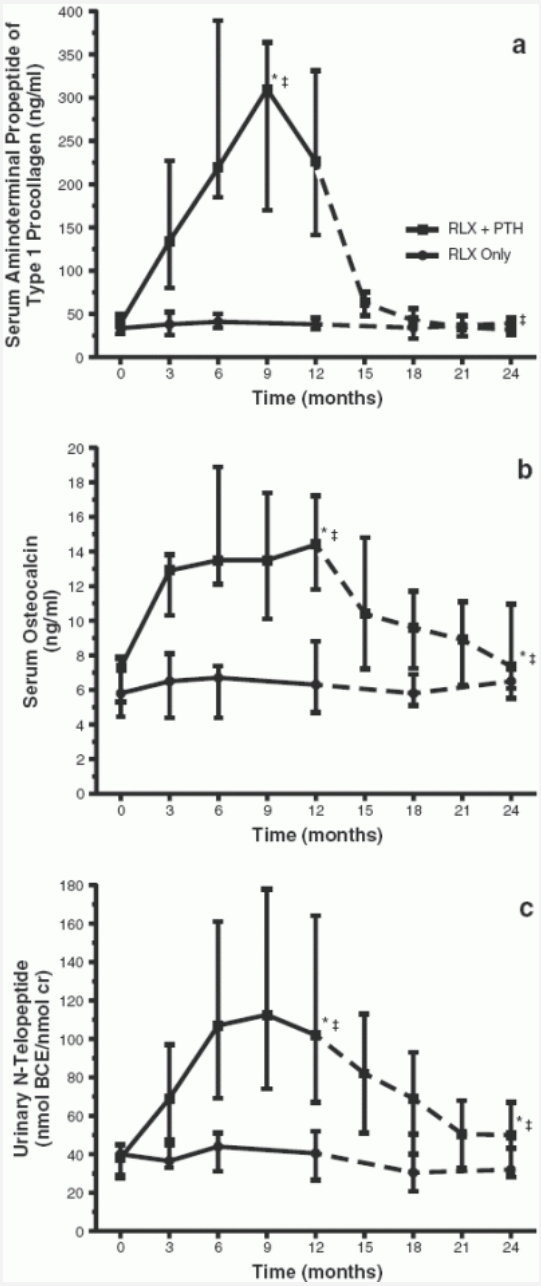


*Fig. 9.3.112a Bone turnover biochemistry in subjects randomized to 1-34PTH treatmentwith ongoing raloxifene compared to raloxifene alone for 1 year (solid lines) followed by continued raloxifene in all subjects for an additional year (dotted lines). Data are presented as medians with interquartile ranges.Within group changes (*p<0.05 at 12 and 24 months vs. baseline, by paired t-tests) and between group differences over 12 months and over 24 months (‡p<0.05 by repeated measures ANOVA). a. Serum aminoterminal propeptide of type I procollagen (ng/ml), b. Serum osteocalcin (ng/ml), c. Urinary N-telopeptide (nmol BCE/nmol cr). Reproduced from Osteoporosis Int 2008;19:529-35 with permission from Springer.*

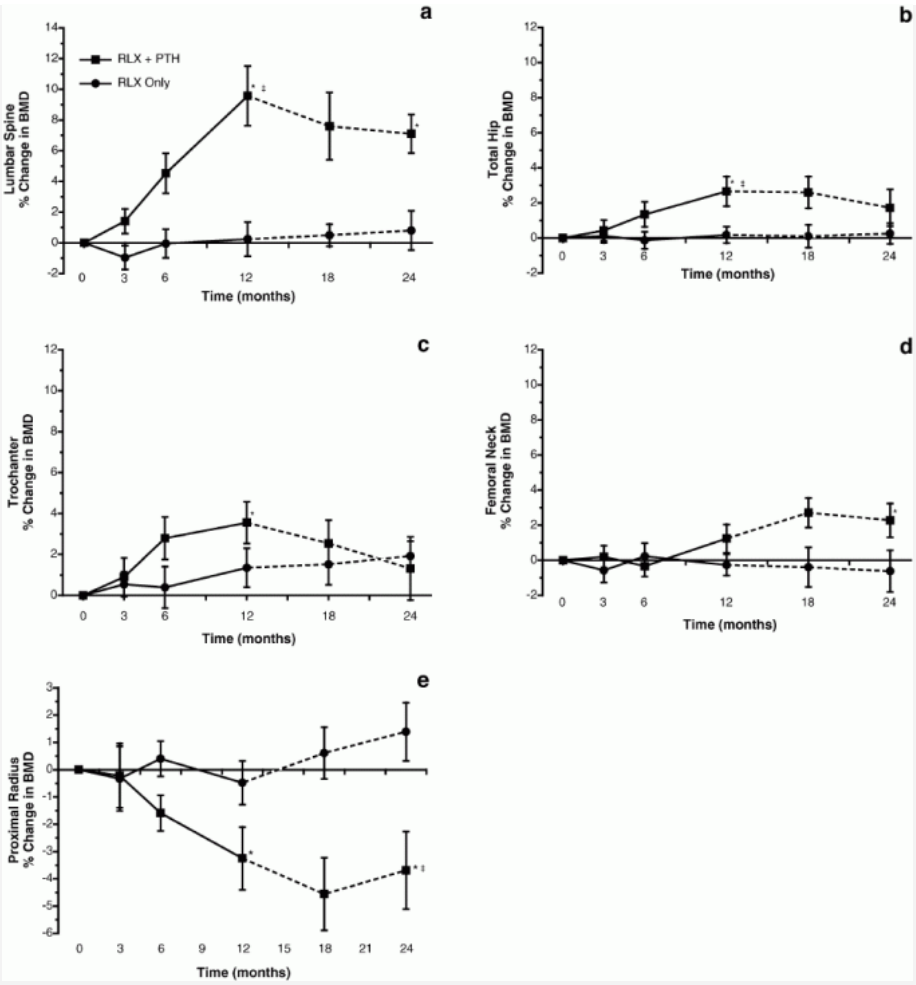


*Fig. 9.3.112b Percent change in bone density in subjects randomized to 1-34PTH treatment with ongoing raloxifene compared to raloxifene alone for 1 year (solid lines), followed by continued raloxifene in all subjects for an additional year (dotted lines). Data are presented as means with standard errors. Within group changes (*p<0.05 at 12 and 24 months vs. baseline, by paired t-tests) and between group differences over 12 months and over 24 months (‡p<0.05 by repeated measures ANOVA). a. Lumbar spine, b. Total hip, c. Trochanter, d. Femoral neck, e. Proximal radius. Reproduced from Osteoporosis Int 2008;19:529-35 with permission from Springer.*

9.3.113 Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo- and active-controlled study

Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM, Woodson G, Levine AB, Constantine G, Delmas PD
J Bone Miner Res 2008;23:525-35

Bazedoxifene is a selective estrogen receptor modulator that increased BMD and bone strength in experimental models, without stimulating breast or uterus. This 24-mo, randomized, double-blind study in postmenopausal women with a BMD T-score at the lumbar spine or femoral neck between -1.0 and -2.5 or clinical risk factors for osteoporosis assigned to bazedoxifene 10, 20, or 40 mg/d, placebo, or raloxifene 60 mg/d. All received calcium. The intent-to-treat population included 1434 women (mean age, 58 yr; mean time from last menstrual period, 11 yr). All doses of bazedoxifene and raloxifene prevented bone loss. Mean differences in percent change in spine BMD from baseline to 24 mo relative to placebo were 1.08±0.28%, 1.41±0.28%, 1.49±0.28%, and 1.49±0.28% for 10, 20, and 40 mg bazedoxifene and 60 mg raloxifene, respectively (p<0.001). Comparable BMD responses were observed at other body sites. Significant and comparable decreases in serum osteocalcin and C-telopeptide levels from baseline and relative to placebo with active treatment were observed as early as 3 mo and were sustained (p<0.001). Adverse events, serious adverse events, and discontinuations caused by adverse events were similar between groups. The most common adverse events included headache, infection, arthralgia, pain, hot flush, and back pain. Bazedoxifene prevented bone loss and reduced turnover as well as raloxifene and was well tolerated.

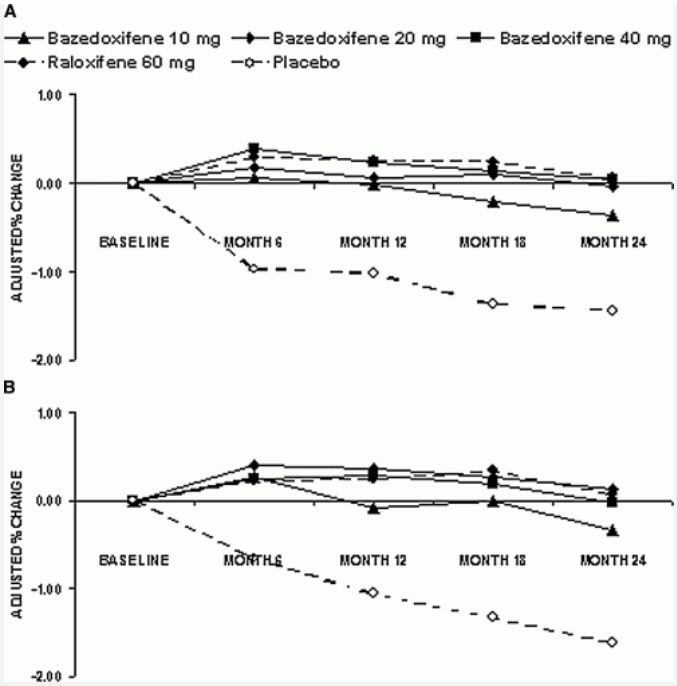


Fig. 9.3.113a (A) Median percent change from baseline in BMD of the lumbar spine (corrected L1-L4; p<0.001) vs. placebo for all bazedoxifene (BZA) groups at each time point. (B) Median percent change from baseline in total hip BMD (p<0.001) vs. placebo for all bazedoxifene (BZA) groups at each time point. Reproduced from J Bone Miner Res 2008;23:525-35 with permission of the American Society of Bone and Mineral Research.

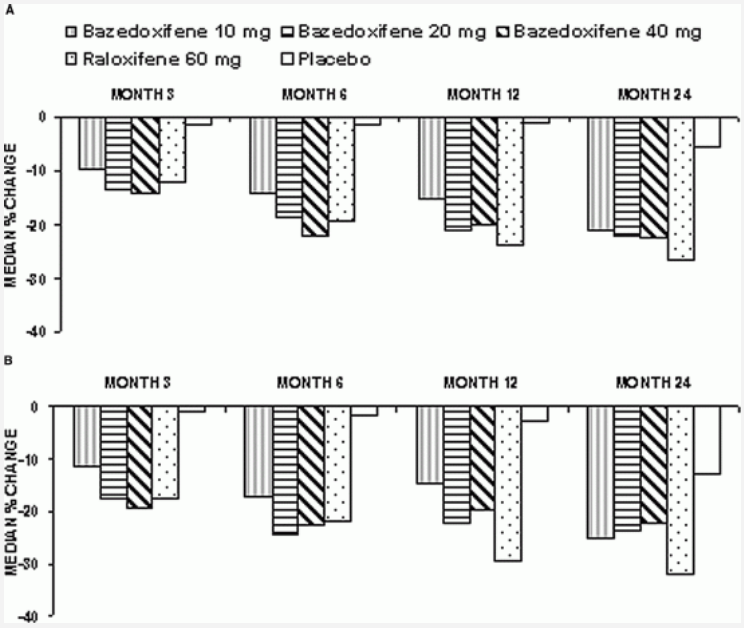


Fig. 9.3.113b (A) Median percent change from baseline in osteocalcin levels (p<0.001), all bazedoxifene and raloxifene treatment groups vs. baseline at all time points; placebo vs. baseline at 24 mo; and all bazedoxifene treatment groups vs. placebo at all time points. (B) Median percent change from baseline in CTX levels (p<0.001), all bazedoxifene and raloxifene treatment groups vs. baseline at all time points; placebo vs. baseline at 24 mo; and all bazedoxifene treatment groups vs. placebo at all time points. Nonparametric ANCOVA. Reproduced from J Bone Miner Res 2008;23:525-35 with permission of the American Society of Bone and Mineral Research.

9.3.114 Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: The DAWN trial

von Muhlen D, Laughlin GA, Kritz-Silverstein D, Bergstrom J, Bettencourt R

Osteoporos Int 2008;19:699-707

In 225 healthy adults aged 55-85 years, DHEA increased serum DHEA and DHEA sulfate levels to concentrations seen in young adults. Testosterone, estradiol and insulin-like growth factor (IGF-1) levels increased in women (all p<0.001), but not men, receiving DHEA. Serum C-terminal telopeptide of type 1 collagen levels decreased in women (p=0.03), but not men, whereas bone-specific alkaline phosphatase levels were not altered. After 12 months, there was a positive effect of DHEA on lumbar spine BMD in women (p=0.03), not hip, femoral neck or total body BMD, and no changes were observed at any site among men. DHEA has a modest and selective beneficial effect on BMD and bone resorption in women, but provides no bone benefit for men.

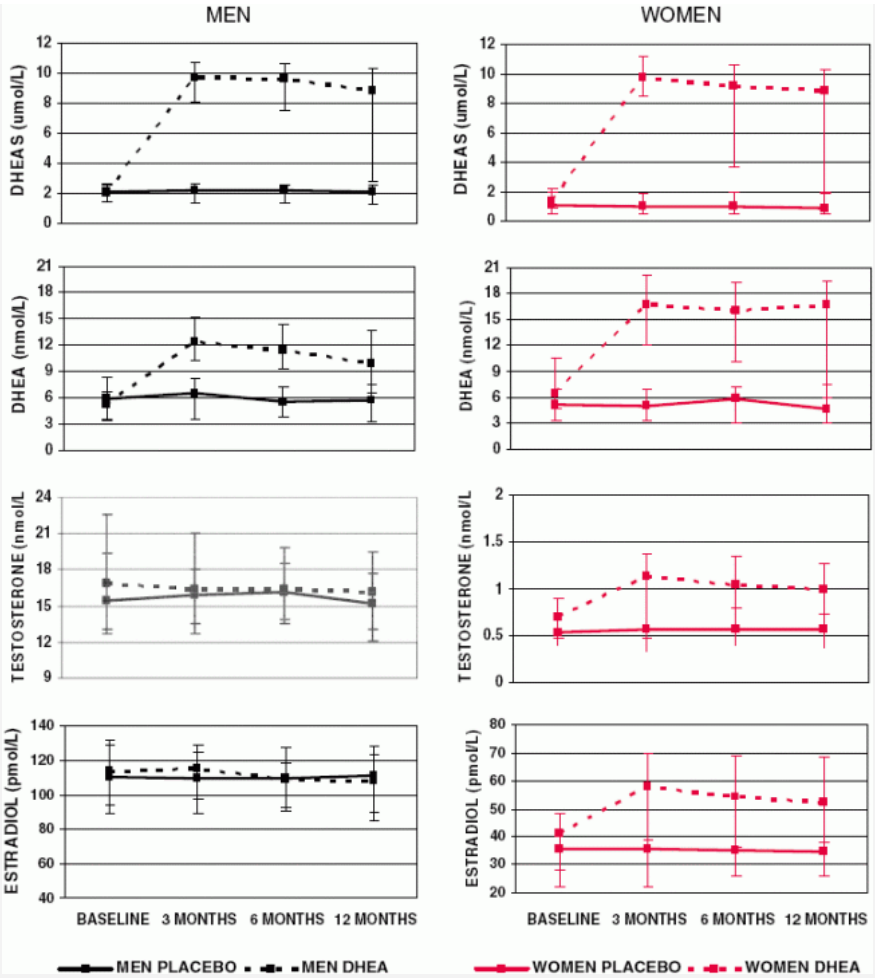


Fig. 9.3.114 Mean (median) and 95%CI (inter-quartile range) for steroids at baseline and follow-up visits, by sex and treatment group. Reproduced from Osteoporosis Int 2008;19:699-707 with permission from Springer.

9.3.115 Randomized trial of once-weekly PTH(1-84) on bone mineral density and remodeling
Black DM, Bouxsein ML, Palermo L, McGowan JA, Newitt D, Rosen E, Majumdar S, Rosen CJ
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Fifty postmenopausal women with femoral neck BMD T-score between -1.0 and -2.0 received daily PTH(1-84) (100 µg) or placebo for one month then weekly injections (PTH or placebo) for 11 months. At 12 months, spine aBMD increased 2.1% in PTH-treated women (p=0.03). Vertebral trabecular vBMD increased 3.8% in PTH-treated (p=0.08). PTH-treated women had higher distal radial trabecular bone volume, number, and thickness (p<0.04). After one month of daily PTH, PINP increased (p<0.0001). Bone resorption indices were unchanged in PTH-treated women and were reduced in placebo group.

9.3.116 Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: A twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial
Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, van der Heijde D, Zhou L, Tsuji W, Newmark R
Arthritis Rheum 2008;58:1299-309

RA patients received subcutaneous placebo (n=75), denosumab 60 or 180 mg injections 6 mthly for 12 months. At 6 months, the increase in the MRI erosion score from baseline was lower in the 60-mg group (mean change 0.13; P=0.118) and 180 mg group (mean change 0.06; P=0.007) than placebo (mean change 1.75). A difference in the modified Sharp erosion score was observed at 6 months in the 180 mg group (P=0.019) compared with placebo, and at 12 months, both the 60 mg (P=0.012) and the 180 mg (P=0.007) groups were different from the placebo. There was no effect on joint space narrowing or RA disease activity. Addition of twice-yearly injections of denosumab to methotrexate inhibited structural damage in patients with RA for up to 12 months.

9.3.117 Pharmacokinetics of a single, large dose of cholecalciferol
Ilahi M, Armas LA, Heaney RP
Am J Clin Nutr 2008;87:688-91

Thirty subjects were supplemented with a single oral dose of 100,000 IU cholecalciferol. A second group (10 subjects) served as a control group. Serum calcidiol rose after dosing from a mean (±SD) baseline of 27.1±7.7 ng/mL to 42.0±9.1 ng/mL. Seven percent of the supplemented cohort failed to achieve 32.1 ng/mL at any time point. The highest achieved concentration in any subject was 64.2 ng/mL. Cholecalciferol (100,000 IU) is a safe, effective, and simple way to increase calcidiol concentrations. The dosing interval should be ≤2 mo to ensure continuous serum calcidiol concentrations above baseline.

9.3.118 Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study
Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT
Osteoporos Int 2008;19:673-9

In 76,507 postmenopausal Caucasian women, vitamin D intake was calculated from milk, fish, supplements and sunlight exposure. BMD was measured at the forearm, finger or heel. Approximately 3 years later, 36,209 participants returned a questionnaire about new fractures. Higher lifetime calcium intake was associated with reduced odds of osteoporosis (peripheral BMD T-score≤-2.5; OR=0.80; 95% CI 0.72, 0.88), as was a higher current calcium (OR=0.75; (0.68, 0.82)) or vitamin D intake (OR=0.73; 95% CI 0.0.66, 0.81). Women reported 2,205 new osteoporosis-related fractures. The 3-year risk of any fracture combined or separately was not associated with intake of calcium or vitamin D.

9.3.119 Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents
Chel V, Wijnhoven HA, Smit JH, Ooms M, Lips P
Osteoporos Int 2008;19:663-71

The effect of equivalent oral doses of vitamin D3 600 IU/day, 4200 IU/week and 18,000 IU/month on vitamin D status was compared in a randomized clinical trial in 10 nursing home residents. 338 subjects (76 male and 262 female), with a mean age of 84 (±SD 6.3 years received oral vitamin D3 600IU/d or 4200 IU/week, or 18,000 IU/month or placebo. After 4 months, calcium was added during 2 weeks, 320 mg/day or 640 mg/day or placebo. At baseline, mean 25(OH)D was 25.0 nmol/L (SD 10.9), and in 98%, it was lower than 50 nmol/L. After 4 months, mean serum 25(OH)D levels increased to daily 69.9 nmol/L, weekly 67.2 nmol/L and monthly 53.1 nmol/L, P<0.001 between groups). Median serum PTH levels decreased by 23% (p<0.001). Bone turnover markers did not decrease. Calcium had no effect on serum PTH and bone turnover. Daily vitamin D was more effective than weekly, and monthly administration was the least effective.

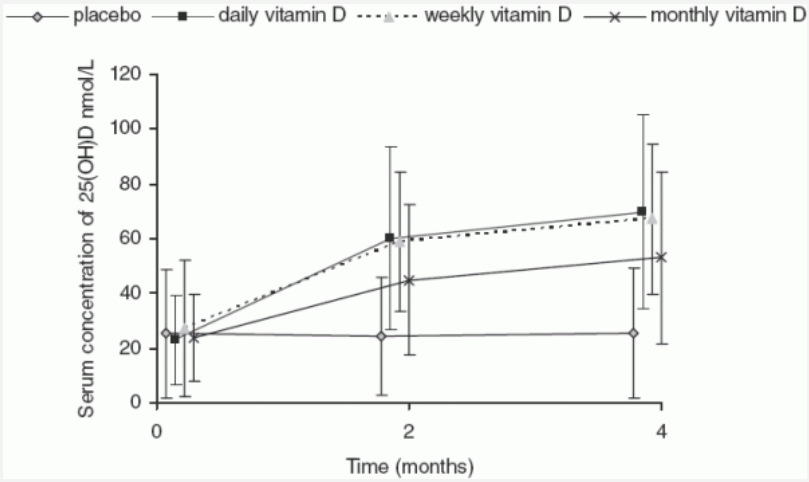


Fig. 9.3.119 Mean (±1.96×SD) serum 25(OH)D concentrations at baseline, 2 and 4 months during treatment with vitamin D daily, weekly, or monthly, or placebo. Reproduced from Osteoporosis Int 2008;19:663-71 with permission from Springer.

9.3.120 Calcium and vitamin D supplementation decreases incidence of stress fractures in female Navy recruits
Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R, Thompson K
J Bone Miner Res 2008;23:741-9

5201 female Navy recruit volunteers randomized to 2000 mg calcium and 800 IU vitamin D/d or placebo. 309 were diagnosed with a SFx (incidence 5.9% per 8 wk. Using intention-to-treat analysis calcium and vitamin D group had a 20% lower incidence of SFx than the control group (5.3% vs. 6.6%, respectively, p=0.0026 for Fisher's exact test). The per protocol analysis, including only the 3700 recruits found a 21% lower incidence of fractures in the supplemented vs. the controls (6.8% vs. 8.6%, respectively, p=0.02).

9.3.121 Association of activated vitamin D treatment and mortality in chronic kidney disease
Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K
Arch Intern Med 2008;168:397-403

Treatment of secondary hyperparathyroidism (SHPT) with activated vitamin D analogues is associated with better survival in patients receiving dialysis. In 520 male US veterans (mean [SD] age, 69.8 [10.3] years; 23.5% black) with CKD stages 3-5 and not yet receiving dialysis (mean [SD] estimated glomerular filtration rate, 30.8 [11.3]), 258 of 520 subjects received calcitriol, 0.25-0.5 µg/d, for a median duration of 2.1 years (range, 0.06-6.0 years). The incidence rate ratios for mortality and combined death and dialysis initiation were significantly lower in treated vs untreated patients (P<0.001 for both in the fully adjusted models). Treatment with calcitriol was associated with a trend toward a lower incidence of dialysis. Treatment with calcitriol appears to be associated with greater survival in patients with CKD not yet receiving dialysis.

9.3.122 The cost-effectiveness of the treatment of high risk women with osteoporosis, hypertension and hyperlipidaemia in Sweden
Zethraeus N, Strom O, Borgstrom F, Kanis JA, Jonsson B
Osteoporos Int 2008;19:819-27

This paper assessed the cost-effectiveness of the treatment of high risk women with osteoporosis, hypertension and hyperlipidaemia in Sweden. Compared to no intervention, a 5-year treatment of osteoporosis, hypertension, and hyperlipidaemia, is cost effective for most of the assessed high risk female populations. The cost per gained quality adjusted life year (QALY) for the treatment of a 70-year-old woman never exceeded SEK 330,000 (US$44,000).

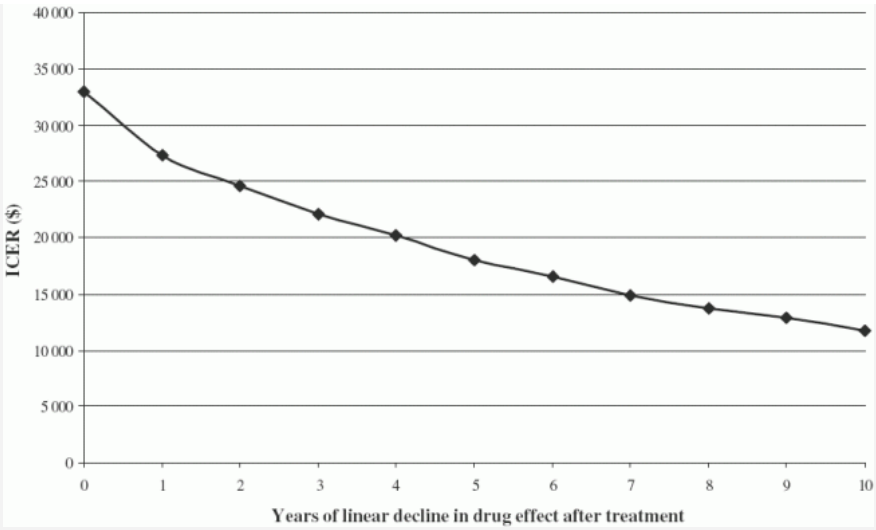


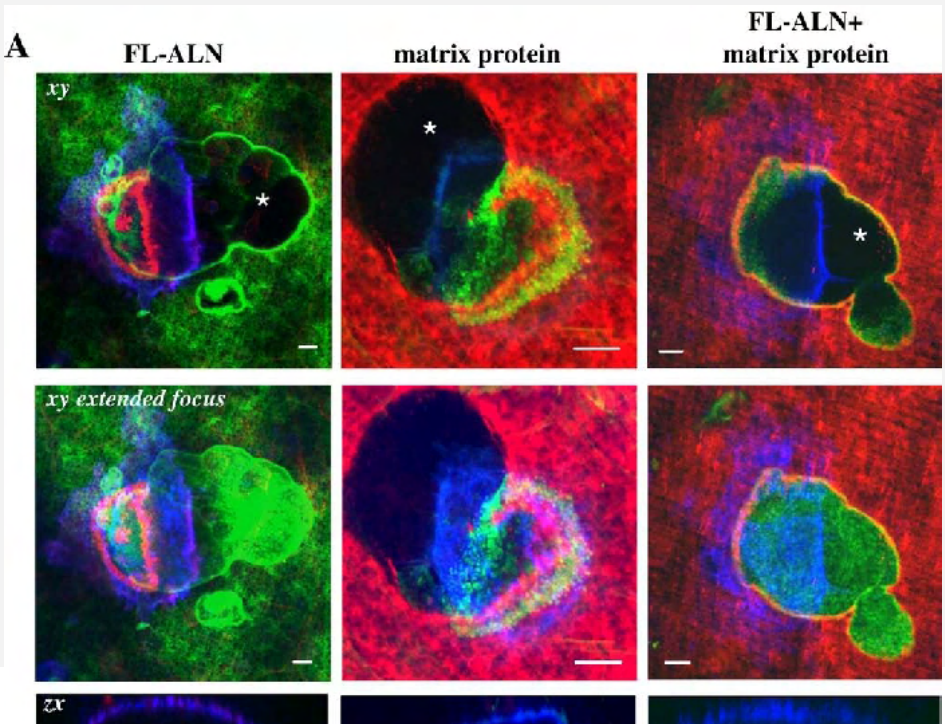
Fig. 9.3.122 Sensitivity analysis of residual effect on the incremental cost-effectiveness ratio (ICER) after stopping treatment in 70 years old women with T-score -2.5 and a previous vertebral fracture. Reproduced from Osteoporos Int 2008;19:819-27 with permission from Springer.

9.3.123 Effects of treatment with parathyroid hormone 1-84 on quantity and biomechanical properties of thoracic vertebral trabecular bone in ovariectomized rhesus monkeys
Fox J, Newman MK, Turner CH, Guldberg RE, Varela A, Smith SY
Calcif Tissue Int 2008;82:212-20

At baseline, 9 months after surgery, BMD at T9-T12 was 7% lower in OVX than in sham animals. All PTH(1-84) doses increased BMD to sham levels within 7 months. Micro-computed tomography of T10 vertebrae showed that trabecular bone volume and connectivity were higher in PTH(1-84) treated animals than in sham controls, through a greater trabecular number. Peripheral quantitative computed tomography from T11 and T12 confirmed that PTH(1-84) increased BMD. Compression testing of the cores showed that PTH(1-84) increased stiffness, modulus, yield load, and yield stress to levels greater than in sham, with the largest effect in the 10 µg/kg group (35-54% greater than in OVX controls). Thus, PTH(1-84) increased BMD and the biomechanical properties of trabecular bone at the thoracic spine of OVX rhesus monkeys. The 10 µg/kg dose produced the greatest effect on trabecular strength, possibly because the highest dose stimulated bone remodeling excessively.

9.3.124 Visualizing mineral binding and uptake of bisphosphonate by osteoclasts and non-resorbing cells
Coxon FP, Thompson K, Roelofs AJ, Ebetino FH, Rogers MJ
Bone 2008;42:848-60

Bisphosphonates (BPs) target bone due to their high affinity for calcium ions. During resorption, these drugs are released from the acidified bone surface and taken up by osteoclasts, where they inhibit prenylation. Fluorescently labelled alendronate analogue (FL-ALN), was internalized from solution or from the surface of dentine by osteoclasts into intracellular vesicles. Unprenylated Rap1A accumulated to the same extent whether osteoclasts were cultured on RIS-coated dentine or with RIS in solution. J774 macrophages internalised FL-ALN and RIS from solution but took up little from dentine, due to their inability to resorb mineral. Calvarial osteoblasts and MCF-7 tumour cells internalized less FL-ALN and RIS, both from solution and from the surface of dentine. The viability of J774 and MCF-7 cells was reduced when cultured with RIS in solution, but not when cultured on dentine precoated with RIS. When J774 macrophages were cocultured with rabbit osteoclasts, J774 cells that were adjacent to resorbing osteoclasts frequently internalized more FL-ALN than J774 cells more distant from osteoclasts. This was possibly a result of increased availability of BP to these J774 cells due to transcytosis through osteoclasts, since FL-ALN partially colocalized with trancytosed, resorbed matrix protein within osteoclasts. In addition, J774 cells occupying resorption pits internalized more FL-ALN than those on unresorbed surfaces.



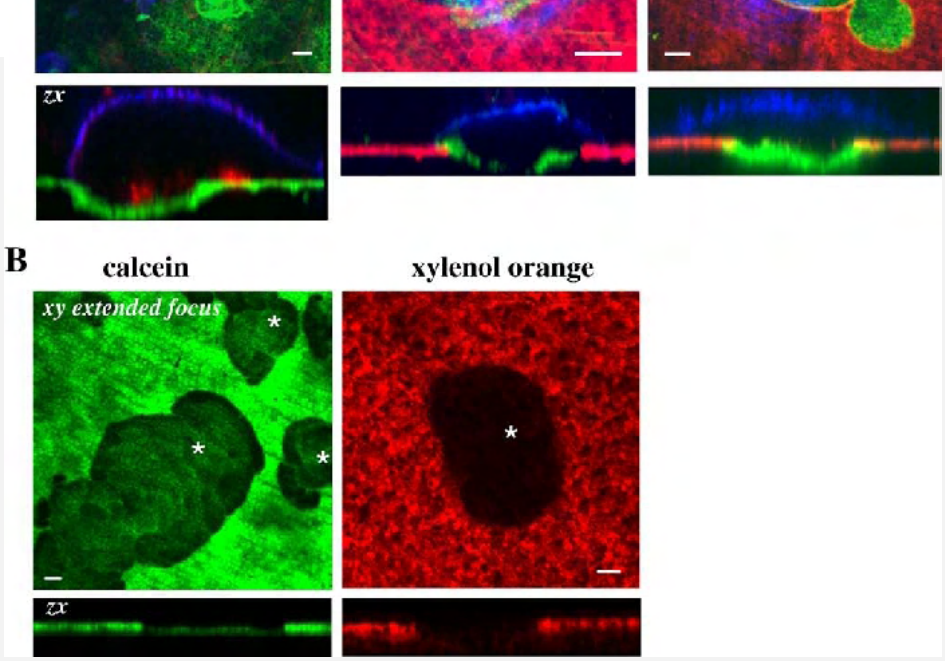


Fig. 9.3.124a Binding and 'recycling' of FL-ALN to the surface of dentine. (A) Rabbit osteoclasts were seeded onto dentine discs that had been pre-coated with FL-ALN (left column; shown in green) or the matrix protein labelled with TAMRA (middle column; shown in red), or labelled with both TAMRA and FL-ALN (right column). Cells were cultured for 18 h, then washed, fixed in 4% formaldehyde, and immunostained for VNR (shown in blue). Actin rings of osteoclasts cultured on FL-ALN or TAMRA coated dentine were also visualized using TRITC-phalloidin (shown in red in left column) or FITC-phalloidin (shown in green in middle column), respectively. Osteoclasts were examined by laser scanning confocal microscopy. Images in upper panels are xy images (3 µm depth) at the surface of the dentine, resorption pits identified by asterisks; images in middle panels are extended focus images of the same osteoclasts from the top of the cell to the bottom of the resorption pit; images in lower panels are zx sections of the same osteoclasts. The detector gain was optimised for the intense fluorescence from the FL-ALN and TAMRA bound to the surface of the dentine, at which no intracellular FL-ALN or TAMRA could be seen. (B) Rabbit osteoclasts were seeded onto dentine discs that had been precoated with calcein or xylenol orange, then cultured as in (A). Upper panels are extended focus images from the dentine surface to the bottom of the resorption pits (identified by asterisks); lower panels show zx sections through the same area of dentine. Note that osteoclasts are not stained in these images. Bar=10 µm. Reproduced from Bone, 42:848-60, Copyright (2008), with permission from Elsevier.

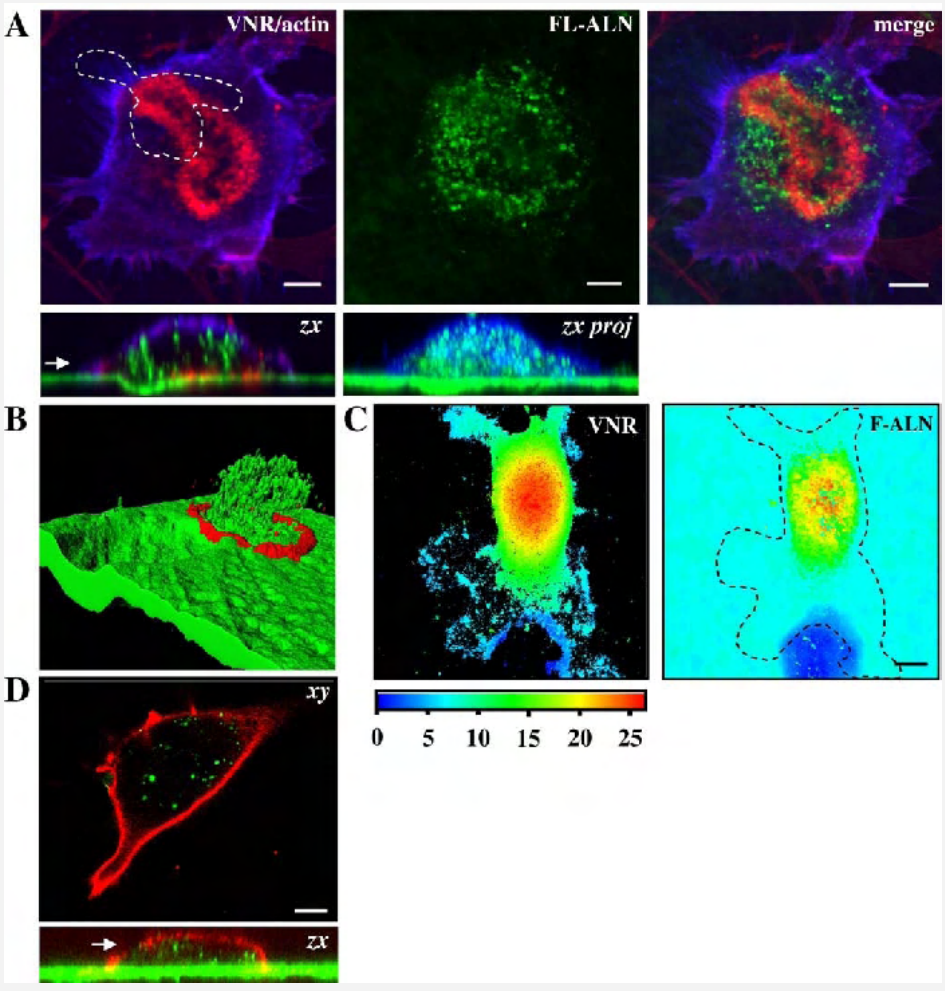


Fig. 9.3.124b Uptake of FL-ALN from dentine by rabbit osteoclasts. Rabbit osteoclasts were cultured for 24 h on dentine slices that had been pre-coated with 100 µM FLALN (green). Cells were then washed, fixed in 4% formaldehyde, and counterstained before examining by laser scanning confocal microscopy. (A) Resorbing osteoclast identified by immunostaining for the VNR (blue). F-actin was visualized by staining with TRITC-phalloidin (red). Left: VNR/actin staining shown in a 3 µm extended focus xy image at the level of the dentine surface; middle: FL-ALN shown in a 1 µm optical section 3 µm above the dentine surface, as indicated by the arrow in the zx reconstruction image (below); right: Merged image showing intracellular punctate localisation of FL-ALN. zx proj shows the sum of the internalised FL-ALN in the cell, compared to a 1 µm optical section in the zx image. (B) Isosurface rendered image generated from a z series of a resorbing osteoclast. F-actin was stained with TRITC-phalloidin (red). Note

the extensive accumulation of FL-ALN within the resorbing osteoclast above the actin ring. The resorption pit can also be clearly seen adjacent to the osteoclast. For clarity, VNR staining of the osteoclast was omitted from the image. (C) Depth-coded image of a resorbing osteoclast showing the spatial orientation of FL-ALN containing vesicles within the cell (right panel) and the basolateral surface of the osteoclast by staining for VNR (left panel). Coloured scale represents distance (height; µm) from the bottom of the resorption pit; dashed line indicates the outline of the osteoclast. Note that the vesicles are distributed throughout the depth of the cell. (D) 1 µm optical sections in the xy and zx planes of a non-resorbing osteoclast, stained for VNR (red). Note the lack of resorption pit and reduced FL-ALN uptake compared to the resorbing osteoclast in (A). The data shown are representative of six independent experiments. Reproduced from Bone, 42:848-60, Copyright (2008), with permission from Elsevier.

9.3.125 Bone degeneration and recovery after early and late bisphosphonate treatment of ovariectomized wistar rats assessed by in vivo micro-computed tomography

Brouwers JE, Lambers FM, Gasser JA, van Rietbergen B, Huiskes R

Calcif Tissue Int 2008;82:202-11

Twenty-nine female Wistar rats were ovx (OVX, n=5), OVX and given zoledronic acid (ZOL) at week 0 (n=8), OVX and ZOL at week 8 (n=7), and sham (n=9). At week 16, all groups were different in BV/TV, connectivity density, and trabecular number (Tb.N), except for the early ZOL and control groups which were not. After ZOL at week 8, BV/TV, structure model index, Tb.N, and trabecular thickness improved in the late ZOL group. The OVX and ZOL groups showed, respectively, higher and lower bone formation rates than the control group. Early ZOL inhibited all bone microstructural changes seen after OVX. Late ZOL improved bone microstructure, although the structure did not recover to original levels. Early ZOL resulted in a better microstructure than late treatment. However, late treatment was still better than no treatment.

9.3.126 Long-term protective effects of zoledronic acid on cancellous and cortical bone in the ovariectomized rat

Gasser JA, Ingold P, Venturiere A, Shen V, Green JR

J Bone Miner Res 2008;23:544-51

Once yearly ZOL 5 mg increases BMD and reduce fracture rate in postmenopausal women with low BMD. Female Wistar rats (10 per group) received single intravenous doses of ZOL 0.8, 4, 20, 100, or 500 µg/kg, alendronate 200 µg/kg, or isotonic saline 4 days before bilateral ovariectomy. Mass and density of cancellous and cortical bone (pQCT) were measured at 4-wk intervals for 32 wk. Bone architecture (µCT), bone formation and strength in compression were assessed at 32 wk. Ovariectomy-associated BMD loss was attenuated for 32 wk by ZOL≥4 µg/kg for total BMD, ZOL≥20 µg/kg for cortical BMD, and ZOL≥4 µg/kg for cancellous BMD. Alendronate 200 µg/kg was of equivalent potency to ZOL 20 µg/kg. Ovariectomy-associated decreases in trabecular architectural parameters were dose-dependently attenuated by ZOL. Alendronate 200 µg/kg was equivalent to ZOL 20 µg/kg. The bone resorption marker TRACP5b indicated transient suppression of elevated osteoclast activity by ZOL relative to OVX-rats even at the lowest dose of 0.8 µg/kg, whereas at 100-500 µg/kg, the effect was significant relative to the OVX control for the duration of the study of 32 wk. Bone formation parameters were not affected by ZOL 20 µg/kg but were reduced by ZOL 100-500 µg/kg. Alendronate 200 µg/kg was equivalent to ZOL 100 µg/kg. ZOL produced dose-related improvements in bone strength parameters after ovariectomy. Alendronate 200 µg/kg was of similar potency to ZOL 20 µg/kg. The duration and magnitude of the bone-protecting effect of a single intravenous dose of ZOL in ovariectomized rats is dose dependent and lasts for up to 32 wk. Compared with alendronate, ZOL shows 10-fold higher potency in preventing bone loss.

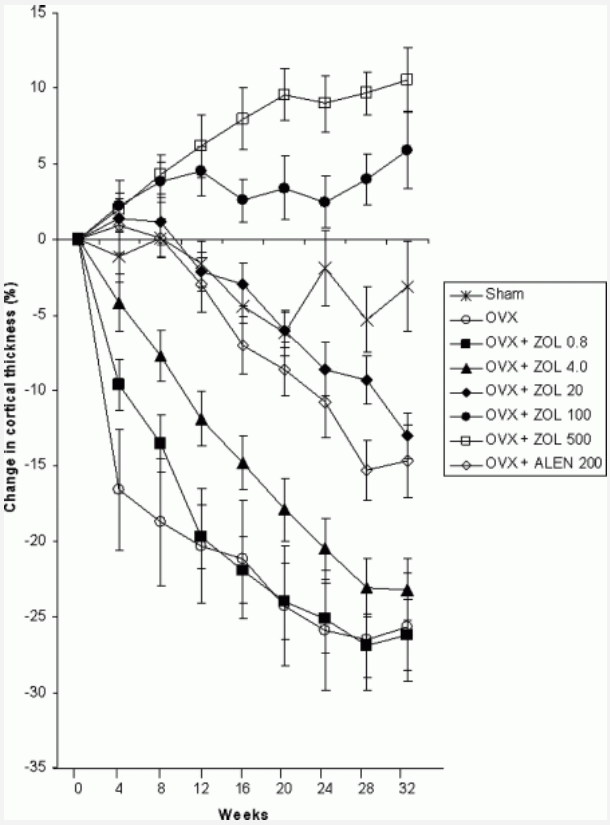


Fig. 9.3.126a Effect of zoledronic acid 0.8-500 µg/kg and alendronate 200 µg/kg on cortical thickness±SE in OVX rats as measured by qCT in the proximal tibia metaphysis. Sham, sham operated; OVX, ovariectomized; ZOL, zoledronic acid; ALEN, alendronate. Mean±SE; N=10 per group, except OVX (N=8). Reproduced from J Bone Miner Res 2008;23:544-51 with permission of the American Society of Bone and Mineral Research.

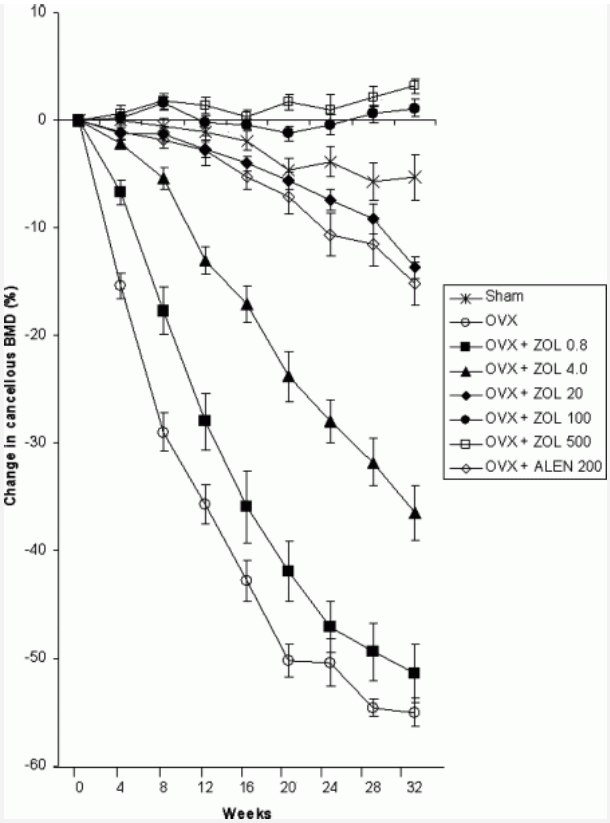


Fig. 9.3.126b Effect of zoledronic acid 0.8-500 µg/kg and alendronate 200 µg/kg on cancellous BMD±SE in OVX rats as measured by qCT in the proximal tibia metaphysis. Sham, sham operated; OVX, ovariectomized; ZOL, zoledronic acid; ALEN, alendronate. Mean±SE; N=10 per group, except OVX (N=8). Reproduced from J Bone Miner Res 2008;23:544-51 with permission of the American Society of Bone and Mineral Research.

9.3.127 Comparison of the effects of genistein and zoledronic acid on the bone loss in OPG-deficient mice

Liu J, Xu K, Wen G, Guo H, Li S, Wu X, Dai R, Sheng Z, Liao E

Bone 2008;42:950-9

OPG(-/-) mice were divided into: (1) genistein treated mice (Gen) (0.8 mg/day); (2) E(2) injected with 0.03 µg/day; (3) DMSO control mice (4) zoledronic acid treated mice (Zol) 150 µg/kg twice per week; and (5) H_2O control mice. Total BMD of the femur was not altered in the Gen, E(2), H_2O, and DMSO groups. The three-point bending test revealed no differences in the biomechanical parameters, and µCT analysis revealed that the microarchitectural parameters of the trabecular and cortical bone did not differ among the groups. Genistein and E(2) did not alter the serum TRACP-5b, B-ALP, or RANKL levels. However, in addition to increasing the bone mass, zoledronic acid improved biomechanical parameters and prevented deterioration of the architecture in the OPG(-/-) mice. The effects of genistein and E(2) on bone were lost in OPG-deficient mice, suggesting that the effect of these agents on bone metabolism seems to be entirely dependent on OPG. In contrast, zoledronic acid suppressed bone resorption and prevented the bone loss in the OPG(-/-) mice - an effect that is likely to be independent of the OPG pathway.

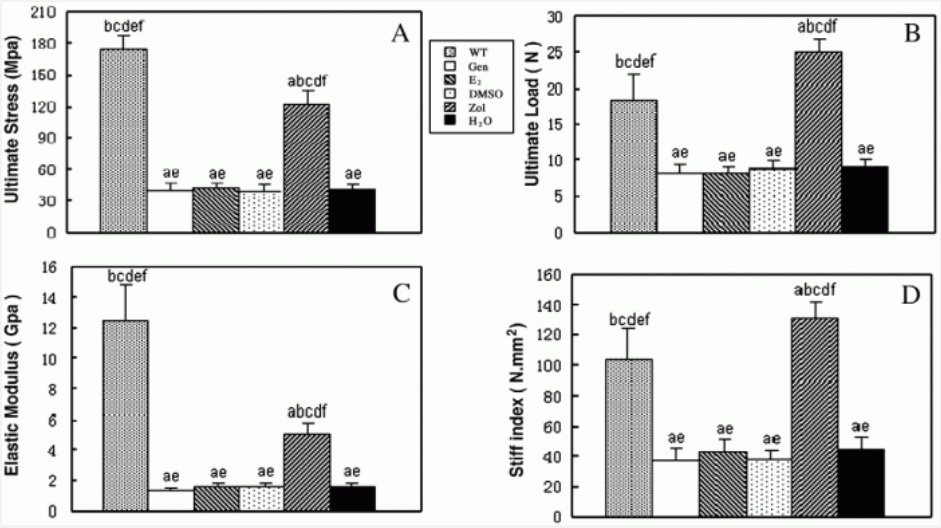


Fig. 9.3.127a Changes in the biomechanical parameters of the femur. A: Ultimate stress; B: Ultimate load; C: Elastic modulus; D: Stress index. The values are the means±SD; n=8. Significant differences (P<0.05) as compared to the [a]WT, [b]Gen, [c]E(2), [d]DMSO, [e]Zol, and [f]H_2O groups. Reproduced from Bone, 42:950-9, Copyright (2008), with permission from Elsevier.

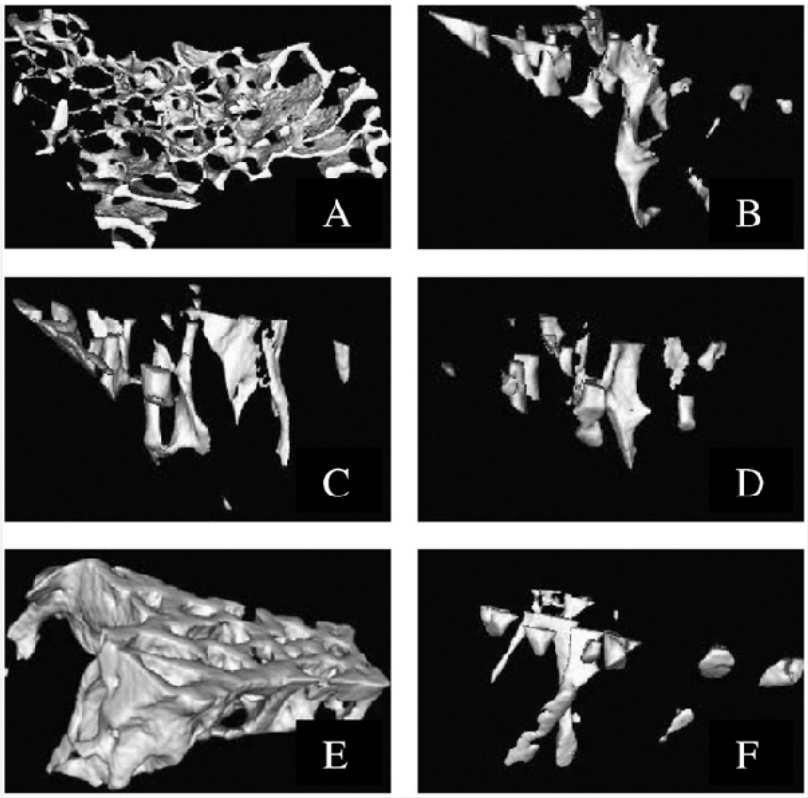


Fig. 9.3.127b Three-dimensional μCT images of the tibia trabecular. A: WT; B: Gen; C: E(2); D: DMSO; E: ZoL; F: H_2O. Reproduced from Bone, 42:950-9, Copyright (2008), with permission from Elsevier.

9.3.128 Aminobisphosphonates cause osteoblast apoptosis and inhibit bone nodule formation in vitro
Idris AI, Rojas J, Greig IR, Van't Hof RJ, Ralston SH
Calcif Tissue Int 2008;82:191-201

Pamidronate and alendronate inhibited osteoblast growth, caused osteoblast apoptosis, and inhibited protein prenylation in osteoblasts in a dose-dependent manner over the concentration range 20-100 μM. Further studies showed that alendronate in a dose of 0.1 mg/kg inhibited protein prenylation in calvarial osteoblasts in vivo, indicating that alendronate can be taken up by osteoblasts in sufficient amounts. Pamidronate and alendronate inhibited nodule formation at concentrations 10-fold lower than those required to inhibit osteoblast growth. These effects were not observed with nonnitrogen-containing bisphosphonates or with other inhibitors of protein prenylation and were only partially reversed by cotreatment with a 4-fold molar excess of ss-glycerol phosphate. Aminobisphosphonates cause osteoblast apoptosis in vitro at micromolar concentrations and inhibit osteoblast differentiation at nanomolar concentrations by mechanisms that are independent of effects on protein prenylation and may be due in part to inhibition of mineralization. Bisphosphonates exert inhibitory effects on cells of the osteoblast lineage at similar concentrations to those that cause osteoclast inhibition.

9.3.129 Comparative effects of 17beta-estradiol, raloxifene and genistein on bone 3D microarchitecture and volumetric bone mineral density in the ovariectomized mice
Cano A, Dapia S, Noguera I, Pineda B, Hermenegildo C, Del Val R, Caeiro JR, Garcia-Perez MA
Osteoporos Int 2008;19:793-800

Twelve-week-old female C57BL/6 mice were assigned to (1) SHAM-operated + vehicle; (2) OVX+vehicle; (3) OVX+17β-estradiol (5 μg/kg); (4) OVX+raloxifene (1 mg/kg); (5) OVX+genistein (25 mg/kg), during 4-weeks. Raloxifene maintained microarchitecture and vBMD, estradiol prevented deterioration of trabecular thickness (Tb.Th), trabecular bone pattern factor (Tb.Pf), and cortical periosteal perimeter (Ct.Pe.Pm), but did not completely block the loss in vBMD. Mice treated with genistein preserved only cross-sectional bone area (B.Ar) and Ct.Pe.Pm in cortical bone.

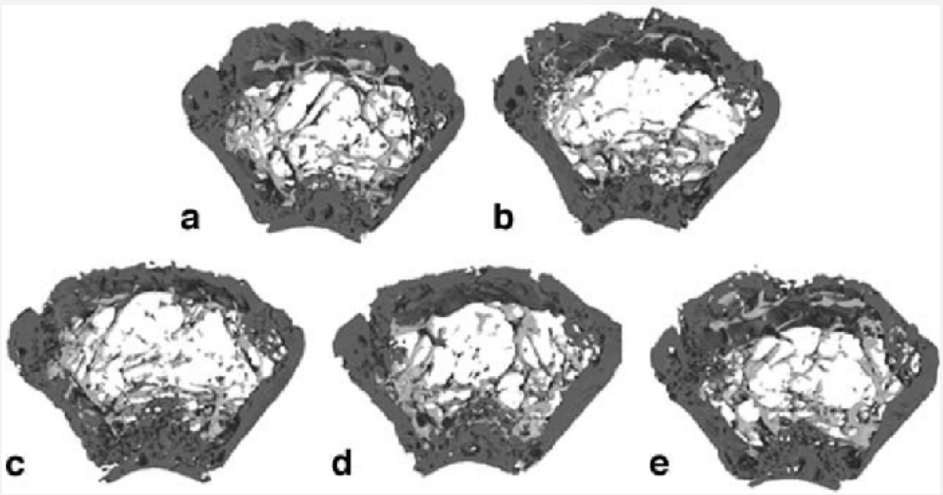


Fig. 9.3.129 3D trabecular microarchitectural images of distal mouse femora by means of µCT. a) SHAM group. b) OVX group at 4 weeks postsurgery. c) E2 group after 4 weeks of estradiol treatment d) RAL group after 4 weeks of raloxifene treatment. e) GEN group after 4 weeks of genistein treatment. Reproduced from Osteoporos Int 20008;19:793-800 with permission from Springer.

9.3.130 RANKL inhibition with osteoprotegerin increases bone strength by improving cortical and trabecular bone architecture in ovariectomized rats

Ominsky MS, Li X, Asuncion FJ, Barrero M, Warmington KS, Dwyer D, Stolina M, Geng Z, Grisanti M, Tan HL, Corbin T, McCabe J, Simonet WS, Ke HZ, Kostenuik PJ

J Bone Miner Res 2008;23:672-82

Rats were OVX at 3 mo of age and treated with Veh or human OPG-Fc (10 mg/kg, 2/wk). OVX was associated with greater serum RANKL and osteoclast surface and with reduced areal and volumetric BMD. OPG reduced osteoclast surface and serum TRACP5b while preventing OVX-associated bone loss. Vertebrae from OPG-treated rats had increased dry and ash weight, with no differences in tissue mineralization versus OVX controls. µCT showed trabeculae in OVX-OPG rats had greater bone volume fraction, vBMD, bone area, trabecular thickness, and number, whereas their cortical compartments had greater bone area. OPG improved cortical area in L(5) and the femur neck to levels that were greater than OVX or sham controls ($p<0.05$). Biomechanical testing of L5 and femur necks showed greater maximum load values in the OVX-OPG group ($p<0.05$ vs. OVX-Veh). Bone strength at both sites was linearly correlated with total bone area ($r(2)=0.54-0.74$, $p<0.0001$), which was also increased by OPG ($p<0.05$ vs. OVX).

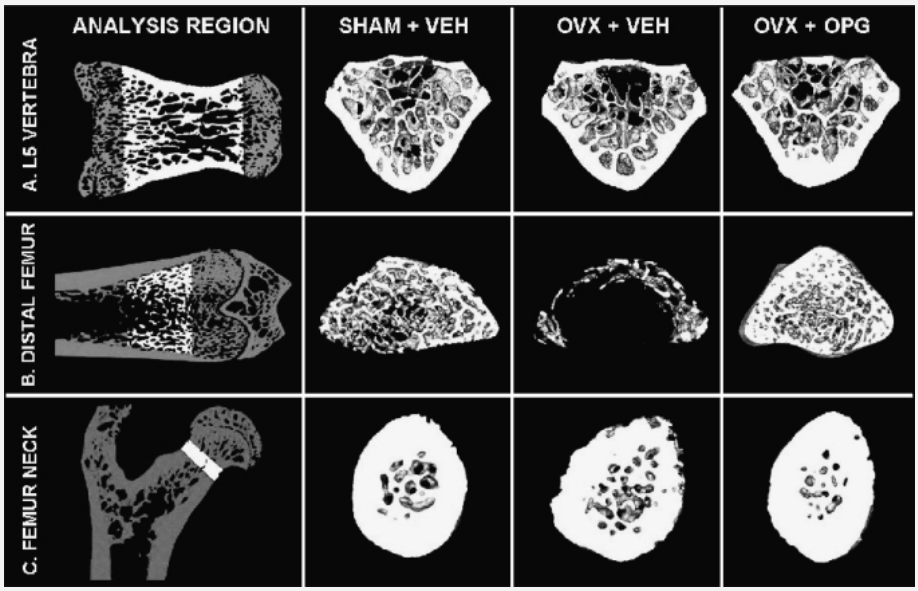


Fig. 9.3.130a Representative µCT images of the (A) fifth lumbar vertebra, (B) distal femur, and (C) femur neck. Vertebral and distal femur images were selected based on the median total bone area and trabecular bone volume fraction values, respectively, with a threshold of 500 mg-HA/cm^3. Femur neck images were selected based on the median total bone area for each group, with a threshold of 750 mg-HA/cm^3. The panels on the left highlight the region of analysis for each site in a frontal section. The remaining panels are representative cross-sectional 3D images of each site. For L_5 vertebra and distal femur, a central 1-mm region was rendered for clarity, whereas the entire 0.35-mm region is shown for the femur neck. Reproduced from J Bone Miner Res 2008;23:672-82 with permission of the American Society of Bone and Mineral Research.

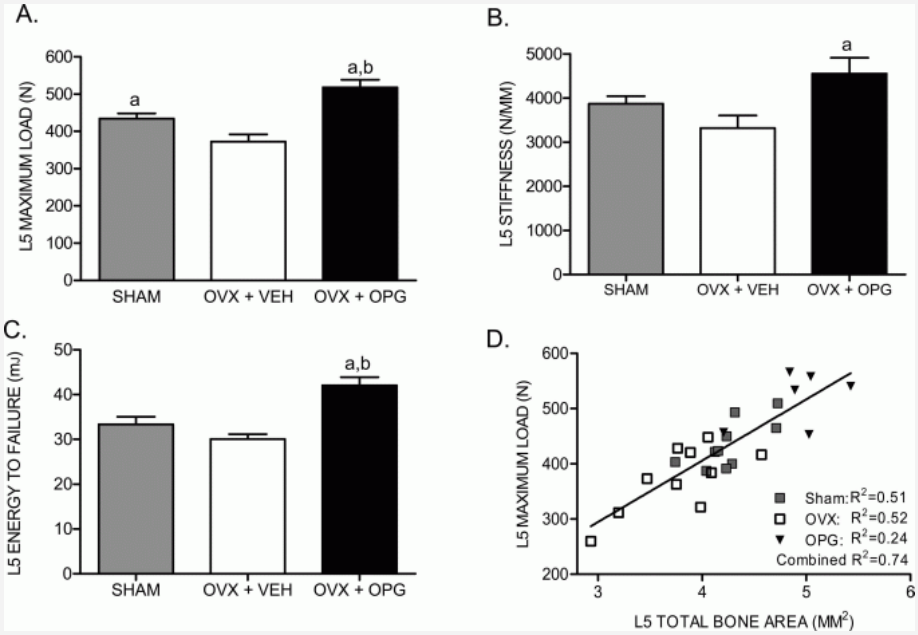


Fig. 9.3.130b Extrinsic bone strength parameters for the fifth lumbar vertebrae. (A-C) Vertebrae were obtained at the end of the 6-wk treatment and tested to failure by a compression test. Data represent means and SEs for 6-11 rats per group. [3a]Significantly different from OVX+Veh, $p<0.05$; [b]significantly different from sham control, $p<0.05$. (D) Regression analysis of total bone area of L_5 (cortical and cancellous) vs. maximum load of L_5 for all animals showed a correlation (r^2) of 0.74 ($p<0.0001$). Reproduced from J Bone Miner Res 2008;23:672-82 with permission of the American Society of Bone and Mineral Research.

9.3.131 Continuous PGE(2) leads to net bone loss while intermittent PGE(2) leads to net bone gain in lumbar vertebral bodies of adult female rats
Tian XY, Zhang Q, Zhao R, Setterberg RB, Zeng QQ, Iturria SJ, Ma YF, Jee WS
Bone 2008;42:914-20

Six months old female rats were divided into 6 groups with 2 control groups and 1 or 3 mg PGE(2)/kg given either continuously or intermittently for 21 days. Continuous PGE(2) led to bone catabolism while intermittent administration led to anabolism. Both routes stimulated bone remodeling, but the continuous PGE(2) stimulated more than the intermittent route to expose more basic multicellular units (BMUs) to the negative bone balance. The continuous PGE(2) caused cancellous bone loss by stimulating bone resorption greater than formation (i.e., negative bone balance) and shortening the formation period. It caused more cortical bone loss than gain, the magnitude of the negative endocortical bone balance and increased intracortical porosity bone loss was greater than for periosteal bone gain. The anabolic effects of intermittent PGE(2) resulted from cancellous bone gain by positive bone balance from stimulated bone formation and shortened resorption period; while cortical bone gain occurred from endocortical bone gain exceeding the decrease in periosteal bone and increased intracortical bone loss.

9.3.132 L -carnitine fumarate and isovaleryl-L -carnitine fumarate accelerate the recovery of bone volume/total volume ratio after experimetally induced osteoporosis in pregnant mice
Patano N, Mancini L, Settanni MP, Strippoli M, Brunetti G, Greco G, Tamma R, Vergari R, Sardelli F, Koverech A, Colucci S, Zallone A, Grano M
Calcif Tissue Int 2008;82:221-8

L -carnitine fumarate (LC) and isovaleryl-L -carnitine fumarate (Iso-V-LC), stimulated osteoblast proliferation and differentiation. Fifty-nine inbred adult female CD1 mice in pregnancy were assigned to (1) controls, mice fed a standard normocalcemic pre- and postpartal diet; (2) Hypo, mice fed a low calcium isocaloric prepartal diet and a standard postpartal diet; (3) LC, mice fed a group 2-type diet supplemented postpartum with LC; (4) Iso-V-LC, mice fed a group 2-type diet supplemented postpartum with Iso-V-LC. L3 and L4 vertebral bodies BV/TV and all osteoblast-based indexes were higher in LC and Iso-V-LC than in Hypo mice at each time point, and Iso-V-LC at the end of the treatment attained levels observed in controls. Iso-V-LC and, to a lesser extent, LC accelerated the recovery of normal BV/TV level after a hypocalcemic diet.

9.3.133 Greater first year effectiveness drives favorable cost-effectiveness of brand risedronate versus generic or brand alendronate: Modeled Canadian analysis
Grima DT, Papaioannou A, Thompson MF, Pasquale MK, Adachi JD
Osteoporos Int 2008;19:687-97

9.3.134 Effects of growth hormone administration on bone mineral metabolism, PTH sensitivity and PTH secretory rhythm in postmenopausal women with established osteoporosis
Joseph F, Ahmad AM, Ul-Haq M, Durham BH, Whittingham P, Fraser WD, Vora JP
J Bone Miner Res 2008;23:721-9

9.3.135 Stimulation of fracture-healing with systemic intermittent parathyroid hormone treatment
Barnes GL, Kakar S, Vora S, Morgan EF, Gerstenfeld LC, Einhorn TA
J Bone Joint Surg Am 2008;90 Suppl 1:120-7

9.3.136 Short-term and long-term safety of weekly high-dose vitamin D3 supplementation in school children
Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, El-Hajj Fuleihan G
J Clin Endocrinol Metab 2008;[Epub ahead of print]

9.3.137 Improving evaluation and treatment for osteoporosis following distal radial fractures: A prospective randomized intervention
Rozental TD, Makhni EC, Day CS, Bouxsein ML
J Bone Joint Surg Am 2008;90:953-61

9.3.138 Enhanced gap filling and osteoconduction associated with alendronate-calcium phosphate-coated porous tantalum
Garbuz DS, Hu Y, Kim WY, Duan K, Masri BA, Oxland TR, Burt H, Wang R, Duncan CP
J Bone Joint Surg Am 2008;90:1090-100

9.3.139 Minimal invasive short posterior instrumentation plus balloon kyphoplasty with calcium phosphate for burst and severe compression lumbar fractures
Korovessis P, Hadjipavlou A, Repantis T
Spine 2008;33:658-67

9.3.140 Gene therapy applications for fracture healing
Carofino BC, Lieberman JR
J Bone Joint Surg Am 2008;90 Suppl 1:99-110

9.3.141 Bisphosphonate related osteonecrosis of the palate: Report of a case managed with free tissue transfer
Engroff SL, Coletti D
Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:580-2

9.3.142 Effects of long-term estrogen replacement therapy on bone turnover in periarticular tibial osteophytes in surgically postmenopausal cynomolgus monkeys

Olson EJ, Lindgren BR, Carlson CS

Bone 2008;42:907-13

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

Volume 9, Issue 3, 2008

Exercise

9.3.143 Influence of calcium intake and physical activity on proximal femur bone mass and structure among pre- and postmenopausal women: A 10-year prospective study
Uusi-Rasi K, Sievanen H, Pasanen M, Beck TJ, Kannus P
Calcif Tissue Int 2008;82:171-81

This 10-year follow-up evaluated the effect of physical activity and calcium intake on proximal femur bone mass (BMC) and structural indices (CSA and Z) and physical performance in 133 premenopausal and 134 postmenopausal women. Among premenopausal women, the femoral neck BMC was 3.8% and the trochanter BMC 6.7% greater in the physically active group. There was no difference between the Ca-intake groups. Among postmenopausal women, the mean femoral neck BMC was 4.2% greater in the Ca(+) group than in the Ca(-) group and 6.9% (2.2 to 11.8%) greater in the PA(+) group than in the PA (-) group. For trochanter BMC, the corresponding differences were 2.7% (-1.6 to 7.2%) and 5.5% (0.9 to 10.3%). The mean differences in CSA and Z were 3.8% (-0.9 to 8.7%) and 4.4% (-2.1 to 11.4%) in favor of the Ca(+) group and 6.8% (1.9 to 12.0%) and 9.6% (2.5 to 17.1%) in favor of the PA(+) group, respectively. Proximal femur BMC declined generally, but the initial differences between the physical activity and the calcium intake groups were maintained.

9.3.144 High impact exercise is more beneficial than dietary calcium for building bone strength in the growing rat skeleton
Welch JM, Turner CH, Devareddy L, Arjmandi BH, Weaver CM
Bone 2008;42:660-8

Forty growing F-344 female rats were fed diets containing either 100% (Ca(+); 0.5% Ca) or 40% (Ca(-); 0.2% Ca) of their requirements. Half was subjected to impacts. Freefall impact resulted in greater bone strength, cross-sectional moments of inertia, and endosteal and periosteal circumferences in the shaft. Ca(+) resulted in greater shaft vBMD not strength. In the bone ends, both Impact(+) and Ca(+) affected density and structure of cortical and trabecular bone but Impact(+) were more pervasive. In the proximal end, Impact(+) resulted in greater BV/TV in the trabecular greater trabecular thickness, and cortical thickness was greater due to a smaller endosteal circumference. Impact(+) exerted a compensatory effect on vBMD and BV/TV in Ca(-) rats at the proximal site. In Impact(-) rats only, Ca(+) resulted in greater total and cortical vBMD and BV/TV in the proximal ulna. Impact(+) and Ca(+) exerted additive effects on cortical bone area (BA) in the proximal ulna and on total BA, periosteal circumference, and trabecular vBMD in the distal ulna.

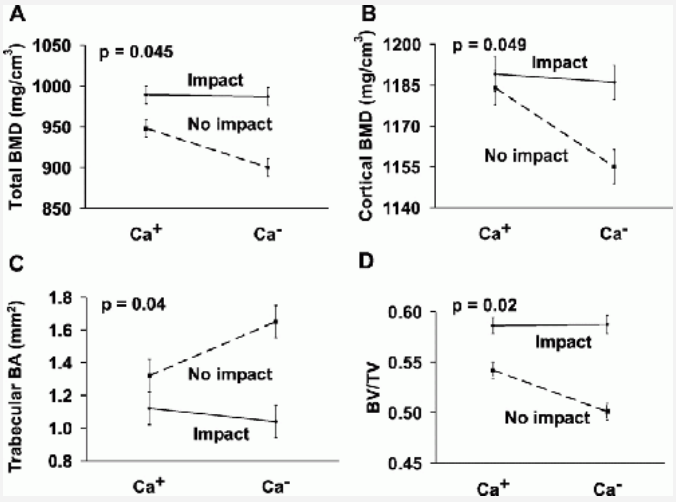


Fig. 9.3.144a Interactive effects of impact exercise and a low calcium diet on the proximal ulna of growing rats as measured by pQCT and μCT. A. Total BMD; B. Cortical BMD; C. Trabecular BA; D. BV/TV. The p-values represent the significance of the interaction between calcium and impact. Reproduced from Bone, 42:660-8, Copyright (2008), with permission from Elsevier.

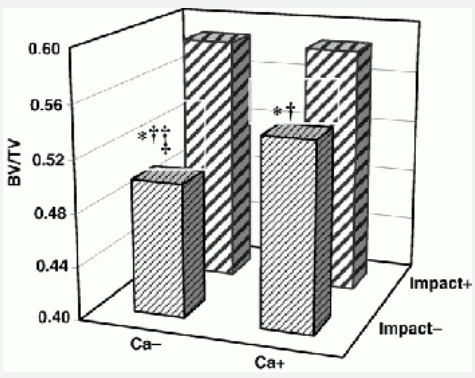


Fig. 9.3.144b Additive effects of impact exercise and a low calcium diet on the ulna in growing rats as measured by pQCT and μCT. A. Cortical BA in proximal site; B. Total BA in distal site; C. Periosteal circumference in distal site; D. Conn.D in proximal site. Additive effects are not interactive so no significant interactions were found. Reproduced from Bone, 42:660-8, Copyright (2008), with permission from Elsevier.

9.3.145 32 wk old C3H/HeJ mice actively respond to mechanical loading
Poliachik SL, Threet D, Srinivasan S, Gross TS
Bone 2008;42:653-9

C3H mice are mildly responsive to loading compared to C57. High baseline periosteal osteoblast activity in 16 wk C3H mice allowed to age until periosteal bone formation was equivalent to that of 16 wk C57 mice. The right tibiae of 32 wk old C3H mice and 16 wk old C57 mice were subjected to low magnitude rest-inserted loading (peak strain: 1235 muvarepsilon) and then exposing the right tibiae of 32 wk C3H mice to low (1085 muvarepsilon) or moderate (1875 muvarepsilon) magnitude cyclic loading showed that at 32 wk of age, C3H mice responded with elevated periosteal mineralizing surface, mineral apposition rate and bone formation compared to unloaded contralateral bones. The periosteal bone formation induced by low magnitude loading in C3H mice exceeded that induced in 16 wk C57 mice. At 32 wk of age, C3H mice also demonstrated an elevated response to increased magnitudes of cyclic loading. High level osteoblast function appears to overwhelm the ability of the tissue to respond loading. However, when basal surface osteoblast activity is equivalent to that of 16 wk C57 mice, C3H mice demonstrate a clear ability to respond to either rest-inserted or cyclic loading.

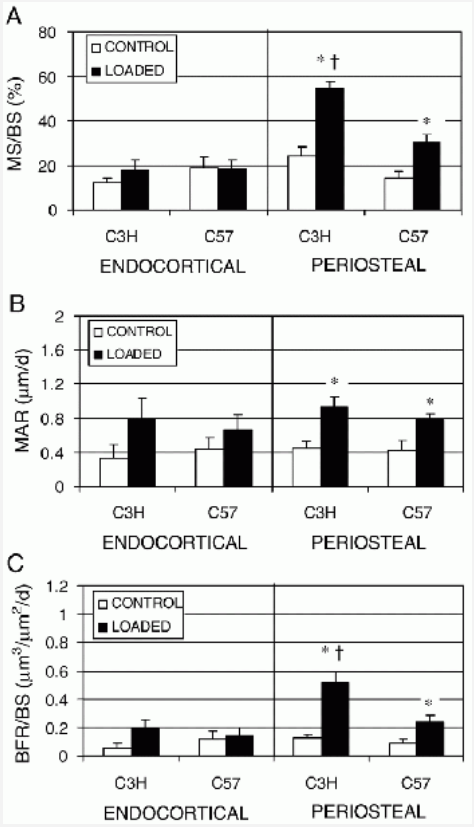
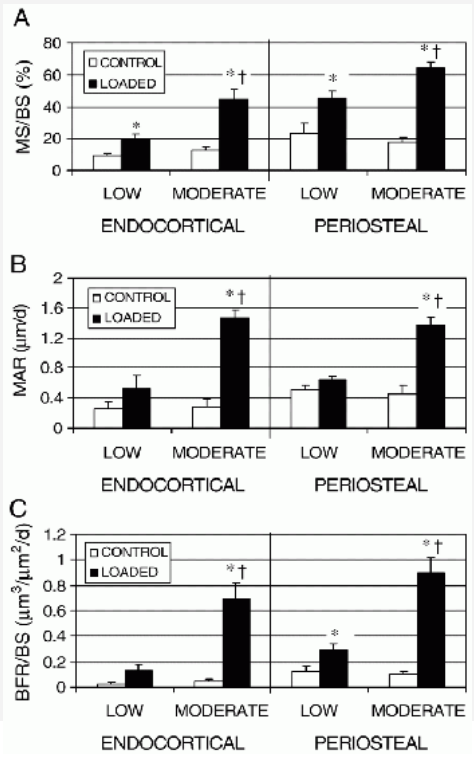


Fig. 9.3.145a Endocortical and periosteal (mean+SE)MS/BS (A), MAR(B) and BFR/BS (C) induced by rest-inserted loading in 16 wk C57 and 32 wk C3H mice. Peak periosteal normal strains were equivalent between groups. Response measures attaining significance are noted (: p<0.05, loaded tibiae vs. non-loaded contralateral tibiae; †: p<0.05, C3H vs. C57). Reproduced from Bone, 42:653-9, Copyright (2008), with permission from Elsevier.*



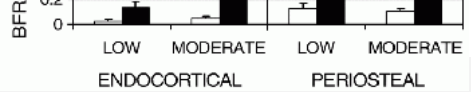


Fig. 9.3.145b Endocortical and periosteal (mean±SE) MS/BS (A), MAR (B) and BFR/BS (C) induced by cyclic mechanical loading of 32 wk C3H mice at peak periosteal strains of 1085 με (Low) and 1875 με (Moderate). Response measures attaining significance are noted (: p<0.05, loaded tibiae vs. non-loaded contralateral tibiae; †: p<0.05, Low vs. Moderate). Reproduced from Bone, 42:653-9, Copyright (2008), with permission from Elsevier.*

9.3.146 Bone mass is preserved and cancellous architecture altered due to cyclic loading of the mouse tibia after orchidectomy

Fritton JC, Myers ER, Wright TM, van der Meulen MC

J Bone Miner Res 2008;23:663-71

Ten-week-old male C57BL/6 mice had in vivo cyclic axial compressive loads applied to one tibia every day, 5 d/wk, for 6 wk after ORX or sham. Cyclic loading inhibited bone loss after ORX, maintaining absolute bone mass at age-matched sham levels. Relative to sham, ORX resulted in loss of cancellous bone volume (-78%) and trabecular number (-35%), increased trabecular separation (67%), no change in trabecular thickness, and smaller loss of diaphyseal cortical properties, consistent with other studies. Proximal cancellous bone volume fraction was greater with loading (ORX: 290%, sham: 68%) than in contralateral nonloaded tibias while trabeculae thickened with loading (ORX: 108%, sham: 48%). Dynamic cancellous bone histomorphometry indicated that loading was associated with greater mineral apposition rates (ORX: 32%, sham: 12%) and smaller percent mineralizing surfaces (ORX: -47%, sham: -39%) in the final week. Loading resulted in greater BMC (ORX: 21%, sham: 15%) and maximum moment of inertia (ORX: 39%, sham: 24%) at the cortical midshaft.

9.3.147 Ovariectomy sensitizes rat cortical bone to whole-body vibration

Rubinacci A, Marenzana M, Cavani F, Colasante F, Villa I, Willnecker J, Moro GL, Spreafico LP, Ferretti M, Guidobono F, Marotti G

Calcif Tissue Int 2008;82:316-26

Rats underwent whole-body vibration (20 minutes/day, 5 days/week) on a vibration platform for 2 months: a sham control (SHAM); a sham vibrated (SHAM-V) at 30 Hz, 0.6 g; a SHAM-V at 30 Hz, 3g; an ovariectomized control (OVX); an ovariectomized vibrated (OVX-V) at 30 Hz, 0.6 g; and an OVX-V at 30 Hz, 3g were studied. In the SHAM-V group, vibration had no effect. In the OVX-V group, vibration induced increasez compared to the OVX group of the cortical and medullary areas (P<0.01) and of the periosteal (P<0.01) and endosteal (P<0.05) perimeters at the 3 g vibration. The strain strength index increased in the OVX-V group (P<0.01) at the higher vibration. Low-amplitude, high-frequency whole-body vibration is anabolic to bone in OVX animals. The osteogenic potential is limited to the modeling of the bone cortex and depends on the amplitude of the vibration.

9.3.148 BMD decreases over the course of a year in competitive male cyclists

Barry DW, Kohrt WM

J Bone Miner Res 2008;23:484-91

9.3.149 Activation of extracellular-signal regulated kinase (ERK1/2) by fluid shear is Ca(2+)- and ATP-dependent in MC3T3-E1 osteoblasts

Liu D, Genetos DC, Shao Y, Geist DJ, Li J, Ke HZ, Turner CH, Duncan RL

Bone 2008;42:644-52

Volume 9, Issue 3, 2008

Men

9.3.150 Screening for osteoporosis in men: 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;148:680-4

The American College of Physicians recommends that clinicians (1) periodically perform individualized assessment of risk factors for osteoporosis in older men, (2) obtain dual-energy x-ray absorptiometry for men who are at increased risk for osteoporosis and are candidates for drug therapy, and (3) further research to evaluate osteoporosis screening tests in men.

9.3.151 Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline
Liu H, Paige NM, Goldzweig CL, Wong E, Zhou A, Suttorp MJ, Munjas B, Orwoll E, Shekelle P
Ann Intern Med 2008;148:685-701

To identify asymptomatic men who should receive BMD testing, meta-analysis of 167 studies evaluating risk factors for low BMD-related fracture in men and women found high-risk factors to be increased age (>70 years), low body weight (body mass index <20 to 25 kg/m^2), weight loss (>10%), physical inactivity, prolonged corticosteroid use, and previous osteoporotic fracture. At a T-score threshold of -1.0, calcaneal ultrasonography had a sensitivity of 75% and specificity of 66% for identifying DXA-determined osteoporosis (DXA T-score, -2.5). At a risk score threshold of -1, the Osteoporosis Self-Assessment Screening Tool had a sensitivity of 81% and specificity of 68% to identify DXA-determined osteoporosis. Key risk factors for low BMD-mediated fracture include increased age, low body weight, weight loss, physical inactivity, prolonged corticosteroid use, previous osteoporotic fracture, and androgen deprivation therapy. Non-DXA tests either are too insensitive or have insufficient data to reach conclusions.

9.3.152 The osteoporosis care gap in men with fragility fractures: The Canadian Multicentre Osteoporosis Study
Papaioannou A, Kennedy CC, Ioannidis G, Gao Y, Sawka AM, Goltzman D, Tenenhouse A, Pickard L, Olszynski WP, Davison KS, Kaiser S, Josse RG, Kreiger N, Hanley DA, Prior JC, Brown JP, Anastassiades T, Adachi JD
Osteoporos Int 2008;19:581-7

Between February 1996 and September 2002, 2,187 participants were followed. Diagnosis and treatment in men with clinical fragility fractures was low: at baseline and year five only 2.3% and 10.3% of men with a clinical fracture reported an osteoporosis diagnosis, respectively. At year five, 90% of men with a clinical fragility fracture were untreated. Hip fractures were the most commonly treated (37.5% by year five). A diagnosis of osteoporosis resulted in greater treatment: 67% of participants with diagnosed osteoporosis were treated with a bisphosphonate and 87% were taking calcium and/or vitamin D (year five).

9.3.153 Rate and circumstances of clinical vertebral fractures in older men
Freitas SS, Barrett-Connor E, Ensrud KE, Fink HA, Bauer DC, Cawthon PM, Lambert LC, Orwoll ES
Osteoporos Int 2008;19:615-23

5995 men aged ≥65 years followedfor an average of 4.7 years. One percent (n=61) sustained incident clinical vertebral fractures (2.2/1,000 person-years). The rate of fracture rose with age (0.7% in men 65-69 years and 5% ≥85 years). Fractured men were more likely frail (8.2% vs. 2.2%), more often fell (36.1% vs. 21%) and had lower total hip and lumbar spine BMD (all p values ≤0.002). In 73.8% of cases fractures were precipitated by no known trauma or by low-energy trauma, including falls in 57.3% Fractures were thoracic in 33% and lumbar in 56%. Men with an incident vertebral fracture were more likely to be osteoporotic (13% vs. 2%, p<0.0001), but most men with incident fractures did not have osteoporosis.

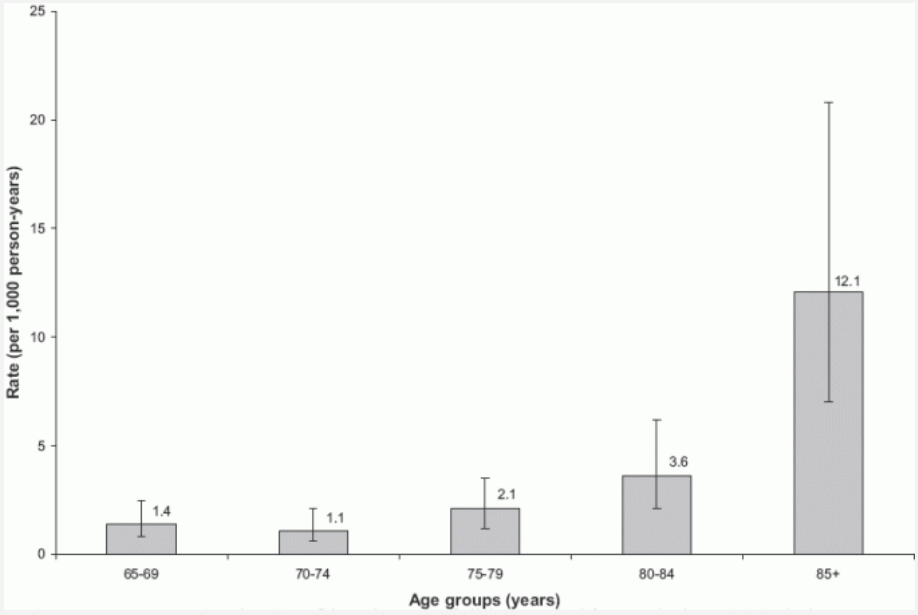


Fig. 9.3.153 Rates (per 1,000 person-years) and 95% confidence intervals of clinical vertebral fractures in the MrOS Study, by 5-year age categories. Reproduced from Osteoporosis Int 2008;19:615-623 with permission from Springer.

9.3.154 The skeletal benefits of calcium- and vitamin D3-fortified milk are sustained in older men after withdrawal of supplementation: An 18-mo follow-up study
Daly RM, Petrass N, Bass S, Nowson CA
Am J Clin Nutr 2008;87:771-7

In a 2-y randomized controlled trial, calcium- and vitamin D(3)-fortified milk slowed bone loss in older men. Withdrawal of the supplementation 109 men who completed a 2-y fortified milk trial and followed for 18 mo, the benefits on femoral neck and ultradistal radius BMD at the end of the intervention (1.8% and 1.5%, respectively; P<0.01 for both) were sustained. There were no lasting benefits at the lumbar spine.

9.3.155 Regulation of bone turnover by sex steroids in men
Sanyal A, Hoey KA, Modder UI, Lamsam JL, McCready LK, Peterson JM, Achenbach SJ, Oursler MJ, Khosla S
J Bone Miner Res 2008;23:705-14

59 men (median age, 69 yr) underwent suppression of sex steroids using a GnRH agonist and aromatase blocker and were replaced with testosterone (T; 5 mg/d) and estradiol (E; 37.5 μg/d) and randomized to sex steroid deficiency (-T, -E), E alone (-T, +E), T alone (+T, -E), or both (+T, +E) and restudied 3 wk later. Serum CTX and TRACP5b increased (by 71% and 15%, p<0.01 and p<0.001, respectively) in the -T, -E group despite a 60% suppression of serum FSH (p<0.001) by the GnRH agonist. E (but not T) prevented increases in serum CTx and TRACP. There was a trend (p=0.122) for E to suppress RANKL mRNA in marrow osteoblastic cells. Changes in mRNA for other cytokines (TNFα, interleukin (IL)-1α, IL-1β, IL-1ra, IFN-gamma) in marrow cells were not significant. E has greater suppressive effects on bone resorption than T, and increased bone resorption after sex steroid deficiency can occur independently of changes in FSH. E effects on bone resorption may be mediated by regulation of RANKL production by osteoblastic cells.

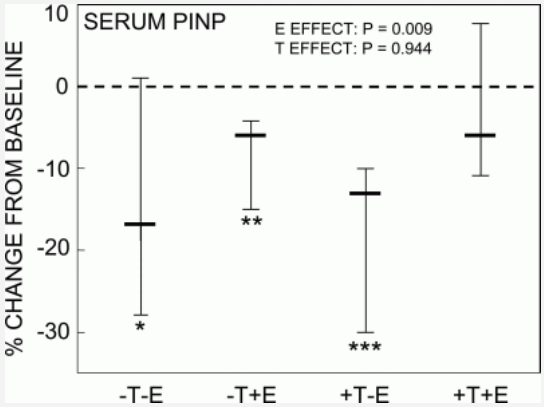


*Fig. 9.3.155 Percent change from baseline in serum PINP levels. **p<0.01, and ***p<0.001 for change from baseline. The overall effect of E and T on serum PINP levels was analyzed using the two-factor ANOVA model described in the Materials and Methods section. Shown are the medians and interquartile ranges. Reproduced from J Bone Miner Res 2008;23:705-14 with permission of the American Society of Bone and Mineral Research.*

9.3.156 Cortical bone loss in androgen-deficient aged male rats is mainly caused by increased endocortical bone remodeling
Reim NS, Breig B, Stahr K, Eberle J, Hoeflich A, Wolf E, Erben RG
J Bone Miner Res 2008;23:694-704

One hundred seventy 13-mo-old rats were ORX. 9-mo-old ORX rats were supplemented with testosterone undecanoate weekly 6 mg/kg for 4 mo. SHAM rats did not show age-related bone loss at the tibial diaphysis. pQCT analysis and bone histomorphometry showed cortical bone osteopenia in ORX rats, beginning from 2 mo after surgery. Androgen deficiency induced a decrease in periosteal bone formation but the reduction in total cross-sectional area reached significance only at 4 mo after surgery. The major mechanism for cortical bone loss was a expansion of the marrow cavity associated with an initial increase in endocortical eroded perimeter followed by a sustained increase in endocortical bone formation. All these changes were prevented by testosterone in an insulin-like growth factor system-independent fashion. Androgen deficiency-induced cortical bone loss in aged, nongrowing rats is mainly caused by augmented endocortical bone remodeling.

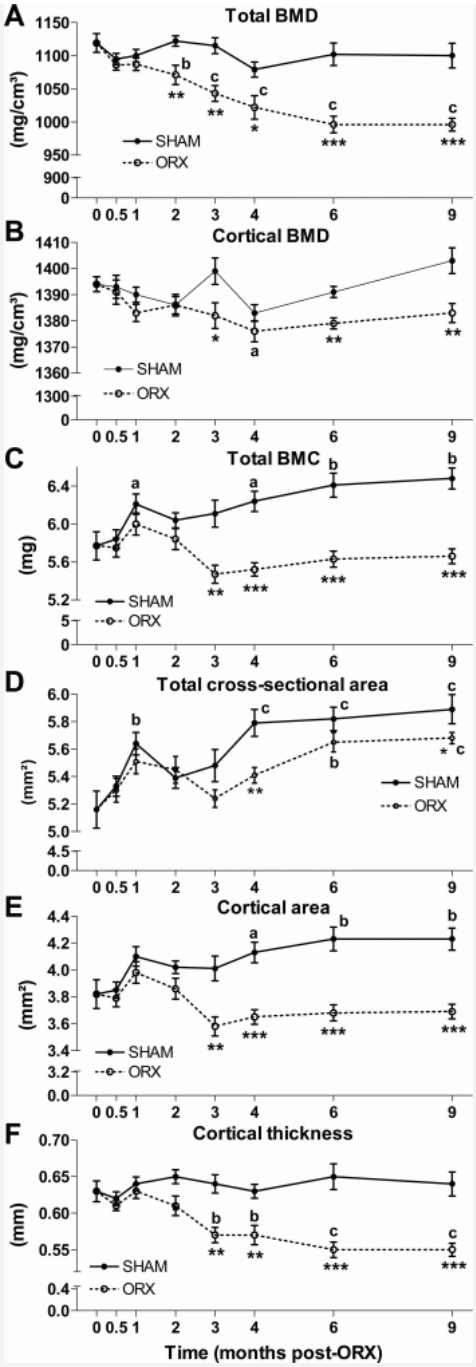


*Fig. 9.3.156a Total BMD (A), cortical BMD (B), total BMC (C), total cross-sectional area (D), cortical area (E), and cortical thickness (F) of the tibial shaft in aged SHAM and ORX rats measured by pQCT and plotted as a function of time after surgery. Each data point represents the mean±SE of 8-15 animals. *p<0.05, **p<0.01, ***p<0.001 vs. SHAM group by t-test. [a]p<0.05, [b]p<0.01, [c]p<0.001 vs. baseline group by ANOVA followed by Dunnett's test. Reproduced from J Bone Miner Res 2008;23:694-704 with permission of the American Society of Bone and Mineral Research.*

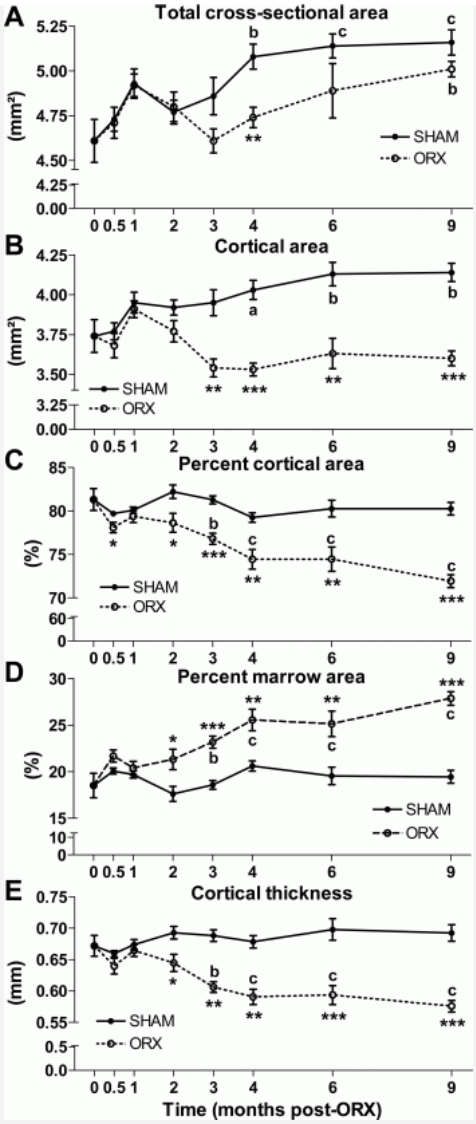


*Fig. 9.3.156b Total cross-sectional area (A), cortical area (B), percent cortical area (C), percent marrow area (D), and cortical thickness (E) of the tibial shaft in SHAM and ORX rats measured by bone histomorphometry and plotted as a function of time after surgery. Each data point represents the mean ± SE of 8–15 animals. *p<0.05, **p<0.01, ***p<0.001 vs. SHAM group by t-test. [a]p<0.05, [b]p<0.01, [c]p<0.001 vs. baseline group by ANOVA followed by Dunnett's test. Reproduced from J Bone Miner Res 2008;23:694-704 with permission of the American Society of Bone and Mineral Research.*

Volume 9, Issue 3, 2008

Reviews

General

9.3.157 Relationships between fat and bone
Reid IR
Osteoporos Int 2008;19:595-606

Body weight impacts both bone turnover and bone density, making it, therefore, an important risk factor for vertebral and hip fractures and ranking it alongside age in importance. The effect of body weight is probably contributed to by both fat mass and lean mass, though in postmenopausal women, fat mass has been more consistently demonstrated to be important. A number of mechanisms for the fat-bone relationship exist and include the effect of soft tissue mass on skeletal loading, the association of fat mass with the secretion of bone active hormones from the pancreatic beta cell (including insulin, amylin, and preptin), and the secretion of bone active hormones (e.g., estrogens and leptin) from the adipocyte. These factors alone probably do not fully explain the observed clinical associations, and study of the actions on bone of novel hormones related to nutrition is an important area of further research. An understanding of this aspect of bone biology may open the way for new treatments of osteoporosis. More immediately, the role of weight maintenance in the prevention of osteoporosis is an important public health message that needs to be more widely appreciated.

9.3.158 European guidance for the diagnosis and management of osteoporosis in postmenopausal women
Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R
Osteoporos Int 2008;19:399-428

9.3.159 Molecular bases of the sympathetic regulation of bone mass
Takeda S, Karsenty G
Bone 2008;42:837-40

9.3.160 Strategies to reverse bone loss in women with functional hypothalamic amenorrhea: A systematic review of the literature
Vescovi JD, Jamal SA, De Souza MJ
Osteoporos Int 2008;19:465-78

9.3.161 Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1)
Schindeler A, Little DG
Bone 2008;42:616-22

9.3.162 Growth hormone, insulin-like growth factors, and the skeleton
Giustina A, Mazziotti G, Canalis E
Endocr Rev 2008;[Epub ahead of print]

9.3.163 Wnt and hedgehog signaling pathways in bone development
Day TF, Yang Y
J Bone Joint Surg Am 2008;90 Suppl 1:19-24

Remodelling Markers

9.3.164 Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy
Reginster JY, Collette J, Neuprez A, Zegels B, Deroisy R, Bruyere O
Bone 2008;42:832-6

Osteocytes

9.3.165 Osteocytes, mechanosensing and Wnt signaling
Bonewald LF, Johnson ML
Bone 2008;42:606-15

Wnt/β-catenin signaling pathway is important in osteoblasts for differentiation, proliferation and the synthesis bone matrix. Whereas osteocytes appear to use the Wnt/β-catenin pathway to transmit signals of mechanical loading to cells on the bone surface and may be triggered by crosstalk with the prostaglandin pathway in response to loading, which then leads to a decrease in expression of Sost and Dkk1, negative regulators of bone formation.

Risk Factors

9.3.166 Assessment of 10-year absolute fracture risk: A new paradigm with worldwide application
Siris E, Delmas PD
Osteoporos Int 2008;19:383-4

9.3.167 Amount and type of protein influences bone health
Heaney RP, Layman DK
Am J Clin Nutr 2008;87:1567S-70S

Treatment

9.3.168 Mechanisms of action of bisphosphonates: Similarities and differences and their potential influence on clinical efficacy
Russell RG, Watts NB, Ebetino FH, Rogers MJ
Osteoporos Int 2008;19:733-59

Mineral binding affinities differ among the BPs and may influence their differential distribution within bone, their potency, and duration of action. The antiresorptive effects of the nitrogen-containing BPs (including alendronate, risedronate, ibandronate, and zoledronate) appear to result from their inhibition of the enzyme farnesyl pyrophosphate synthase (FPPS) in osteoclasts. a key enzyme in the mevalonate pathway which generates isoprenoid lipids utilized for the post-translational modification of small GTP-binding proteins that are essential for osteoclast function. Each BP has a unique profile that may help to explain potential clinical differences among them, in terms of their speed and duration of action, and effects on fracture reduction.

9.3.169 Lack of association between oral bisphosphonates and osteonecrosis using jaw surgery as a surrogate marker
Pazianas M, Blumentals WA, Miller PD
Osteoporos Int 200;19:773-9

A claims database was used to identify female patients ≥45 years of age with jaw surgery claims from January 1, 2002 to December 31, 2005. Four controls (patients with no claims for jaw surgery) were matched to each jaw surgery case. 697 jaw surgery cases and 2,808 controls were identified. Of those jaw surgery cases, 96 (13.8%) received at least one prescription for an oral bisphosphonate. After adjustment for confounding variables, receiving at least one oral bisphosphonate prescription was not shown to increase the risk of jaw surgery (odds ratioadjusted=0.91; 95% CI 0.70-1.19).

9.3.170 Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis
Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY
Bone 2008;42:841-7

9.3.171 European regulatory perspectives for innovative therapies
Ormarsdottir S, Reginster JY, Abadie E
Osteoporos Int 2008;19:725-31

9.3.172 Salmon calcitonin: A review of current and future therapeutic indications
Chesnut CH, 3rd, Azria M, Silverman S, Engelhardt M, Olson M, Mindeholm L
Osteoporos Int 2008;19:479-91

9.3.173 Influence of osteoporosis on fracture fixation - a systematic literature review
Goldhahn J, Suhm N, Goldhahn S, Blauth M, Hanson B
Osteoporos Int 2008;19:761-72

Men

9.3.174 Osteoporosis in men
Khosla S, Amin S, Orwoll E
Endocr Rev 2008;[Epub ahead of print]

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

Volume 9, Issue 3, 2008

Invest in Your Bones Campaign

Campaign vision

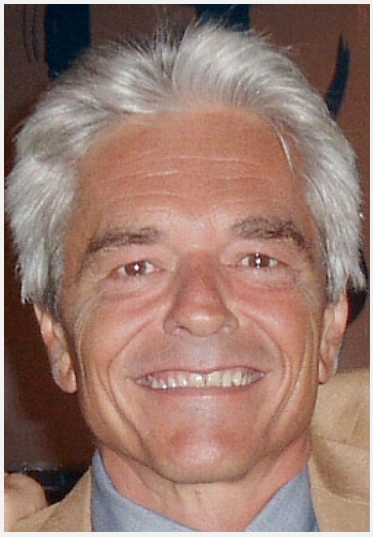
The IOF Invest in Your Bones campaign vision is of a world without osteoporotic fractures through increasing awareness and understanding of osteoporosis. The emphasis is also on improving quality of life and on the healthcare budget. In addition, the Invest in Your Bones campaign aims to sensitise health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



This issue is dedicated to
the memory of Pierre D. Delmas

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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 9, Issue 4, 2008

Literature Review

Invest In Your Bones Campaign

IOF News

Pierre D. Delmas
It is with great sadness that we announce the untimely passing of Professor Pierre D. Delmas in Lyon, France on July 23, 2008 at the age of 58.
Obituary

IOF World Congress on Osteoporosis
December 3-7, 2008
Bangkok, Thailand
More information

IOF Advanced Training Course on Osteoporosis
February 3-5, 2009
Lyon, France
More information

IOF hails WHO Fracture Risk Assessment Report and FRAX™ website
Diagnosis of fracture risk becomes much easier, bringing benefits to those at risk and cost savings...
Read more

Progress in
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editor E. Seeman

Volume 9, Issue 4, 2008

Pierre

Wish You Were Here

We have lost a masterpiece. Great works of art hang the museum of the human heart and are illuminated gently by hews of light for all to see. Pierre needed no light, he illuminated all around him in his aura. He was a luminary, now a celestial body, towering with the psalms and nightingales.[1] His soul is but a little way above our heads[2], so his presence, his warmth, strength, lucid directness, playfulness and humour, his rapier wit and repartee are still palpable. He made the grapes of the vine richer, the champagne bubbles sing more sweetly, the science so relevant and so right. These things of him never die, they are within us and we give them life, him life, when we remember.

They are within you both. Gauthier, you are his voice, his intelligence, his clarity and the poet of him. Olivia, you will be the Wild Wind of him, later, not now. For now you are the rustling breeze, the gentle zephyr among the rolling wild flowers and a distant thunder across the Corsican Hills he loved so much. Have no fear. The Lioness of Lyon will fiercely protect you and the lion will watch over you. Speak to him when you need him …he will answer. He will answer, but his wish for you is to be…..you…..so often he will say decide yourself…you are grown.

Come closer don't be shy
Stand beneath a rainy sky
The moon is over the rise
Think of me as a train goes by

God took the stars and he tossed 'em
Can't tell the birds from the blossoms
You'll never be free of me
He'll make a tree from me

Don't say good bye to me
Describe the sky to me
Stand in the shade of me
Things are now made of me

Lay your head where my heart used to be
Hold the earth above me
Lay down in the green grass
Remember when you loved me[3]

Pierre loved life with a volcanic intensity. He ferociously harnessed the clouds and soared amongst them, first class of course, with the wings of an eagle fastened with wax, often very close to the sun.[4] He navigated its wonder, the world was not enough, he strutted with those wide steps whooshing the wind and ski slopes and the waters of and coral reefs of all continents with his cell phone and bestrode the Atlantic, a mere puddle between Europe and the Americas organising satellite meetings on Venus, Mars and Jupiter; Pluto was a bit of a problem; low registrations.

Remember when you were young
You shone like the sun.
You were caught on the crossfire
Of childhood and stardom

Blown on the steel breeze.
Come on you stranger you legend you martyr and shine!

You reached for the secret too soon,
You cried for the moon.
Come on you raver, you seer of visions,
Come on you painter, you piper, you prisoner, and shine!
Shine on you crazy diamond.[5]

He is an immortal masterpiece in the Museum of our Heart, a leader whose courage and vision made songs from silence, colour from bleakness, opportunity from adversity, light from darkness, clarity from confusion and uncertainty, information from noise and chaos. He was masterpiece of action and gave us the voice we could not find within ourselves.
Deborah, you made everything possible.

You danced him to the wedding now, danced him on and on.
Danced him very tenderly and danced him very long.
You showed him slowly what he only knew the limits of
You danced him to the end of love.

You danced him to your beauty with a burning violin.
You danced him to the children who are waiting to be born
Danced him to though the curtains that your kisses have outworn
Danced him through the panic till he was gathered safely in
You danced him to the end of love.[6]

His life existed before him, it preceded him, occupied him. He harnessed all parts of it, fearlessly, with courage, that, like all the things worth knowing, can never be taught[7], he then left… all too soon.

We own nothing, not even the skin we briefly occupy. And so it is with our friendship, it existed before us, before we met at Mayo Clinic when his spirit burst through the door as an eagle, a panther, a tornado in denim jeans. Friendship enters us, occupies us and waits for us again. We grew old together but not old enough.

How I wish, how I wish you were here.
We're just two lost souls
Swimming in a fish bowl,
Year after year,
Running over the same old ground.
What have we found?
The same old fears.
Wish you were here.[8]

There will be a time for his legacy to be realized.
So come, my friends, be not afraid.
We are so lightly here.
It is in love that we are made;
In love we disappear.[9]

Life is a gift, enjoy the miracle of it, of each other. But for now, it is time for tears.

The stars are not wanted now: put out every one;
Pack up the moon and dismantle the sun;
Pour away the ocean and sweep up the wood.
For nothing now can ever come to any good. [10]

Eulogy delivered by Ego Seeman in Lyon, France, July 28, 2008.

Excerpts from
1. In My Art or Sullen Craft. Dylan Thomas.
2. Romeo and Juliet. W. Shakespeare.
3. Green Grass, Real Gone. T. Waits.
4. Greek Myths, Escape from Crete, Icarus.
5. Shine On You Crazy Diamond, Dark Side of the Moon, Pink Floyd.
6. Dance Me to the End of Love. L Cohen.
7. Picture of Dorian Gray, Oscar Wilde.
8. Wish You Were Here. Dark Side of the Moon, Pink Floyd.
9. Boogie Street. Ten New Songs. L. Cohen.
10. Stop All the Clocks, Cut Off the Telephone. W. Auden.

Progress in
OSTEOPOROSIS
Summaries and Critical Analyses of the Current Literature
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Volume 9, Issue 4, 2008

"My Big Tree" by Gauthier Delmas

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MY BIG TREE

Il est très grand il vit très très longtemps
Il peut changer d'humeur il peut changer de couleur
Il n'est jamais méchant il est toujours content
C'est mon grand arbre

Quand il est blessé personne ne vient l'aider
Quand il a mal tout le monde trouve ça normal
Quand il suffoque tout le monde s'en moque
C'est mon grand arbre

Qui souffre comme ça nuit et jour
Sans que personne ne lui vienne en secours
Il essaye de s'en sortir
Tout en gardant le sourire
C'est mon grand arbre

Quand je reviendrai de vacances il prendra de l'importance
Je m'occuperai de lui jours et nuits
Pour qu'il soit heureux et qu'il oublie les jours malheureux
C'est mon grand arbre

Quand tu auras vécu de longues années
Tu pourras mourir en paix
Sans penser à moi
Sans t'occuper de moi
C'est mon grand arbre

Gauthier Delmas
12 years of age, Lyon, France, 1999

Progress in
OSTEOPOROSIS
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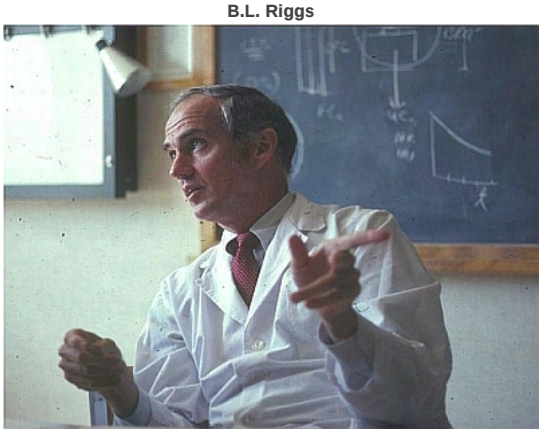
editor E. Seeman

Volume 9, Issue 4, 2008

Pierre and Mentors

P.J. Meunier

B.L. Riggs



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

Volume 9, Issue 4, 2008

Reunion for B.L. Riggs

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Summaries and Critical Analyses of the Current Literature
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Volume 9, Issue 4, 2008

Pierre and Staff

INSERM Research Unit 831

Association de Prevention des Maladies Osseuses

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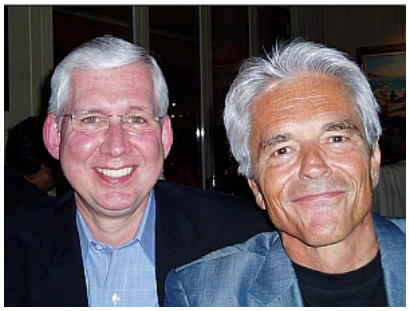
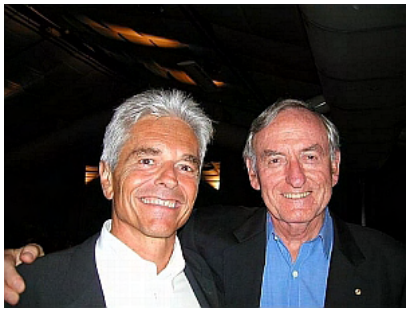
Volume 9, Issue 4, 2008

Pierre and Friends





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Summaries and Critical Analyses of the Current Literature
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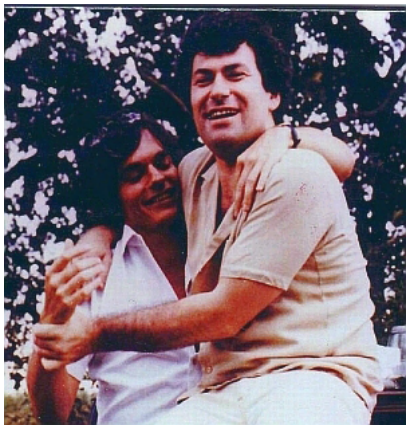
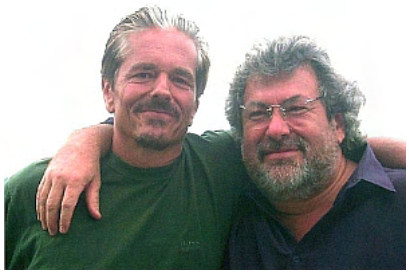
Volume 9, Issue 4, 2008

We grew old together but not old enough





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Volume 9, Issue 4, 2008

Overview

Progress in Osteoporosis is the result of an idea that Pierre had in 1993. I distinctly remember him emerging from a meeting saying, "I have an idea..." He honored me by asking me to take on this task because he wanted to provide an educational resource that brought the world of research in osteoprosis to the homes of as many individuals as possible, particularly to those without ready access to the main journals. This was 15 years ago and his idea lives on bigger than ever as *Progress in Osteoporosis* is now on the internet. It is freely available because of his vision and efforts to sustain the journal with the support of the IOF Invest In Your Bones Campaign.

This issue is dedicated to his memory and to his extraordinary life captured in pictures collected over many wonderful years of friendship, fun, and joy. Pictures are taken by different individuals, all his friends, all part of the life he loved, part of the life we love and are blessed in having.

Ego Seeman
Editor

Strontium and sustained fracture risk reduction during 5 years

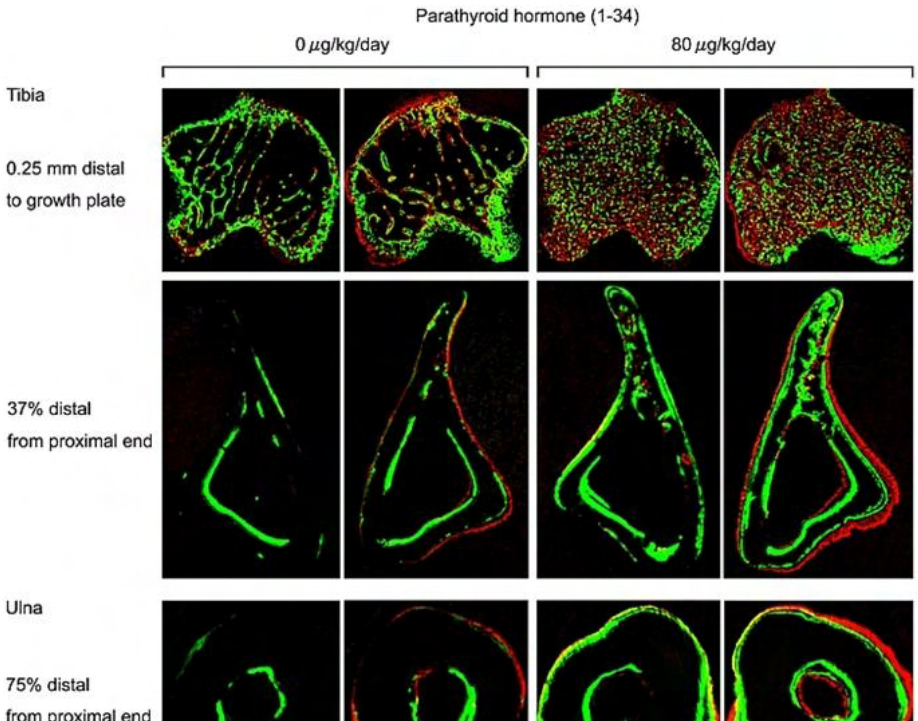
There is little long term antifracture data available in the literature. Indeed, veracity of claims of anti-fracture efficacy of alendronate during 10 years are difficult to evaluate because a control group randomized at the onset of the study was not available and the controls used were from the SOF study, a prospective cohort study (Bone et al, NEJM 2004;350:1189). Most other treatments that claimed to have a sustained benefit suffer from problems with attrition of the inception cohort. **Reginster et al** report that in 5091 postmenopausal women with osteoporosis randomized to strontium ranelate, 2714 (53%) completed the study up to 5 years. The risk of nonvertebral fracture was reduced by 15%. The risk of hip fracture was reduced by 43% and the risk of vertebral fracture was reduced by 24%. **Arthritis Rheum 2008;31;58:1687-95**

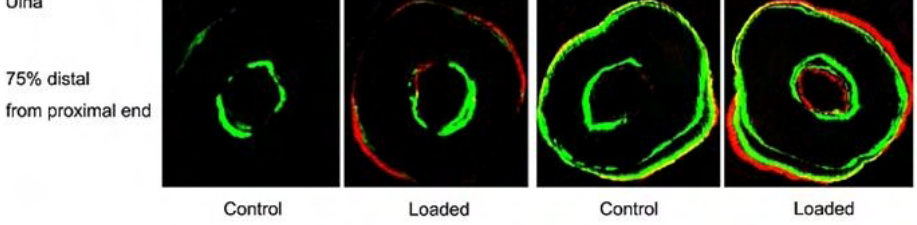
RANKL inhibition

Miller et al report that denosumab, a human monoclonal antibody inhibits RANKL, osteoclast formation, function, and survival, bone turnover and increased BMD. Continuous treatment increased BMD. Discontinuation was associated with a decrease in BMD within the first 12 months and retreatment increased spine BMD. This treatment appears to offer a way of regulating remodelling rate and this may be most important because bone resorption is not necessarily a bad thing (see below). Rumor has it that denosumab also now reduces fracture risk but don't tell anyone. **Bone 2008;43:222-9**

PTH administration, exercise, and tunneling

Bone adapts to the loading requirements imposed on it. Loading may be a way of targeting drug therapy. **Sugiyama et al** report that mice given daily PTH (1-34) with unilateral loading of the tibiae and ulnae had an anabolic response to low dose PTH at trabecular bone and in the proximal and middle cortical bone treated with all doses. In the ulna, loading that did not stimulate osteogenesis was osteogenic at the distal site with 80 µg/kg/day iPTH. At both levels of loading, there were synergistic effects in cortical bone volume of the proximal tibia and distal ulna between loading and high dose iPTH from increases in endosteal and periosteal bone formation. **Bone 2008;43:238-48**





Representative transverse confocal microscope images of the trabecular and cortical bone in 19 week old female C57BL/6 mice treated with 6-weeks of intermittent parathyroid hormone (iPTH) (1-34) and 2-weeks of mechanical loading. Levels of peak load: sufficient to engender an osteogenic response in the tibia and insufficient to do so in the ulna. Green: double calcein labels injected on the first days of iPTH (1-34) treatment (day 1) and mechanical loading (day 29). Red: single alizarin label injected on the last day of mechanical loading (day 41). Reproduced from Bone, 43:238-48, Copyright (2008), with permission from Elsevier.

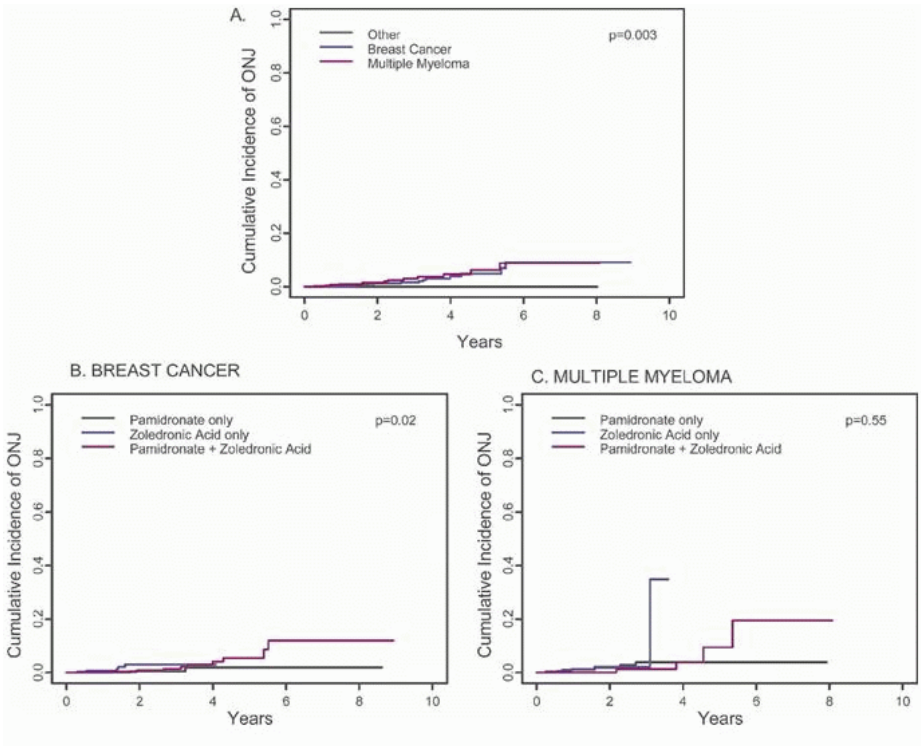
Miller et al report that daily human PTH(1-84) increases trabecular bone volume, number and connectivity at lumbar vertebra-3 and thoracic vertebra-10. Intratrabecular tunneling increased in PTH(1-84)-treated animals and occurred at all skeletal sites. A modest but significant increase in trabecular thickness occurred only at the iliac crest. **Bone 2008;42:1175-83**

McManus et al report that Fish Fugu parathyroid hormone 1 (fPth1) given to male rats increased TbBV/TV, TbTh, TbN, mineral apposition rate (MAR) and bone formation rate/bone surface (BFR/BS) with a concomitant decrease in osteoclast surface and number. OVX osteopenic rats and sham operated (SHAM) rats were injected intermittently with 500 µg/kg for 11 weeks. This dose increased TbBV/TV and TbTh in the proximal tibiae due to increased bone formation as assessed by BFR/BS and MAR with restoration of TbBV/TV to SHAM levels without any effect on bone resorption. fPth1 also increased TbBV/TV and TbTh in the vertebrae (L6) and cortical thickness in the mid-femora, thus increasing bone strength at these sites. **Bone 2008;42:1164-74**

Is bisphosphonate therapy safe?

Bone resorption is not necessarily a bad thing; remodelling with resorptive removal of old or damaged bone is essential to maintaining bone's material and structural strength. **Allen et al** report that bisphosphonates reduce remodelling in dog rib, but no adverse effects were noted in dose said to be equivalent to those used in postmenopausal women . While reduced bone toughness is documented in vertebrae, data in the rib following 3 years bisphosphonate are not available. Doses of alendronate estimated to be five times higher than that used in postmenopausal women reduced toughness (ability to absorb energy without cracking) by 33%, but neither ultimate stress nor modulus were reduced relative to controls. There was no difference in overall microdamage accumulation among the groups. Moreover, microdamage burden may differ from region to region. Damage burden in the rib may be less than in regions loaded more greatly. The point is that it is probably unwise to dismiss the possibility that prolonged exposure to antiresorptive agents is entirely safe. **Calcif Tissue Int 2008;82:354-60**

Hoff et al analyzed 4019 patients treated with intravenous bisphosphonates and report 16/1338 patients with breast cancer (1.2%) and 13/548 patients with myeloma (2.4%) developed ONJ. The median dose and duration of treatment with pamidronate or zoledronic acid were higher in patients with ONJ (p<0.0001). Zoledronic acid was associated with a HR=15.01), pamidronate followed by zoledronic acid (HR=4.00), and dental extractions (HR=53.19) as risks for ONJ in breast cancer. In multiple myeloma, dental extractions (HR=9.78) and osteoporosis (HR=6.11), 13/29 patients were followed for a median of 17.1 months, lesions healed in 3 patients. **J Bone Miner Res 2008;23:826-36**



Estimate of cumulative incidence of ONJ. (A) Cumulative incidence of ONJ in 3994 patients with breast cancer (blue line), multiple myeloma (red line), or other disorders (black line). The estimated cumulative incidence of ONJ at 3 yr was 1.6% (95% CI: 0.005-0.027) in breast cancer, 3% (95% CI: 0.009-0.050) in multiple myeloma, and 0% in other disorders (p=0.003). The comparable data at 5 yr are 4.8% (95% CI: 1.7-7.9%); 6.2% (95% CI: 1.9-10.4%); and 0%. (B and C) Cumulative incidence of ONJ at 3 yr in breast cancer and multiple myeloma patients analyzed by type of bisphosphonate used. In the breast cancer group at 3 yr (B), the estimated cumulative incidence of ONJ is 0.5% (95% CI: 0.000-0.016) with pamidronate, 3.0% (95% CI: 0.000-0.058) with zoledronic acid, and 1.4% (95% CI: 0.000-0.031) with pamidronate followed by zoledronic acid (p=0.02). The comparable data for the breast cancer group at 5 yr are 2% (95% CI: 0-4.9%), inadequate numbers for zoledronic acid, and 5.4% (95% CI: 1.1-9.7%). The differences are significant at 5 yr. In the multiple myeloma group, the estimated cumulative incidence of ONJ or maxilla at 3 yr is 3.9% (95% CI: 0.004-0.074) with pamidronate, 2.2% (95% CI: 0.000-0.047) with zoledronic acid, and 1.3% (95% CI: 0.000-0.039) with pamidronate followed by zoledronic acid (p=0.55). The comparable data for the multiple myeloma group at 5 yr are 3.9% (95% CI: 0.4-7.4%), inadequate for zoledronic acid, and 9.4% (95% CI: 0-21.7%). Reproduced from J Bone Miner Res 2008;23:826-36 with permission of the American Society of Bone and Mineral Research.

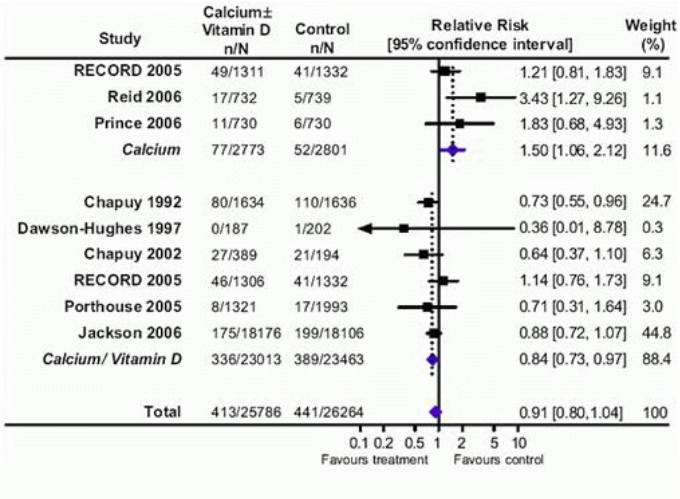
incidence of ONJ of maxilla at 3 yr is 3.9% (95% CI: 0.004-0.074) with pamidronate, 2.2% (95% CI: 0.000-0.047) with zoledronic acid, and 1.3% (95% CI: 0.000-0.039) with pamidronate followed by zoledronic acid (p=0.55). The comparable data for the multiple myeloma group at 5 yr are 3.9% (95% CI: 0.4-7.4%), inadequate for zoledronic acid, and 9.4% (95% CI: 0-21.7%). Reproduced from J Bone Miner Res 2008;23:826-36 with permission of the American Society of Bone and Mineral Research.

Hess et al report the results of a systematic review to identify cases of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer. Ninety-nine cases were identified (85 osteoporosis, 10 Paget's disease, 2 with rheumatoid arthritis, 1 with diabetes, and 1 patient with maxillary fibrous dysplasia). The mean age was 69.4 years, 87.3% were female, and 83.3% were receiving oral bisphosphonates. Of the 63 patients, 88.9% had a dental procedure before the onset of osteonecrosis. **Am J Med. 2008;121:475-83**

Visekruna et al report three subjects experienced spontaneous or minimal trauma "chalk-stick" type metadiaphyseal femoral fractures on long term bisphosphonate after long term, combined antiremodelling therapy. All three had concomitant circumstances (endogenous estrogen) or medications (glucocorticoids, hormone replacement therapy, raloxifene). Biochemical markers of bone turnover were low or in the low premenopausal range. Double tetracycline labeled bone biopsy showed low activation frequency in one subject and limited single tetracycline label in a second consistent with severely suppressed bone turnover. **J Clin Endocrinol Metab 2008 [Epub ahead of print]**

Is calcium supplementation safe?

There is a notion that various supplements “can’t do any harm”. This may be a layman’s approach to disease prevention but surely cannot be condoned by a so called learned society that prides itself on decision making based on evidence. **Reid et al** report an increased risk for hip fracture (relative risk 1.50, 95% CI 1.06-2.12) in 5,500 women involved in trials of calcium monotherapy. While this observation is interesting and certainly provocative, the data need to be looked at critically. Most of the trials examining the effects of calcium alone or with vitamin D have serious flaws in design (most patients are not calcium or vitamin D deficient) and execution (such as large numbers lost to follow up). Thus, any interpretation benefit or harm lacks a strong evidence base. There is no substitute for design, not even statistics can save a poorly designed trial even by squeezing out a p<0.05 with huge sample sizes. As the authors conclude, “Until there are further trial results to clarify this area, the present findings suggest that reliance on high calcium intakes to reduce the risk of hip fracture in older women is not appropriate.” **Osteoporos Int 2008;19:1119-23**



Effect of calcium, or calcium in combination with vitamin D, on hip fracture risk reduction. Reproduced from Osteoporos Int 2008;19:1119-23 with permission from Springer.

Is calcium supplementation efficacious?

Aloia et al published a lovely paper that will be an education to any young investigator interested in understanding remodelling and how a so called antiresorptive agent ‘increases’ BMD. In this study, the authors reported no differences in the effect of calcium vs. calcium + 800 IU vitamin D3 on BMD. A transient increase in BMD was observed during the first year of study followed by a decline. This observation is consistent with the notion that remodelling cycles initiated before intervention go to completion by bone formation within each BMU increasing BMD then at a new steady state, when remodelling is slower, bone loss again occurs because the negative BMU is not corrected. **Osteoporos Int 2008;19:1001-9**

Is exercise safe?

Clark et al report that in 2692 children, 193 (7.2%) reported at least one fracture over two years. Children who reported daily or more episodes of vigorous physical activity had double the fracture risk compared with those children who reported less than four episodes per week (OR, 2.06) despite having higher bone mass. **J Bone Miner Res 2008;23:1012-22**

Vitamin D deficiency

Vitamin D deficiency is fashionable but is there more to it? **Dobnig et al** reported that in 22.6% of 3258 male and females due for coronary angiography died during 7.7 years. The hazards ratio was increased in those in the lower two 1,25-D quartiles compared with the highest quartile for all-cause mortality (HR, 2.08 and 1.53, respectively) and cardiovascular mortality (HR, 2.22 and 1.82, respectively). Similar results were obtained for patients in the lowest 1,25-D quartile. **Arch Intern Med 2008;168:1340-9**

Giovannucci et al report in a case-control study of 18,225 men aged 40-75 years free of cardiovascular disease, that during 10 years 454 developed nonfatal myocardial infarction or fatal coronary heart disease. Controls (n=900) were selected in a 2:1 ratio. Men deficient in 25(OH)D (≤15 ng/ml were at increased risk for myocardial infarction (relative risk 2.42). **Arch Intern Med 2008;168:1174-80**

Associations of this kind in observational cohort studies are difficult to interpret. The implication is that deficiency in vitamin D contributed to death, but it is possible that individuals who were unwell avoid sunlight and may have lower vitamin D so the association is not causal? It is not clear what proportion of the mortality was attributable to vitamin D deficiency, nor that repletion would have reduced that mortality. There are more questions than answers.

Zhu et al report that in 302 elderly women with serum 25(OH)D <60 nM receiving 1000 mg calcium citrate per day with 1000 IU vitamin D2 or placebo, increases in BMD occurred but were no different and there was no change in serum PTH. The increase in 25(OH)D had no extra effect on active fractional intestinal calcium absorption, which fell equally in both groups. **J Bone Miner Res 2008;23:1343-8**

Bone is a gastrointestinal organ?

To investigators interested in bone, everything in bone is for bone but that may be a blinkered approach. Bone may be more or less, depending on the perspective taken. For example, there is evidence from the Karsenty group that bone may be an endocrine organ participating in energy metabolism with uncarboxylated osteocalcin regulating insulin sensitivity and secretion. Now **Niemeier et al** report chylomicron remnants (CR) injected into mice were cleared by liver and bone. Uptake of CR by murine osteoblasts and hepatocytes was similar in vitro. Electron microscopy revealed CR uptake into sinusoidal endothelial cells, macrophages and osteoblasts. Injection of vitamin K(1)-enriched CR resulted in an increase in osteocalcin carboxylation in vivo while total osteocalcin remained unaffected, so osteoblasts process CR in vivo. **Bone 2008;43:230-7**

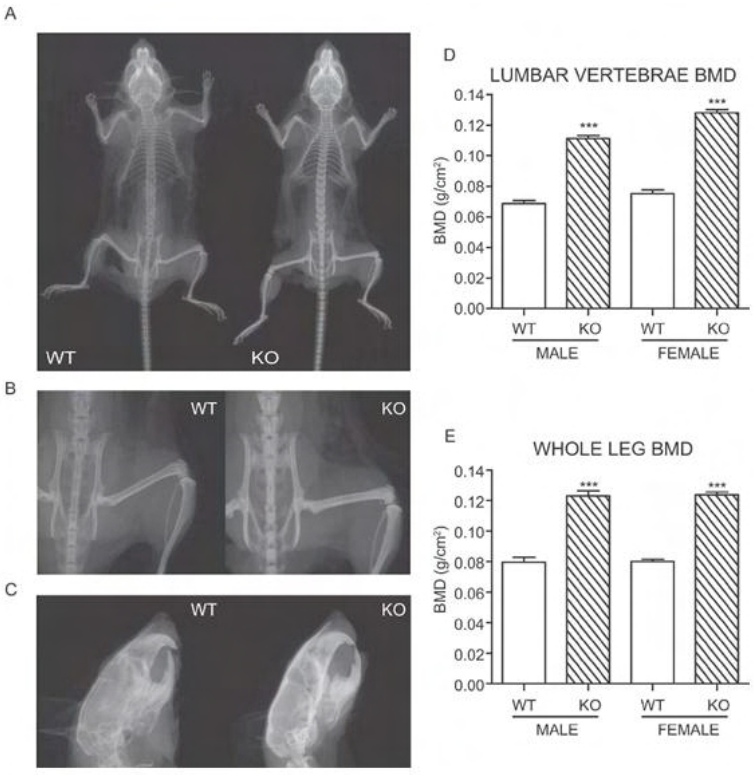
GAP junctions and loading

Grimston et al report that gap junctional intercellular communication mediated by connexin 43 (Cx43) plays a role in the cellular response to mechanical stimulation. Genetic deficiency of the Cx43 gene (Gja1) in mice with a conditional Gja1 ablation in osteoblasts (ColCre; Gja1−/flox), wildtype (Gja1+/flox) and heterozygotes (Gja1−/flox) were subjected to a three-point bending. Mutants had thinner cortices, larger tibial diaphysial marrow area and total CSA. These mice needed 40% more force to generate endocortical strain. In wildtype mice, loading produced double labels at the endocortical surface, whereas single labels were seen in mutants, and mineral apposition rate and bone formation rate were lower (54.8% and 50.2%, respectively) in mutants relative to wildtype. Cx43 plays a role in adaptive responses to physical stimuli. **J Bone Miner Res 2008;23:879-86**

Osteocytes, sclerostin knockouts, apoptotic bodies

Sugawara et al report that the elastic modulus of peripheral regions of cells was higher than in their nuclear regions. The elastic modulus of the peripheral region of osteoblasts was 12053±934 Pa, that of osteoid osteocytes was 7971±422 Pa and that of mature osteocytes was 4471±198 Pa so the level of elastic modulus of bone cells was proportional to the stage of development. The focal adhesion area of osteoblasts was higher than that of osteocytes. **Bone 2008;43:19-24**

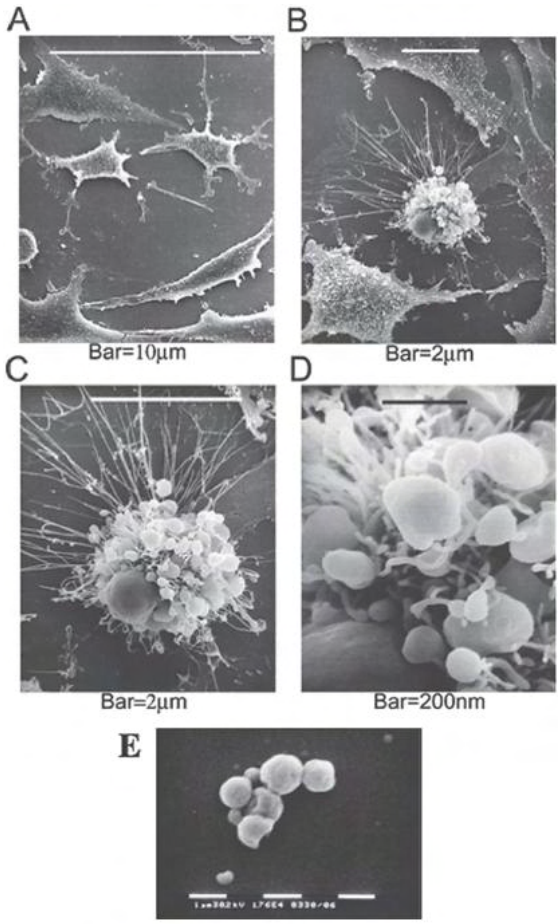
Li et al generated SOST knockout mice and report increased radiodensity throughout the skeleton. Lumbar vertebrae and whole leg showed increased BMD (>50%). µCT analysis of femur showed that bone volume was increased in the trabecular and cortical compartments. Histomorphometry revealed increased osteoblast surface and no change in osteoclast surface. The bone formation rate in SOST knockout mice was increased for trabecular bone (>9-fold) at the distal femur, as well as for the endocortical and periosteal surfaces of the femur midshaft. Mechanical testing of lumbar vertebrae and femur showed that bone strength was increased. **J Bone Miner Res 2008;23:860-9**



Increased BMD in SOST KO mice. (A) Whole body radiographs of 4-mo-old female WT and KO mice showing increased radiodensity throughout the skeleton of KO mice. (B) Enlargement of radiographs showing pelvic region. (C) Enlargement of radiographs showing skull. (D) BMD of lumbar vertebrae and (E) whole leg as assessed by DXA in 5- to 6.5-mo-old male and female WT and KO mice showing increased areal BMD in KO mice. Values are mean±SE, n=11-17 per group. ***p<0.001 vs. sexmatched WT. Reproduced from J Bone Miner Res 2008;23:860-9 with permission of the American Society of Bone and Mineral Research.

Kogianni et al report that osteocyte apoptosis colocalizes with osteoclastic bone resorption. Osteocyte apoptotic bodies (OABs) from MLO-Y4 osteocyte-like cell line and primary murine osteocytes and apoptotic bodies (ABs) from primary

murine osteoblasts support osteoclastogenesis in vitro and in vivo. Addition of OABs to mononuclear osteoclast precursors (OPs) in vitro resulted in the maintenance of OP cell numbers and an increase in the proportion and activity of TRACP+ cells. The osteoclastogenic capacity of OABs was independent of RANKL but dependent on the induction of TNF-α production by OP. Dying osteocytes target bone destruction through the distribution of OAB associated signals. **J Bone Miner Res 2008;23:915-27**



Size of ABs. SEM images of MLOY4 osteocytes in culture. (A) MLO-Y4 osteocytes were induced to undergo apoptosis, (B) which caused cells to shrink to ~20% of the initial size and (C) undergo extensive blebbing that (D) produced ABs that ranged in size between 20 nm and 1 µm. (E) SEM images of purified ABs. Reproduced from J Bone Miner Res 2008;23:915-27 with permission of the American Society of Bone and Mineral Research.

MY BIG TREE

He is my Big Tree
He is very strong and lives very long
His humour may change, his colour may change
He is nevery nasty, he is always happy
He is my Big Tree

When he is burned out, no one helps him out
When he feels harmed, everyone thinks it's normal
When he staggers, no one thinks it matters

He is my Big Tree

Who suffers day and night
Without a soul to help him right
He tries to come to terms with it
He is my Big Tree

When I come back from Mom's town
More important he will have grown
I shall take care of his day and nights
So that he be happy and forget about his plights
He is my Big Tree

When you have grown old
You will die in peace
Without thinking about me
You are my Big Tree

Gauthier Delmas
12 years of age, Lyon, France, 1999

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 9, Issue 4, 2008

Epidemiology

9.4.1 Stabilizing incidence of low-trauma ankle fractures in elderly people Finnish statistics in 1970-2006 and prediction for the future

Kannus P, Palvanen M, Niemi S, Parkkari J, Jarvinen M

Bone 2008;43:340-2

The number of low-trauma ankle fractures among 60-year old or older Finnish persons increased steadily between 1970 (369 fractures) and 1997 (1668 fractures), but leveled off (1670 fractures in 2006). The raw incidence was 57/100,000 persons in 1970 to 169 in 1997, to 144 in 2006. During 1970-1997, the age-adjusted incidence of low-trauma ankle fracture rose in both women and men, but thereafter, the incidence declined; in women, from 199 in 1997 to 173 in 2006, and in men, from 123 in 1997 to 100 in 2006.

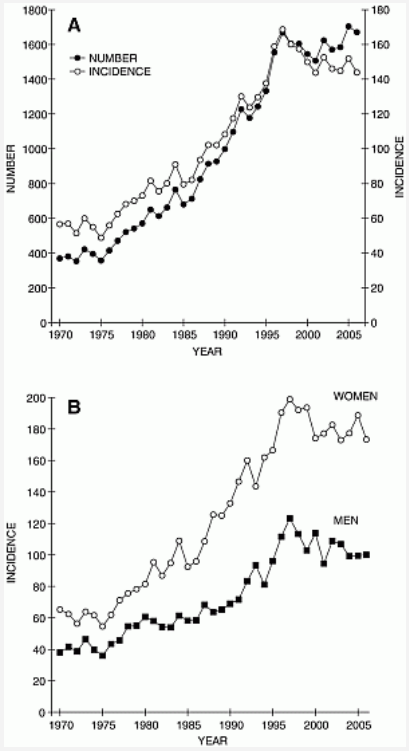


Fig. 9.4.1 Low-trauma ankle fractures in Finland in women and men 60 years of age or older between 1970 and 2006. (A) Number and crude incidence (per 100,000 persons). (B) Age-adjusted incidence (per 100,000 persons). Reproduced from Bone, 43:340-342, Copyright (2008), with permission from Elsevier.

9.4.2 Trend of hip fracture incidence in Germany 1995-2004: A population-based study

Icks A, Haastert B, Wildner M, Becker C, Meyer G

Osteoporos Int 2008;19:1139-45

In Germany 1995-2004, hip fracture incidence per 100,000 increased from 121.2 (95% CI 120.5-121.9 to 140.9 (140.2-141.7). In men aged 40 years or older, incidences increased. In women, there was a tendency of a decrease up to 74 years of age, but also a significant increase in higher age groups. In people 0-39 years, the incidence declined markedly (IRR 1995-2004, men 0.74; 0.69-0.79, women 0.62; 0.55-0.69, both p<0.01). The increase was significantly higher in Eastern compared to Western Germany (interaction: p=0.002), and differences between East and West decreased.

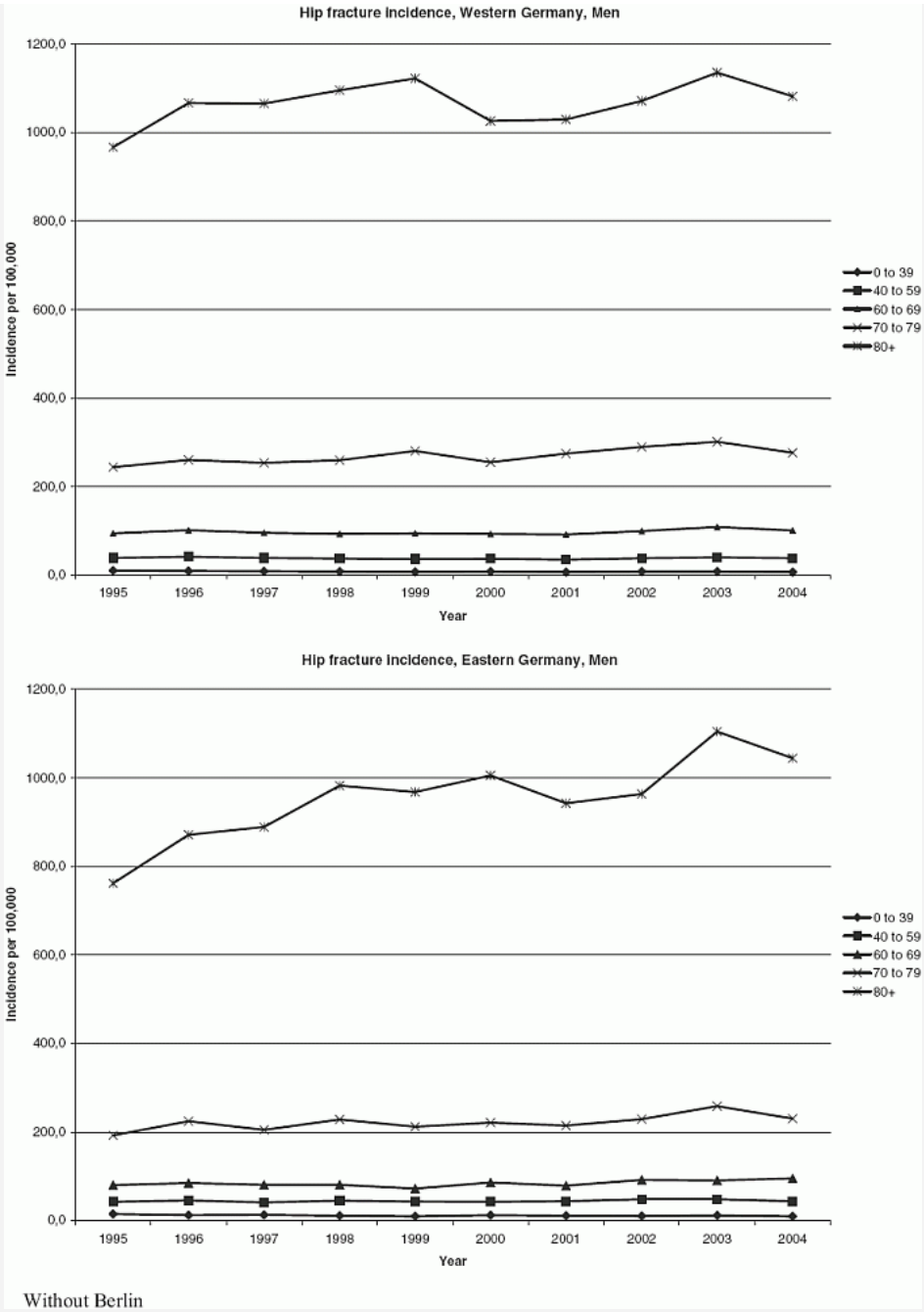


Fig. 9.4.2 Age-sex specific incidences in Eastern and Western Germany. Reproduced from Osteoporos Int 2008;19:1139-45 with permission from Springer.

Progress in
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editor E. Seeman

Volume 9, Issue 4, 2008

Genetics

9.4.3 Mechanisms of the anabolic effects of teriparatide on bone: Insight from the treatment of a patient with pycnodysostosis
Chavassieux P, Asser Karsdal M, Segovia-Silvestre T, Neutzsky-Wulff AV, Chapurlat R, Boivin G, Delmas PD
J Bone Miner Res 2008;23:1076-83

Pycnodysostosis is a genetic osteosclerosis caused by cathepsin K deficiency. We hypothesized that teriparatide, a potent anabolic agent used in the treatment of osteoporosis reduces skeletal fragility by activating turnover. A 37-yr old woman who exhibited short stature, skull and thorax deformities, and a history of severe fragility fractures had Cathepsin K gene sequencing. Before and after 6 mo of 20 µg/d teriparatide, HR-pQCT on the radius and tibia showed augmentation of cortical and trabecular density. Transiliac bone biopsy showed increased bone mass (+63% versus controls), a decrease in remodeling without evidence of active osteoblasts, and a severe decrease in the dynamic parameters of bone formation (mineralizing surfaces, -90% and bone formation rate, -93% versus age- and sex-matched controls). This depressed bone turnover probably explained the increased degree of mineralization. The presence of a novel missense mutation leading to an A141V amino acid substitution confirmed a genetic defect of cathepsin K. The deficiency of active osteoclasts was confirmed by an in vitro study that showed a decreased concentration of CD14(+) monocytes (the precursor of osteoclasts) in blood. These osteoclasts had low resorptive activity when incubated on bone slices. After 6 mo of teriparatide, the structure remained unchanged. Some features of the osteoclastic phenotype - that are absent in pycnodysostosis - are a prerequisite for the anabolic effect of PTH on osteoblasts.

9.4.4 Sex-specific genetic loci for femoral neck bone mass and strength identified in inbred COP and DA rats
Alam I, Sun Q, Liu L, Koller DL, Carr LG, Econs MJ, Foroud T, Turner CH
J Bone Miner Res 2008;23:850-9

The purpose of this study is to identify sex-independent and sex-specific quantitative trait loci (QTLs) for femoral neck density, structure, and strength in inbred Copenhagen 2331 (COP) and Dark Agouti (DA) rats. Evidence of linkage ($p<0.01$) for sex-independent QTLs were detected for (1) femoral neck vBMD on chromosomes (Chrs) 1, 6, 10, and 12, (2) femoral neck structure on Chrs 5, 7, 10, and 18, and (3) biomechanical properties on Chrs 1 and 4. Male-specific QTLs were discovered on Chrs 2, 9, and 18 for total vBMD, on Chr 17 for trabecular vBMD, on Chr 9 for total bone area, and on Chr 15 for ultimate force. A female-specific QTL was discovered on Chr 2 for ultimate force. The effect size of the individual QTL varied between 1% and 4%.

9.4.5 TIEG-null mice display an osteopenic gender-specific phenotype
Hawse JR, Iwaniec UT, Bensamoun SF, Monroe DG, Peters KD, Ilharreborde B, Rajamannan NM, Oursler MJ, Turner RT, Spelsberg TC, Subramaniam M
Bone 2008;42:1025-31

TGFbeta inducible early gene-1 (TIEG) was cloned from osteoblasts (OB) and has a role in TGFbeta/Smad signaling, regulation of gene expression and OB growth and differentiation. Congenic TIEG-null (TIEG(-/-)) female, not male mice of 2 months of age have femurs and tibias with decreases in BMD, and area and reduced strength with increased flexibility. µCT analysis of femurs revealed decreases in cortical bone and histomorphometric evaluation of the distal femur revealed that female TIEG(-/-) mice also display a 31% decrease in cancellous bone area, primarily due to a decrease in trabecular number. Female TIEG(-/-) mice exhibit a 42% reduction in bone formation rate due to a reduction in double labeled perimeter, not mineral apposition rate. Female TIEG(-/-) mice are osteopenic mainly due to a decrease in the total number of functional/mature OBs.

9.4.6 Bone structural effects of variation in the TNFRSF1B gene encoding the tumor necrosis factor receptor 2
Mullin BH, Prince RL, Dick IM, Islam FM, Hart DJ, Spector TD, Devine A, Dudbridge F, Wilson SG
Osteoporos Int 2008;19:961-8

9.4.7 The Asn19Lys substitution in the osteoclast inhibitory lectin (OCIL) gene is associated with a reduction of bone mineral density in postmenopausal women
Pineda B, Laporta P, Cano A, Garcia-Perez MA
Calcif Tissue Int 2008;82:348-53

9.4.8 A C>T polymorphism located at position -1 of the Kozak sequence of CD40 gene is associated with low bone mass in Spanish postmenopausal women
Pineda B, Laporta P, Hermenegildo C, Cano A, Garcia-Perez MA
Osteoporos Int 2008;19:1147-52

9.4.9 Identification of differentially expressed genes in mandibular condylar and tibial growth cartilages using laser microdissection and fluorescent differential display: Chondromodulin-I (ChM-1) and tenomodulin (TeM) are differentially expressed in mandibular condylar and other growth cartilages
Watahiki J, Yamaguchi T, Enomoto A, Irie T, Yoshie K, Tachikawa T, Maki K
Bone 2008;42:1053-60

9.4.10 Identification of quantitative trait loci affecting murine long bone length in a two-generation intercross of LG/J and SM/J mice
Norgard EA, Roseman CC, Fawcett GL, Pavliev M, Morgan CD, Pletscher LS, Wang B, Cheverud JM
J Bone Miner Res 2008;23:887-95

9.4.11 Trabecular bone deterioration in col9a1+/- mice associated with enlarged osteoclasts adhered to collagen IX deficient bone

Wang CJ, Iida K, Egusa H, Hokugo A, Jewett A, Nishimura I

J Bone Miner Res 2008;23:837-49

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

Volume 9, Issue 4, 2008

Measurement of Bone Mass

9.4.12 Routine versus targeted vertebral fracture assessment for the detection of vertebral fractures
Middleton ET, Steel SA
Osteoporos Int 2008;19:1167-73

6388 women over 65 underwent DXA during the period of targeted vertebral fracture assessment (VFA) and 2,176 during routine VFA. Routine VFA detected 420 (20.0%) women with fracture. Most vertebral fractures (56.2%) occurred in women with osteopenia. Routine VFA would be expected to alter the management of 1 in 6 osteopenic women. Targeted VFA was performed in 332 (5.2%) women detecting 122 (1.9%) women with fractures. It was estimated that targeted VFA only detected 9.6% of women with a vertebral fracture. Targeted VFA failed to detect fractures in 18.1% of the population attending for DXA and in 29% of those with osteoporosis. Routine VFA detects vertebral fractures in 20% of women over 65. Targeted VFA greatly reduces the number of VFAs performed but only detects a minority of the women with vertebral fractures.

9.4.13 Compromised bone marrow perfusion in osteoporosis
Griffith JF, Yeung DK, Tsang PH, Choi KC, Kwok TC, Ahuja AT, Leung KS, Leung PC
J Bone Miner Res 2008;23:1068-75

120 females (mean age, 74 yr; age range, 67-89 yr) underwent DXA of the hip, proton MR spectroscopy, and dynamic contrast-enhanced MR imaging of the right proximal femur, acetabulum, and adductor thigh muscle. In all bone areas perfusion indices were reduced in subjects with osteoporosis compared with subjects with osteopenia or normal BMD. As marrow perfusion decreased in the proximal femur, marrow fat increased (r=0.827). This increase in fat content seemed to account for the decrease in marrow perfusion more than a reduction in BMD. For normal BMD subjects, perfusion parameters in the femoral head were one third of those in the femoral neck or shaft and one fifth of those in the acetabulum. Perfusion throughout the proximal femur is reduced in osteoporotic subjects compared with osteopenic and normal subjects. This reduction in perfusion only affects bone.

9.4.14 Quantitative micro-computed tomography: A non-invasive method to assess equivalent bone mineral density
Nazarian A, Snyder BD, Zurakowski D, Muller R
Bone 2008;43:302-11

9.4.15 Clinical interest of bone texture analysis in osteoporosis: A case control multicenter study
Lespessailles E, Gadois C, Kousignian I, Neveu JP, Fardellone P, Kolta S, Roux C, Do-Huu JP, Benhamou CL
Osteoporos Int 2008;19:1019-28

9.4.16 Geographical variation in DXA bone mineral density in young European men and women: Results from the network in Europe on male osteoporosis (NEMO) study
Kaptoge S, da Silva JA, Brixen K, Reid DM, Kroger H, Nielsen TL, Andersen M, Hagen C, Lorenc R, Boonen S, de Vernejoul MC, Stepan JJ, Adams J, Kaufman JM, Reeve J
Bone 2008;43:332-9

9.4.17 Longitudinal trends in use of bone mass measurement among older americans, 1999-2005
Curtis JR, Carbone L, Cheng H, Hayes B, Laster A, Matthews R, Saag KG, Sepanski R, Tanner SB, Delzell E
J Bone Miner Res 2008;23:1061-7

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

Volume 9, Issue 4, 2008

Bone Material

9.4.18 Bone quality determined by Fourier transform infrared imaging analysis in mild primary hyperparathyroidism
Zoehrer R, Dempster DW, Bilezikian JP, Zhou H, Silverberg SJ, Shane E, Roschger P, Paschalis EP, Klaushofer K
J Clin Endocrinol Metab 2008;[Epub ahead of print]

The ratio pyr/deH-DHLNL crosslinks in 46 iliac crest biopsies from patients with PHPT (14 men, aged 28-68; 32 women, aged 26-74) was assessed by Fourier transform infrared imaging (FTIRI). PHPT patients had lower pyr/deH-DHLNL cross-links ratio compared to controls. Parathyroidectomy restored values. Females had a lower ratio compared to either male PHPT patients or normal controls. The ratio correlated with rate of bone formation, and mineralizing surface, in individual patients and with bone mineralization density distribution.

9.4.19 The anatase phase of nanotopography titania plays an important role on osteoblast cell morphology and proliferation
He J, Zhou W, Zhou X, Zhong X, Zhang X, Wan P, Zhu B, Chen W
J Mater Sci Mater Med 2008;[Epub ahead of print]

Three crystal phases of titania film (rutile, anatase and amorphous titania) with similar roughness were synthesized. The surface roughness of each film was about 8-10 nm. Primary rat osteoblasts were used to observe changes in morphology and to evaluate cell behavior at the film surface. The number of the osteoblasts on anatase film was higher than rutile and amorphous films after 36 and 72 h incubation. More importantly, synthesis of alkaline phosphatase was greater by osteoblasts cultured on anatase film than on rutile and amorphous films after 7 and 14 days. In addition, the cells grown on the anatase phase film had the largest spreading area; the actin filaments in cells with regular directions were well defined and fully spreaded. The results indicate that the anatase phase of titania with nanoscale topography yield the best biological effects for cell adhesion, spreading, proliferation and differentiation.

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

Volume 9, Issue 4, 2008

Bone Structure

9.4.20 Development of in vivo μCT evaluation of neovascularisation in tissue engineered bone constructs
Bolland BJ, Kanczler JM, Dunlop DG, Oreffo RO
Bone 2008;43:195-202

Quantification and 3D visualization of new vessel networks remain a problem in tissue engineering constructs. A novel technique utilising a radio-opaque dye and micro-computed tomography (μCT) has been developed and applied to study angiogenesis in an impaction bone graft model. Tissue-engineered constructs combining human bone marrow stromal cells (HBMSC) with natural allograft and synthetic grafts (PLA) were impacted and implanted into the subcutis of MF-1 nu/nu mice for a period of 28 days. Analysis of 3D μCT reconstructions demonstrated an increase in vessel volume and vessel number in the impacted scaffolds/HBMC compared to scaffolds alone. Vessel volume: allograft/HBMSC=0.57 mm(3)±0.19; allograft=0.04 mm (3)±0.04; PLA/HBMSC=1.19 mm(3)±0.31; and PLA=0.12 mm(3)±0.01. Penetrating vessel number: allograft/HBMSC=22.33 ±3.21; allograft=3.67±1.153; PLA/HBMSC=32.67±8.33; and PLA=7.67±3.06. Type 1 collagen and von Willebrand factor immunohistochemistry in scaffold/HBMSC constructs indicated the osteogenic cell phenotype, and new blood vessel formation respectively. Contrast-enhanced 3D reconstructions facilitated the visualization and quantification of neovascularisation.

9.4.21 Shape, structural properties, and cortical stability along the femoral neck: A study using clinical QCT
Yang L, Maric I, McCloskey EV, Eastell R
J Clin Densitom 2008;[Epub ahead of print]

Quantitative computer tomography (QCT) was used to obtain detailed structural properties of cross-sections along the femoral neck (FN) in 27 postmenopausal women (mean age 81, range 65-86yr) with osteoporosis. The cross-sectional shape was increasingly elliptic and both tensile and compressive section moduli increased from the proximal to distal half of the FN. The section modulus was maximal when falling 20 degrees anterior and minimum when falling 50 degrees posterior on the greater trochanter. The cortex was thinner in the anterior, superoanterior, superior, superoposterior, and posterior octants than the inferomedial aspect. Multiple measurements are required for a assessment of FN structural properties.

9.4.22 Side-to-side and within-side variability of 3D bone microarchitecture by conventional micro-computed tomography of paired iliac crest biopsies
Chappard C, Marchadier A, Benhamou CL
Bone 2008;43:203-8

A Bordier needle trephine was used to collect biopsies from 30 postmenopausal female cadavers (mean age, 73.7±10.7 years; range, 55-96 years). Biopsies were chemically defatted then imaged using a desktop μCT scanner (voxel size, 10.77 μm). For trabecular bone parameters, reproducibility as assessed from two μCT acquisitions ranged from 4.1% to 6.9%. The mean difference in absolute individual percent variation (mAbsDelta(ind)) between the two sides ranged from 10.8% to 14.8% for all trabecular parameters except Tb.Pf (74%) and SMI (84%). In cortical bone, mAbsDelta(ind) were 11.6% for Po.Dm, 15.1% for Cort.Porosity, and 27.6% for Cort.Th. To assess within-side variability, we divided the trabecular iliac crest volume into three equal parts, one adjacent to each cortex and one in the middle. Values of mAbsDelta(ind) versus the middle part were ranging from 7.6% for Tb.Sp to 26.2% for BV/TV. Thus, within-side variability was similar in magnitude to side-to-side variability.

9.4.23 Relationships of trabecular bone structure with quantitative ultrasound parameters: In vitro study on human proximal femur using transmission and backscatter measurements
Padilla F, Jenson F, Bousson V, Peyrin F, Laugier P
Bone 2008;42:1193-202

In 37 specimens of trabecular bones from upper parts of fresh human femurs., 8 mm diameter cylindrical cores were extracted. All QUS parameters correlated to BMD (R=0.83 for nBUA, R=0.81 for SOS and R=0.69 for BUB) and to microarchitectural parameters (R=-0.79 between nBUA and Tb.Sp, R=-0.81 between SOS and Tb.Sp, R=-0.65 between BUB and BS/BV) and microstructural parameters adds 10%, 19%, and 4% to the respective BMD alone contribution for the three variables BUA, SOS and BUB. Moreover, the RMSE was reduced by up to 50% for SOS, by up to 21% for nBUA and up to 11% when adding structural variables to BMD in explaining QUS results. The variability of SOS was completely explained by a multivariate model including BMD and independent structural parameters (R(2)=0.94). The predictions (in terms of R(2) or RMSE) of microarchitectural parameters was not enhanced when combining 2 or 3 QUS in multiple linear regressions compared to the prediction obtained with one QUS parameter alone. The best model was found for the prediction of Tb.Th from BUA (R(2) =0.58, RMSE=17 mum). Given the high values of RMSE, these linear models appear of limited clinical value, suggesting that appropriate models have to be derived in order to solve the inverse problem. In this regard, a very interesting multivariate model was found for nBUA and BUB with Tb.Th and Tb.N, in agreement with single scattering theories by random medium. However, the source of residual variability of nBUA and BUB (15% and 45%, respectively) remained unexplained.

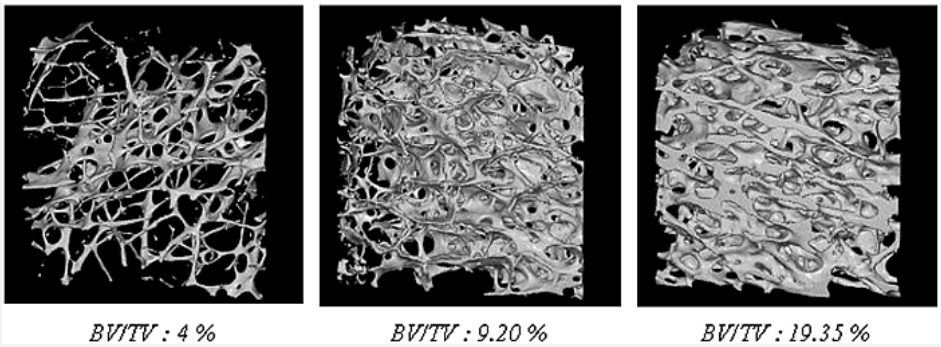

Fig. 9.4.23 Examples of 3D reconstruction from synchrotron µ-CT experiments. Reproduced from Bone, 42:1193-202, Copyright (2008), with permission from Elsevier.

9.4.24 Spatial distribution of anisotropic acoustic impedance assessed by time-resolved 50-MHz scanning acoustic microscopy and its relation to porosity in human cortical bone
Saied A, Raum K, Leguerney I, Laugier P
Bone 2008;43:187-94

Fifteen specimens (human radius) were investigated using a SAM (center frequency of 50 MHz and -6 dB lateral resolution of approximately 23 µm). Tissue acoustic impedance and microstructural features were derived from the morphometric analysis of the segmented impedance images. A higher porosity was found in the inner cortical layer (mean±SD=8.9±2.3%) compared to the peripheral layer (2.7±1.5%) (paired t-test, p<10(-5)). Most of the variance can be explained by the regional effect across the radial direction with a minor contribution due to between-sample variability. Similar to porosity, the number and diameter of pores were greater in the inner layer. In contrast to porosity, impedance variability can mostly be explained by between-specimen variability. After compensation for the between-sample variability the variation in acoustic impedance across the radial direction was much larger than that along the circumferential direction. In addition to the significant difference between the inner cortical layer (8.25±0.4 Mrayl) and peripheral layer (8.0±0.5 Mrayl) (unilateral paired t-test, p<10(-4)), the values in the anterior region (8.2 ±0.5 Mrayl) were higher than the posterior region (7.9±0.6 Mrayl). Impedance mean value of longitudinal sections was lower than mean value measured in transverse cross-sections, resulting in an impedance acoustic anisotropy ratio of 1.17±0.03 in the inner cortical layer and 1.19±0.02 in the peripheral layer.

9.4.25 A model of the intracortical vascular system of long bones and of its organization: An experimental study in rabbit femur and tibia
Pazzaglia UE, Bonaspetti G, Ranchetti F, Bettinsoli P
J Anat 2008;[Epub ahead of print]

The intracortical vessel network was injected with black China ink and assessed by transillumination of full-thickness, decalcified hemicortices. The three-dimensional architecture was highlighted. The formation of the intracortical vessels involved incorporation of the periosteal network and osteonal remodelling. The two systems differ by the diameter of the vessels (the periosteal are larger) and by architecture (the periosteal are convoluted, and the osteonal are longitudinal and straight). Longitudinal vessels form branches or connection with periosteal vessels that meet on the line of their advancement. They enter from either inside the cortex from the metaphyses or from the endosteal surface of the marrow. Connections were established with the advancing of cutting cones from the extremities of the diaphysis. Analysis of the system architecture and the modalities of its progressive organization suggested that the direction of advancement of a forming canal does not necessarily correspond to the final blood flow direction of its central vessel.

9.4.26 Dynamic simulation of three dimensional architectural and mechanical alterations in human trabecular bone during menopause
Liu XS, Huang AH, Zhang XH, Sajda P, Ji B, Guo XE
Bone 2008;43:292-301

9.4.27 Cancellous bone lamellae strongly affect microcrack propagation and apparent mechanical properties: Separation of patients with osteoporotic fracture from normal controls using a 2D nonlinear finite element method (biomechanical stereology)
Wang X, Zauel RR, Rao DS, Fyhrie DP
Bone 2008;42:1184-92

Volume 9, Issue 4, 2008

Biomechanics

9.4.28 An accurate estimation of bone density improves the accuracy of subject-specific finite element models
Schileo E, Dall'ara E, Taddei F, Malandrino A, Schotkamp T, Baleani M, Viceconti M
J Biomech 2008;41:2483-91

Sixty specimens had CT-densities computed and apparent and ash densities measured. The CT/ash-density and ash/apparent-density relationships were calculated. FEA models of 8 femurs were generated to assess strain prediction. CT and ash density correlated linearly, R(2)=0.997, but they were not equivalent (intercept <0, slope >1). A constant ash/apparent-density ratio (0.598±0.004) was found for cortical bone. A lower ratio was found for trabecular bone (0.459±0.100), but it became equal to that of cortical tissue when testing smaller trabecular specimens (0.598±0.036). Introducing the derived relationships in the FE modeling improved accuracy in strain prediction, R(2)=0.95, RMSE=7% suggesting a correction of the densitometric calibration should be used to evaluate ash-density from CT scans, to avoid ash-density under and over estimation for low- and high-density tissue, respectively. The ash/apparent-density ratio can be assumed constant in human femurs and the correction improves the accuracy of the model and should be considered in subject-specific bone modelling.

9.4.29 Bone morphometry strongly predicts cortical bone stiffness and strength, but not toughness, in inbred mouse models of high and low bone mass
Voide R, van Lenthe GH, Muller R
J Bone Miner Res 2008;23:1194-203

Morphometric analysis was performed on 20 murine femora with a low bone mass (C57BL/6J; B6) and 20 murine femora with a high bone mass (C3H/HeJ; C3H) using desktop microCT. Bone strength, stiffness, yield force, yield displacement, and toughness, as well as morphometric traits, were different between the two strains, whereas postyield displacement was not. It was found that bone volume, cortical thickness, and cross-sectional area predicted almost 80% (p<0.05) of bone stiffness, strength, and yield force but postyield properties (toughness) could not be explained by morphometry.

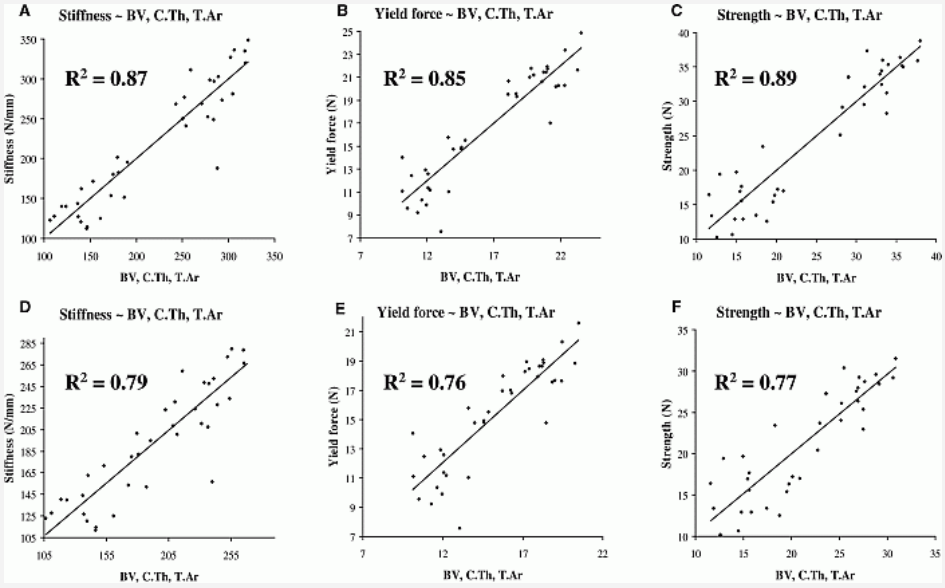

Fig. 9.4.29 Multiple linear regression analyses showed that models based on BV, Ct.Th, and T.Ar were good predictors of stiffness, yield force, and strength. BV, Ct.Th, and T.Ar predicted 87% of stiffness (A), 85% of yield force (B), and 88% of strength (C). Factors were computed to reduce the clustering effect in the correlation coefficients. (E) f=1.2 and r2=0.79, (F) f=1.5 and r2=0.76, and (G) f=1.23 and r2=0.77. Reproduced from J Bone Miner Res 2008;23:1194-203 with permission of the American Society of Bone and Mineral Research.

9.4.30 Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method
Macneil JA, Boyd SK
Bone 2008;42:1203-13

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

Volume 9, Issue 4, 2008

Growth

9.4.31 Bone metabolism in adolescent boys with anorexia nervosa
Misra M, Katzman DK, Cord J, Manning SJ, Mendes N, Herzog DB, Miller KK, Klibanski A
J Clin Endocrinol Metab 2008;[Epub ahead of print]

In 17 anorexia nervosa (AN) boys and 17 controls 12-19 years, boys with AN had lower BMD and corresponding Z-scores at the spine, hip, femoral neck, trochanter, intertrochanteric region, and whole body compared with controls. Height adjusted measures (lumbar BMAD and whole body BMC/height) were also lower. Bone formation and resorption markers were reduced. Testosterone and lean mass predicted BMD. IGF-1 was a predictor of turnover markers. AN boys have low BMD at multiple sites associated with decreased bone turnover markers at a time when bone mass accrual is critical for attainment of peak bone mass.

9.4.32 Effects of once versus twice-daily parathyroid hormone1-34 therapy in children with hypoparathyroidism
Winer KK, Sinaii N, Peterson D, Sainz B, Jr., Cutler GB, Jr.
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Fourteen children aged 4-17 years with chronic hypoparathyroidism were studied in a randomized crossover trial, lasting 28 weeks using once-daily vs. twice-daily PTH1-34. Twice-daily PTH 1-34 increased serum calcium and magnesium levels more effectively than a once-daily dose. PTH 1-34 normalized mean 24 h urine Ca excretion on both treatments. This was achieved with half the PTH 1-34 dose during the twice-daily regimen compared to the once-daily regimen (twice-daily, 25±15 μg/d vs. once-daily, 58±28 μg/d, P<0.001). A twice-daily regimen produced significantly improved metabolic control compared to once-daily PTH 1-34.

9.4.33 Delayed pubertal development by hypothalamic suppression causes an increase in periosteal modeling but a reduction in bone strength in growing female rats
Yingling VR, Taylor G
Bone 2008;42:1137-43

23-day-old female rats were injected with a GnRH-antagonist at 2 dosage levels (n=15/group). The low dose group (1.25 mg/kg/dose) received daily injections for 27 days (sacrifice 49 days). The high dose group received (5.0 mg/kg/dose) only 5 days per week over a 26 day period (sacrifice 48 days). Significant delays in pubertal development. Femoral lengths were shorter in the and serum IGF-1 were higher. Bone strength and stiffness were lower in the GnRH-a groups. Cortical bone area was decreased and total area was not different. There was a decrease in % Ct.Ar/T.Ar. Stress and Young's modulus were also decreased. Endocortical bone formation rates decreased and there was an increase in periosteal labeled surface. A dose response between bone strength and GnRH-antagonist dosage was found.

9.4.34 Tamoxifen impairs both longitudinal and cortical bone growth in young male rats
Karimian E, Chagin AS, Gjerde J, Heino T, Lien EA, Ohlsson C, Savendahl L
J Bone Miner Res 2008;23:1267-77

4-week old Sprague-Dawley rats were gavaged daily with vehicle, tamoxifen (Tam) (40 mg/kg/d; 1 or 4 wk), or estradiol (40 μg/kg/d; 4 wk). Four-week Tam decreased weight, nose-anus distance, spinal and tibial bone lengths, trabecular BMD, cortical periosteal circumference, and bone strength and also reduced serum IGF-I levels (424±54 versus 606±53 ng/ml in control; p<0.05). Analysis ats showed elevated chondrocyte proliferation (BrdU) and apoptosis (TUNEL), as well as decreases in the number of hypertrophic chondrocytes and in the size of terminal hypertrophic chondrocytes. Despite a complete catch-up of body weight after 14 wk of recovery, the tibia was still shorter (p<0.001) and its cortical region was smaller. Tam causes retardation of longitudinal and cortical radial bone growth in young male rats. Our findings suggest that this inhibition results from local effects on the growth plate cartilage and systemic suppression of IGF-I production.

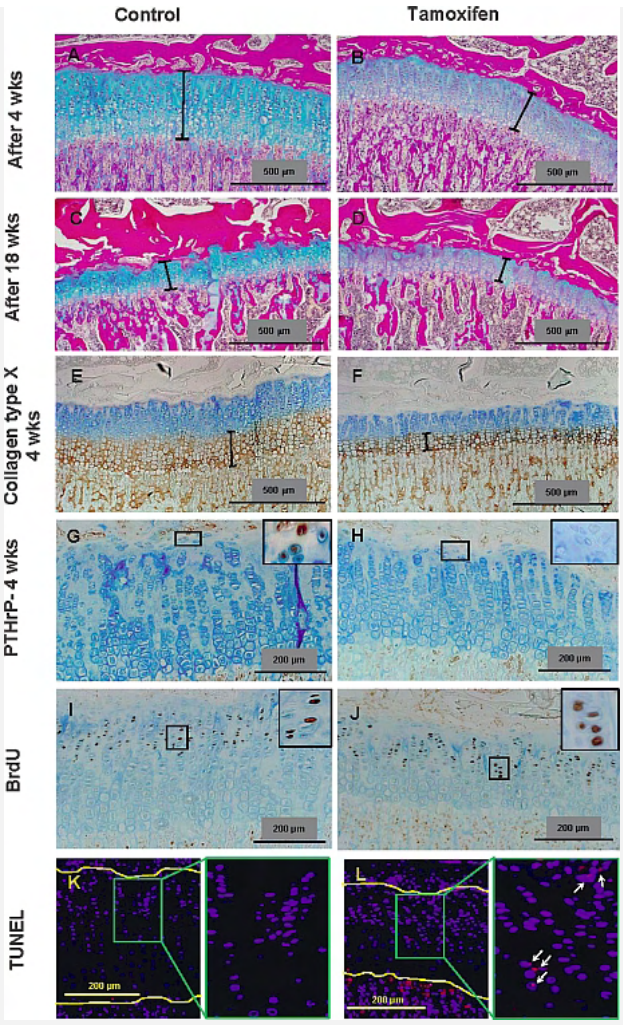

Fig. 9.4.34 Representative stained sections of the tibial growth plate from rats receiving peanut oil (A, C, E, G, I, and K) or Tam dissolved in peanut oil (B, D, F, H, J, and L) for 4 wk and killed (A, B, and E-L) or allowed to recover for 14 wk (C and D). These sections were stained with either Alcian blue/Van Gieson (A–D) or antibodies directed toward type X collagen (E and F) or PTHrP (G and H). The vertical lines indicate the height of the growth plate (A-D) or width of the band staining positively (brown color) for type X collagen (E and F). The horizontal bars depict a distance of 200 (G-L) or 500 µm (A-F). Proliferative BrdU positive chondrocytes in control (I) and Tam 4-wk group (J). TUNEL+ chondrocytes were detected by Alexa-546 (red color), whereas the total number of chondrocytes was detected by DAPI counterstaining (blue colors) in control (K) and Tam 4-wk animals (L). The area between the yellow lines is the growth plate (K and L). High-power magnifications of indicated areas are also included (G-L). Arrows indicate apoptotic cells (L). Reproduced from J Bone Miner Res 2008;23:1267-77 with permission of the American Society of Bone and Mineral Research.

9.4.35 Multigenerational exposure to ethinyl estradiol affects bone geometry, but not bone mineral density in rats
Hotchkiss CE, Weis C, Blaydes B, Newbold R, Delclos KB
Bone 2008;43:110-8

In a multigenerational experiment 0, 2, 10, or 50 ppb ethinyl estradiol (EE) in the diet was fed to intact male and female rats from conception until either weaning, postnatal day 140, or continuously for 2 years. Vertebrae (lumbar and caudal) and femurs were collected at 48 days, 70 days, 140 days, or 2 years of age. Continuous dietary intake of 50 ppb EE decreased body weight by 8-27%. BMD adjusted for body weight was not affected by EE, with the exception of an increase in the caudal vertebrae in males treated with 50 ppb EE. In female rats, continuous treatment with 50 ppb EE decreased length and cross-sectional area of the femur. The length of the femur was decreased in the first two generations following institution of a phytoestrogen-free diet at the initiation of the study in all animals, including controls, but returned to the original length by the third or fourth generation. The cross-sectional area of the femur also varied by generation. High dose of EE throughout the lifespan resulted in decreased bone size in females.

9.4.36 Measures of childhood fitness and body mass index are associated with bone mass in adulthood: A 20-year prospective study
Foley S, Quinn S, Dwyer T, Venn A, Jones G
J Bone Miner Res 2008;23:994-1001

9.4.37 Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis
Huncharek M, Muscat J, Kupelnick B
Bone 2008;43:312-21

9.4.38 Trps1 deficiency enlarges the proliferative zone of growth plate cartilage by upregulation of Pthrp
Nishioka K, Itoh S, Suemoto H, Kanno S, Gai Z, Kawakatsu M, Tanishima H, Morimoto Y, Hatamura I, Yoshida M, Muragaki Y
Bone 2008;43:64-71

9.4.39 ALK1 opposes ALK5/Smad3 signaling and expression of extracellular matrix components in human chondrocytes
Finnson KW, Parker WL, ten Dijke P, Thorikay M, Philip A
J Bone Miner Res 2008;23:896-906

9.4.40 Overexpression of human hydroxysteroid (17beta) dehydrogenase 2 induces disturbance in skeletal development in young male mice
Shen Z, Peng Z, Sun Y, Vaananen HK, Poutanen M
J Bone Miner Res 2008;23:1217-26

9.4.41 Calcium channel TRPV6 is involved in murine maternal-fetal calcium transport
Suzuki Y, Kovacs CS, Takanaga H, Peng JB, Landowski CP, Hediger MA
J Bone Miner Res 2008;23:1249-56

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

Volume 9, Issue 4, 2008

Remodelling Markers

9.4.42 Serum biomarker profile associated with high bone turnover and BMD in postmenopausal women
Bhattacharyya S, Siegel ER, Achenbach SJ, Khosla S, Suva LJ
J Bone Miner Res 2008;23:1106-17

Tte serum proteome of 58 postmenopausal women with high or low/normal bone turnover (training set) was analyzed by surface enhanced laser-desorption/ionization time-of-flight mass spectrometry, and a diagnostic fingerprint was validated in a separate distinct test set, consisting of serum samples from an additional 59 postmenopausal women obtained from the same Mayo cohort, with a gap of 2 yr. Specific protein peaks that discriminate between postmenopausal patients with high or low/normal bone turnover were identified and validated. Multiple supervised learning approaches were able to classify the level of bone turnover in the training set with 80% sensitivity and 100% specificity. In addition, the individual protein peaks were also significantly correlated with BMD measurements in these patients. Four of the major discriminatory peaks in the diagnostic profile were identified as fragments of interalpha-trypsin-inhibitor heavy chain H4 precursor, a plasma kallikrein-sensitive glycoprotein that is a component of the host response system. These data suggest that these serum protein fragments are the serum-borne reflection of the increased osteoclast activity.

9.4.43 Determinants of bone turnover markers in healthy premenopausal women
Adami S, Bianchi G, Brandi ML, Giannini S, Ortolani S, Dimunno O, Frediani B, Rossini M
Calcif Tissue Int 2008;82:341-7

Serum C-telopeptide of type I collagen (CTX), osteocalcin (OC), and N-terminal propeptide of type I procollagen (P1NP), serum calcium, creatinine, phosphate, magnesium, and follicle-stimulating hormone (FSH) were measured in 638 healthy premenopausal women aged 20-50 years. In 83 women on the contraceptive pill (CP), the levels of the three BTMs were 14-26% lower (P<0.005) than in non-CP users. In 18 women considered perimenopausal for serum FSH levels >30 IU/mL despite having regular menses, BTM levels were higher than in age-matched women. This group of subjects and the women on the CP were excluded from further analysis. The three BTMs decreased with advancing age and were negatively and independently correlated with body mass index (P<0.001) and serum phosphate. An increase in BTM concentrations can be observed in perimenopausal women, iBTMs decrease with advancing age, and this appears to be associated with changes in body weight and serum phosphate.

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

Volume 9, Issue 4, 2008

Bone Formation

9.4.44 Demonstration of the presence of independent pre-osteoblastic and pre-adipocytic cell populations in bone marrow-derived mesenchymal stem cells
Post S, Abdallah BM, Bentzon JF, Kassem M
Bone 2008;43:32-9

Mesenchymal stem cells (MSC) clonal cells that are progenitors for osteoblasts and adipocytes. An inverse relationship between bone and fat has been observed suggesting a re-directing of MSC differentiation into one particular lineage. However, bone and fat can change independently. mMSC1 and mMSC2 lines from murine bone marrow were studied and found positive for the murine MSC marker Sca-1 and mMSC1 was also positive for CD13. mMSC1 and not mMSC2 differentiated to adipocytes baring markers (aP2, adiponectin, adipsin, PPARgamma2 and C/EBPa) and the presence of mature adipocytes visualized by Oil Red O staining. mMSC2 and not mMSC1 differentiated to osteoblast lineage (markers CBFA1/RUNX2, Osterix, alkaline phosphatase, bone sialoprotein and osteopontin) and formation of alizarin red stained mineralized matrix in vitro. mMSC2 and not mMSC1 cells, were able to form bone in vivo after subcutaneous implantation in immune-deficient (NOD/SCID) mice. Marrow contains clonal subpopulations of cells that are committed to either osteoblast or adipocyte lineage. These cell populations may undergo independent changes during aging.

9.4.45 Age-related changes in the osteogenic differentiation potential of mouse bone marrow stromal cells
Zhang W, Ou G, Hamrick M, Hill W, Borke J, Wenger K, Chutkan N, Yu J, Mi QS, Isales CM, Shi XM
J Bone Miner Res 2008;23:1118-28

Age-dependent changes in marrow progenitor cell number and differentiation potential between mature (3 and 6 mo old), middle-aged (12 and 18 mo old), and aged (24 mo old) C57BL/6 mice were studied. BMSC/progenitor number and differentiation potential increase between the ages of 3 and 18 mo and decrease rapidly thereafter consistent with the changes of the mRNA levels of osteoblast lineage associated genes. The decline in BMSC number and osteogenic differentiation capacity are important factors contributing to age-related bone loss.

9.4.46 Collagen cross-linking influences osteoblastic differentiation
Turecek C, Fratzl-Zelman N, Rumpler M, Buchinger B, Spitzer S, Zoehrer R, Durchschlag E, Klaushofer K, Paschalis EP, Varga F
Calcif Tissue Int 2008;82:392-400

Osteoblasts express lysyl oxidase (LOX), which is involved in the collagen crosslinking process. Lathyrogens, like ss-aminopropionitrile (ssAPN), inhibit the formation of a stable matrix. MC3T3-E1 cells were seeded and treated with or without 400 µM ssAPN for 1 week. Thereafter, living cells were removed and, on this extracellular matrix, new MC3T3-E1 cells were seeded and cultured for 1 week without ssAPN. The collagen matrix that formed showed a reduction of two major crosslinks of bone collagen, deH-DHLNL and pyr, compared to control cultures. Gene expression studies showed an increase of collagen alpha1 (I) (COL1A1) to 150%. Expression of LOX and osteocalcin (OCN) mRNA was downregulated to about 75%. When fresh MC3T3-E1 cells were seeded on this altered matrix without ssAPN, COL1A1 mRNA expression was upregulated (140%), OCN was downregulated (60%), and LOX mRNA expression remained unaffected. These results indicate that ssAPN not only disrupts collagen cross-link formation but also affects osteoblastic activity and expression. In conclusion, the disrupted matrix produced in the presence of lathyrogen influences, even in its absence, the expression of osteoblastic genes.

9.4.47 EphrinB2 regulation by PTH and PTHrP revealed by molecular profiling in differentiating osteoblasts
Allan EH, Hausler KD, Wei T, Gooi JH, Quinn JM, Crimeen-Irwin B, Pompolo S, Sims NA, Gillespie MT, Onyia JE, Martin TJ
J Bone Miner Res 2008;23:1170-81

To identify pathways and genes regulated by PTH(1-34) and PTH-related protein 1-141 [PTHrP(1-141)] in osteoblasts, mouse marrow stromal cell line, Kusa 4b10, that acquires features of the osteoblastic phenotype with appearance of functional PTH receptor 1 (PTHR1) in Kusa 4b10 cells, were treated with PTH(1-34) or PTHrP(1-141). RNA was subjected to Affymetrix whole mouse genome array. Of the 45,101 probes used on the microarray, 4675 were differentially expressed by ≥1.5-fold, with a false discovery rate <0.1. Among the regulated genes, ephrinB2 mRNA was upregulated in response to both PTH and PTHrP. Increased ephrinB2 protein was also shown in vitro by Western blotting, and immunostaining of femur sections showed ephrinB2 in both osteoclasts and osteoblasts. Production of ephrinB2, as well as other ephrins or Eph family members, did not change during differentiation of Kusa 4b10 cells. Blockade of ephrinB2/EphB4 interaction resulted in inhibition of mineralization of Kusa 4b10 cells. Together with the shown effect of ephrinB2 promoting osteoblast differentiation and bone formation through action on EphB4, the data raise the possibility that PTH or PTHrP regulates ephrinB2 to act in a paracrine or autocrine manner on EphB4 or EphB2 in the osteoblast, contributing as a local event to the anabolic action of PTH or PTHrP.

9.4.48 Genetic variation in the patterns of skeletal progenitor cell differentiation and progression during endochondral bone formation affects the rate of fracture healing
Jepsen KJ, Price C, Silkman LJ, Nicholls FH, Nasser P, Hu B, Hadi N, Alapatt M, Stapleton SN, Kakar S, Einhorn TA, Gerstenfeld LC
J Bone Miner Res 2008;23:1204-16

9.4.49 Interaction between human umbilical vein endothelial cells and human osteoprogenitors triggers pleiotropic effect that may support osteoblastic function
Guillotin B, Bareille R, Bourget C, Bordenave L, Amedee J
Bone 2008;42:1080-91

9.4.50 Effects of phosphodiesterase 7 inhibition by RNA interference on the gene expression and differentiation of human mesenchymal stem cell-derived osteoblasts
Pekkinen M, Ahlstrom ME, Riehle U, Huttunen MM, Lamberg-Allardt CJ
Bone 2008;43:84-91

9.4.51 Differential modulation of RANKL isoforms by human osteoarthritic subchondral bone osteoblasts: Influence of osteotropic factors
Tat SK, Pelletier JP, Lajeunesse D, Fahmi H, Duval N, Martel-Pelletier J
Bone 2008;43:284-91

9.4.52 Modulation of extracellular matrix protein phosphorylation alters mineralization in differentiating chick limb-bud mesenchymal cell micromass cultures
Boskey AL, Doty SB, Kudryashov V, Mayer-Kuckuk P, Roy R, Binderman I
Bone 2008;42:1061-71

9.4.53 Molecular mechanisms of FGF-2 inhibitory activity in the osteogenic context of mouse adipose-derived stem cells (mASCs)
Quarto N, Wan DC, Longaker MT
Bone 2008;42:1040-52

9.4.54 Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro
Wang H, Yoshiko Y, Yamamoto R, Minamizaki T, Kozai K, Tanne K, Aubin JE, Maeda N
J Bone Miner Res 2008;23:939-48

9.4.55 Dense collagen matrix accelerates osteogenic differentiation and rescues the apoptotic response to MMP inhibition
Buxton PG, Bitar M, Gellynck K, Parkar M, Brown RA, Young AM, Knowles JC, Nazhat SN
Bone 2008;43:377-85

9.4.56 Integrin-mediated expression of bone formation-related genes in osteoblast-like cells in response to fluid shear stress: roles of extracellular matrix, Shc, and mitogen-activated protein kinase
Lee DY, Yeh CR, Chang SF, Lee PL, Chien S, Cheng CK, Chiu JJ
J Bone Miner Res 2008;23:1140-9

9.4.57 Diosmetin induces human osteoblastic differentiation through the protein kinase C/p38 and extracellular signal-regulated kinase 1/2 pathway
Hsu Y, Kuo P
J Bone Miner Res 2008;23:949-60

9.4.58 Berberine promotes osteoblast differentiation by Runx2 activation with p38 MAPK
Lee HW, Suh JH, Kim HN, Kim AY, Park SY, Shin CS, Choi JY, Kim JB
J Bone Miner Res 2008;23:1227-37

9.4.59 FGFR2-Cbl interaction in lipid rafts triggers attenuation of PI3K/Akt signaling and osteoblast survival
Dufour C, Guenou H, Kaabeche K, Bouvard D, Sanjay A, Marie PJ
Bone 2008;42:1032-9

9.4.60 Vitamin D receptor-dependent 1 alpha,25(OH)2 vitamin D3-induced anti-apoptotic PI3K/AKT signaling in osteoblasts
Zhang X, Zanello LP
J Bone Miner Res 2008;23:1238-48

9.4.61 AMPK activator, AICAR, inhibits palmitate-induced apoptosis in osteoblast
Kim JE, Ahn MW, Baek SH, Lee IK, Kim YW, Kim JY, Dan JM, Park SY
Bone 2008;43:394-404

9.4.62 ODDD-linked Cx43 mutants reduce endogenous Cx43 expression and function in osteoblasts and inhibit late stage differentiation
McLachlan E, Plante I, Shao Q, Tong D, Kidder GM, Bernier SM, Laird DW
J Bone Miner Res 2008;23:928-38

9.4.63 Osteopenia in transgenic mice with osteoblast-targeted expression of the inducible cAMP early repressor
Chandhoke TK, Huang YF, Liu F, Gronowicz GA, Adams DJ, Harrison JR, Kream BE
Bone 2008;43:101-9

9.4.64 Changes in blood perfusion and bone healing induced by nicotine during distraction osteogenesis
Zheng LW, Ma L, Cheung LK
Bone 2008;43:355-61

9.4.65 Cyclooxygenase-2 expression and prostaglandin E2 production in response to acidic pH through OGR1 in a human osteoblastic cell line
Tomura H, Wang JQ, Liu JP, Komachi M, Damirin A, Mogi C, Tobo M, Nochi H, Tamoto K, Im DS, Sato K, Okajima F
J Bone Miner Res 2008;23:1129-39

9.4.66 Characterizing the BMP pathway in a wild type mouse model of distraction osteogenesis
Haque T, Hamade F, Alam N, Kotsiopriftis M, Lauzier D, St-Arnaud R, Hamdy RC
Bone 2008;42:1144-53

9.4.67 Mechanical signals modulated vascular endothelial growth factor-A (VEGF-A) alternative splicing in osteoblastic cells through actin polymerisation
Faure C, Linossier MT, Malaval L, Lafage-Proust MH, Peyroche S, Vico L, Guignandon A
Bone 2008;42:1092-101

9.4.68 Amelogenin binds to both heparan sulfate and bone morphogenetic protein 2 and pharmacologically suppresses the effect of noggin
Saito K, Konishi I, Nishiguchi M, Hoshino T, Fujiwara T
Bone 2008;43:371-6

9.4.69 Osteoblast-derived TGF-β1 stimulates IL-8 release through AP-1 and NF-κB in human cancer cells
Fong Y, Maa M, Tsai F, Chen W, Lin J, Jeng L, Yang R, Fu W, Tang C
J Bone Miner Res 2008;23:961-70

Progress in
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editor E. Seeman

Volume 9, Issue 4, 2008

Bone Resorption

9.4.70 Estrogen deficiency increases osteoclastogenesis up-regulating T cells activity: A key mechanism in osteoporosis
D'Amelio P, Grimaldi A, Di Bella S, Brianza SZ, Cristofaro MA, Tamone C, Giribaldi G, Ulliers D, Pescarmona GP, Isaia G
Bone 2008;43:92-100

The role of T cells in bone loss was assessed by in vitro osteoclast (OC) formation in pre and post-menopausal women, the latter with or without osteoporosis. Estrogen deficiency enhances the production of the pro-osteoclastogenetic cytokines TNFalpha and RANKL and increases the number of circulating OC precursors. Furthermore, T cells and monocytes from women with osteoporosis exhibit a higher production of TNFalpha than those from the other two groups. Estrogen deficiency stimulates OC formation both by increasing the production of TNFalpha and RANKL and increasing the number of OC precursors. Women with postmenopausal osteoporosis have a higher T cell activity than healthy postmenopausal subjects; T cells thus contribute to the bone loss induced by estrogen deficiency in humans as they do in the mouse.

9.4.71 Follicle-stimulating hormone does not impact male bone mass in vivo or human male osteoclasts in vitro
Ritter V, Thuering B, Saint Mezard P, Luong-Nguyen NH, Seltenmeyer Y, Junker U, Fournier B, Susa M, Morvan F
Calcif Tissue Int 2008;82:383-91

The direct impact of FSH on bone mass of 16-week-old C57BL/6J male mice by either daily intermittent 6 or 60 µg/kg of FSH or continuous delivery via miniosmotic pump of a dose of 6 µg/kg over the course of a month was assessed. FSH-treated mice did not reveal any differences in cancellous and cortical bone compared to sham-treated mice. FSH functionality was verified by demonstrating cAMP induction and activation of a cAMP-response element-containing reporter cell line by FSH. Osteoclastogenesis from human mononuclear cell precursors and from RAW 264.7 cells was not affected by FSH (3, 10, 30 ng/mL) compared to control. No direct effect of FSH on gene regulation was observed by Affymetrix Gene Array on RAW 264.7 cells. Lastly, no expression of FSH receptor (FSHR) mRNA or FSHR was observed by quantitative polymerase chain reaction and Western blot in either human male osteoclasts or RAW 264.7 cells.

9.4.72 The role of nitric oxide in the mechanical repression of RANKL in bone stromal cells
Rahnert J, Fan X, Case N, Murphy TC, Grassi F, Sen B, Rubin J
Bone 2008;43:48-54

Mechanical loading and nitric oxide (NO) have positive influences on bone mass. NO is induced by strain via upregulation of eNOS mRNA and protein. Strain causes decreased RANKL. Primary stromal cells from wild-type (WT) and eNOS(-/-) mice showed strain inhibition of RANKL expression was prevented by NOS inhibitors (L-NAME and L-NMMA) in WT stromal cells. Stromal cells from eNOS(-/-) mice showed mechanical repression of RANKL expression ($p<0.05$). Mechanical strain still increased NO production in the absence of eNOS, and was abolished by SMTC, a specific nNOS inhibitor. nNOS mRNA and protein expression were increased by strain in eNOS(-/-) but not in WT cells, revealing that nNOS was mechanically sensitive. When NO synthesis was blocked with either SMTC or siRNA targeting nNOS in eNOS(-/-) cells however, strain still was able to suppress RANKL expression by 34%. Strain suppression of RANKL can occur through non-NO dependent pathways.

9.4.73 High d(+)glucose concentration inhibits RANKL-induced osteoclastogenesis
Wittrant Y, Gorin Y, Woodruff K, Horn D, Abboud HE, Mohan S, Abboud-Werner SL
Bone 2008;42:1122-30

High d(+)glucose (d-Glc) and l(-)glucose (l-Glc; osmotic control) on RANKL-induced osteoclastogenesis was assessed using RAW264.7 cells and Bone Marrow Macrophages (BMM). High d-Glc inhibits osteoclast formation, ROS production, caspase-3 activity and migration in response to RANKL through a metabolic pathway. High d-Glc may alter RANKL-induced osteoclast formation by inhibiting redox-sensitive NF-kappaB activity through an anti-oxidative mechanism and may alter bone turnover by decreasing osteoclast differentiation and function in diabetes.

9.4.74 Soluble RANKL induces high bone turnover and decreases bone volume, density, and strength in mice
Lloyd SA, Yuan YY, Kostenuik PJ, Ominsky MS, Lau AG, Morony S, Stolina M, Asuncion FJ, Bateman TA
Calcif Tissue Int 2008;82:361-72

For 10 days, 10-week old C57BL/6J female mice were given twice-daily subcutaneous of human recombinant RANKL (0.4 or 2 mg/kg/day) producing a 49-84% greater serum TRAP-5b and 300-400% greater serum alkaline phosphatase, greater endocortical bone erosion surface (79-83%) and periosteal bone formation rate (64-87%) relative to control, reduced trabecular volume fraction (-84%) for both doses of RANKL, femoral diaphysis indicated lower cortical bone volume (-10% to -13%) and greater cortical porosity (8-9%) relative to VEH and femur diaphysis had lower maximum bending load (-19% to -25%) vs. VEH.

9.4.75 Osteoclast polarization is not required for degradation of bone matrix in rachitic FGF23 transgenic mice
Hollberg K, Marsell R, Norgard M, Larsson T, Jonsson KB, Andersson G
Bone 2008;42:1111-21

Hypophosphatemic transgenic (tg) mice overexpressing FGF23 in osteoblasts display disorganized growth plates and reduced BMD characteristic of rickets/osteomalacia. Tg mice had increased mRNA expression of Runx2, alkaline phosphatase and sialoprotein. Expression of alpha1(I) collagen, osteocalcin, dentin matrix protein 1 and osteopontin was unchanged, indicating selective activation of osteoblasts promoting mineralization. The number of osteoclasts was unchanged in tg but serum CTX was increased. The majority of osteoclasts lacked ultrastructural morphological signs of proper polarization. However, they secreted both cathepsin K and MMP-9 comparable to osteoclasts with ruffled borders. Mineralization of bone matrix thus appears essential for inducing osteoclast polarization but not for secretion of osteoclast proteases. Finally, release of CTX by

freshly isolated osteoclasts was increased on demineralized compared to mineralized bovine bone slices, indicating that the mineral component limits collagen degradation. Ruffled borders are implicated in acidification and subsequent demineralization of the bone matrix, however not required for matrix degradation. Osteoclasts, despite absence of ruffled borders, effectively participate in the degradation of hypomineralized bone matrix in rachitic FGF23 tg mice.

9.4.76 Prostaglandin D2 receptors control osteoclastogenesis and the activity of human osteoclasts
Durand M, Gallant MA, de Brum-Fernandes AJ
J Bone Miner Res 2008;23:1097-105

9.4.77 HMGB1 regulates RANKL-induced osteoclastogenesis in a manner dependent on RAGE
Zhou Z, Han JY, Xi CX, Xie JX, Feng X, Wang CY, Mei L, Xiong WC
J Bone Miner Res 2008;23:1084-96

9.4.78 Osteoclast precursors acquire sensitivity to breast cancer derived factors early in differentiation
Guo Y, Tiedemann K, Khalil JA, Russo C, Siegel PM, Komarova SV
Bone 2008;43:386-93

9.4.79 JNK/c-Jun signaling mediates an anti-apoptotic effect of RANKL in osteoclasts
Ikeda F, Matsubara T, Tsurukai T, Hata K, Nishimura R, Yoneda T
J Bone Miner Res 2008;23:907-14

9.4.80 Kinin B1 and B2 receptor expression in osteoblasts and fibroblasts is enhanced by interleukin-1 and tumour necrosis factor-alpha: Effects dependent on activation of NF-kappaB and MAP kinases
Brechter AB, Persson E, Lundgren I, Lerner UH
Bone 2008;43:72-83

Progress in
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Osteocytes

9.4.81 The alteration of a mechanical property of bone cells during the process of changing from osteoblasts to osteocytes
Sugawara Y, Ando R, Kamioka H, Ishihara Y, Murshid SA, Hashimoto K, Kataoka N, Tsujioka K, Kajiya F, Yamashiro T, Takano-Yamamoto T
Bone 2008;43:19-24

Bone cells in embryonic chick calvariae and in isolated culture were identified using fluorescently labeled phalloidin and OB7.3, a chick osteocyte-specific monoclonal antibody. The elastic modulus of living cells was analyzed with atomic force microscopy. Cells were pretreated with GRGDS and GRGES, and then the elastic modulus was analyzed. Focal adhesions in the cells were visualized by immunofluorescence of vinculin. The elastic modulus of peripheral regions of cells in all three populations was higher than in their nuclear regions. The elastic modulus of the peripheral region of osteoblasts was 12053±934 Pa, that of osteoid osteocytes was 7971±422 Pa and that of mature osteocytes was 4471±198 Pa so the level of elastic modulus of bone cells was proportional to the stage of metaphorphosis. The focal adhesion area of osteoblasts was higher than that of osteocytes. The focal adhesion area of osteoblasts was decreased after treatment with GRGDS, however, that of osteocytes was not. The elastic modulus of osteoblasts and osteoid osteocytes were decreased after treatment with GRGDS. However, that of mature osteocytes was not changed.

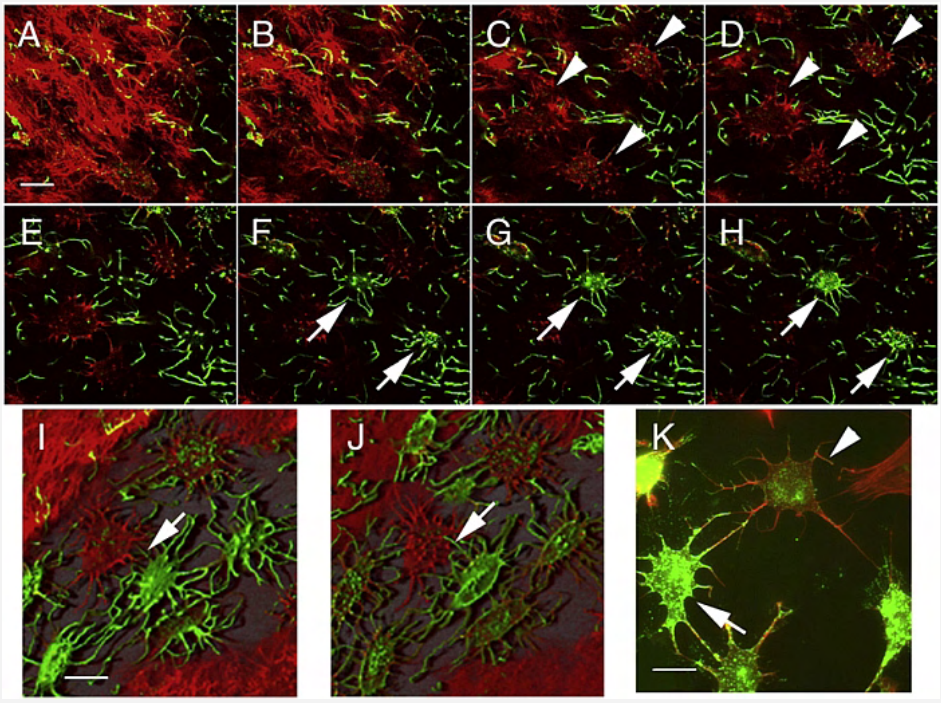

Fig. 9.4.81 Osteocytes in chick calvaria and in isolated culture. (A-H) Serial histotomography by confocal laser scanning microscopy. Fluorescent images show cells stained with Texas Red-X phalloidin (red) and OB7.3 (green) at (A) 3 μm, (B) 3.6 μm, (C) 4.2 μm, (D) 4.8 μm, (E) 5.4 μm, (F) 6.0 μm, (G) 6.6 μm, (H) 7.2 μm in depth from the bone side of the osteoblast layer. Arrowheads in C and D show osteocytes partially stained with OB7.3. Arrows in F, G and H show osteocytes fully stained with OB7.3. (I and J) Three-dimensional reconstruction of osteocytes in chick calvaria by IMARIS. I shows the view from the osteoblast layer, and J shows the view from the bone side at the same location. Arrows in I and J show the process of a fully stained osteocyte. (K) This is a fluorescent image of a mixed culture of osteoblasts and osteocytes. Osteocytes that were stained partially and fully with OB7.3 were observed in

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9.4.82 Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength
Li X, Ominsky MS, Niu Q, Sun N, Daugherty B, D Agostin D, Kurahara C, Gao Y, Cao J, Gong J, Asuncion F, Barrero M, Warmington K, Dwyer D, Stolina M, Morony S, Sarosi I, Kostenuik PJ, Lacey DL, Simonet WS, Ke HZ, Paszty C
J Bone Miner Res 2008;23:860-9

SOST KO mice had increased radiodensity throughout the skeleton, with morphology being normal. DXA analysis of vertebrae and whole leg showed that there was An increase in BMD (>50%) at both sites. μCT analysis of femur showed that bone volume was increased in the trabecular and cortical compartments. Histomorphometry of trabecular bone revealed increased osteoblast surface and no change in osteoclast surface. The bone formation rate in SOST KO mice was increased for trabecular bone (>9-fold) at the distal femur, as well as for the endocortical and periosteal surfaces of the femur midshaft. Mechanical testing of lumbar vertebrae and femur showed that bone strength was increased at both sites.

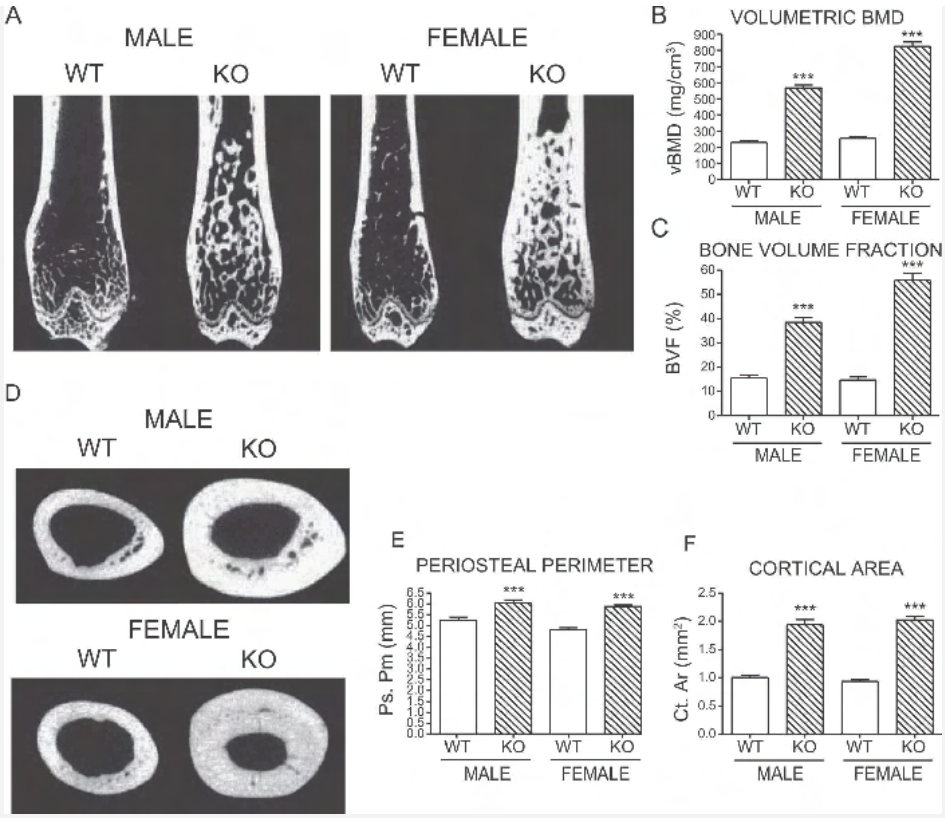


*Fig. 9.4.82a µCT analysis of distal femoral metaphysis and femur midshaft. (A) µCT images of distal femur showing increased trabecular bone volume in both male and female KO mice. Images represent the group medians for bone volume fraction (BVF). (B) Increased trabecular volumetric BMD (vBMD) and (C) BVF in male and female KO mice. (D) µCT images of femur midshaft representing the group medians for cortical area. Greater bone size, decreased marrow cavity area, and increased cortical thickness are visible in KO mice. (E) Increased periosteal perimeter (Ps. Pm) and (F) cortical area (Ct.Ar) in male and female KO mice. Values are mean±SE, n=11-17 per group. ***p<0.001 vs. sex-matched WT. Reproduced from J Bone Miner Res 2008;23:860-9 with permission of the American Society of Bone and Mineral Research.*

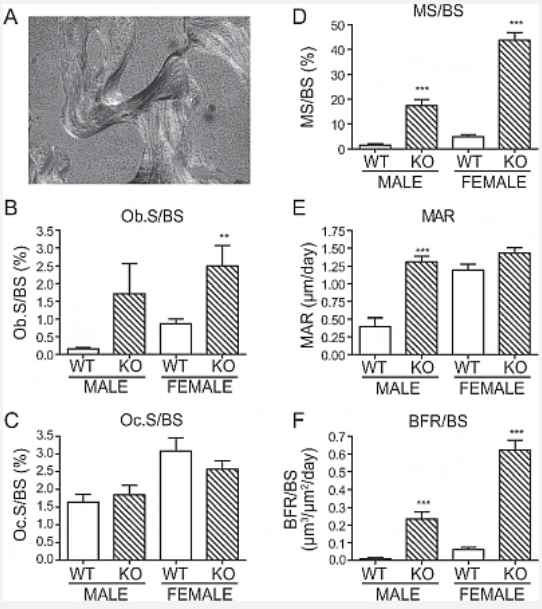


*Fig. 9.4.82b Histology and histomorphometric analysis of distal femoral metaphysis showing increased trabecular bone formation in KO mice. (A) Polarized light photomicrograph of trabecular bone from KO mouse femur showing normal lamellar bone structure. (B) Osteoblast surface (Ob.S/BS). (C) Osteoclast surface (Oc.S/BS). (D) Mineralizing surface (MS/BS). (E) Mineral apposition rate (MAR). (F) Bone formation rate (BFR/BS). Values are mean±SE, n=10-12 per group. **p<0.01, ***p<0.001 vs. sex-matched WT. Reproduced from J Bone Miner Res 2008;23:860-9 with permission of the American Society of Bone and Mineral Research.*

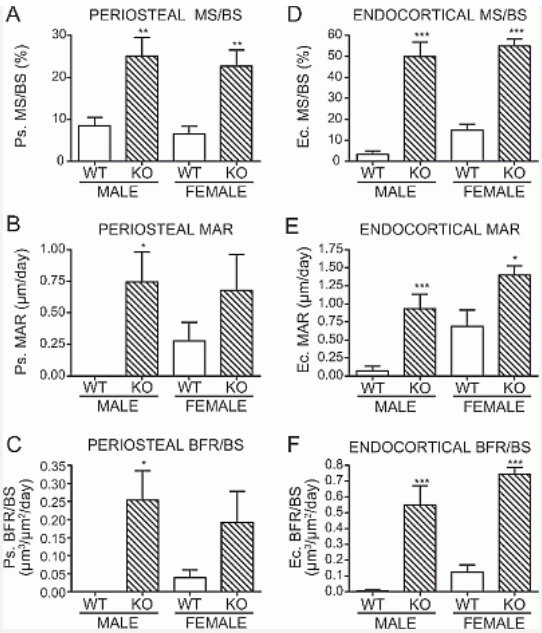
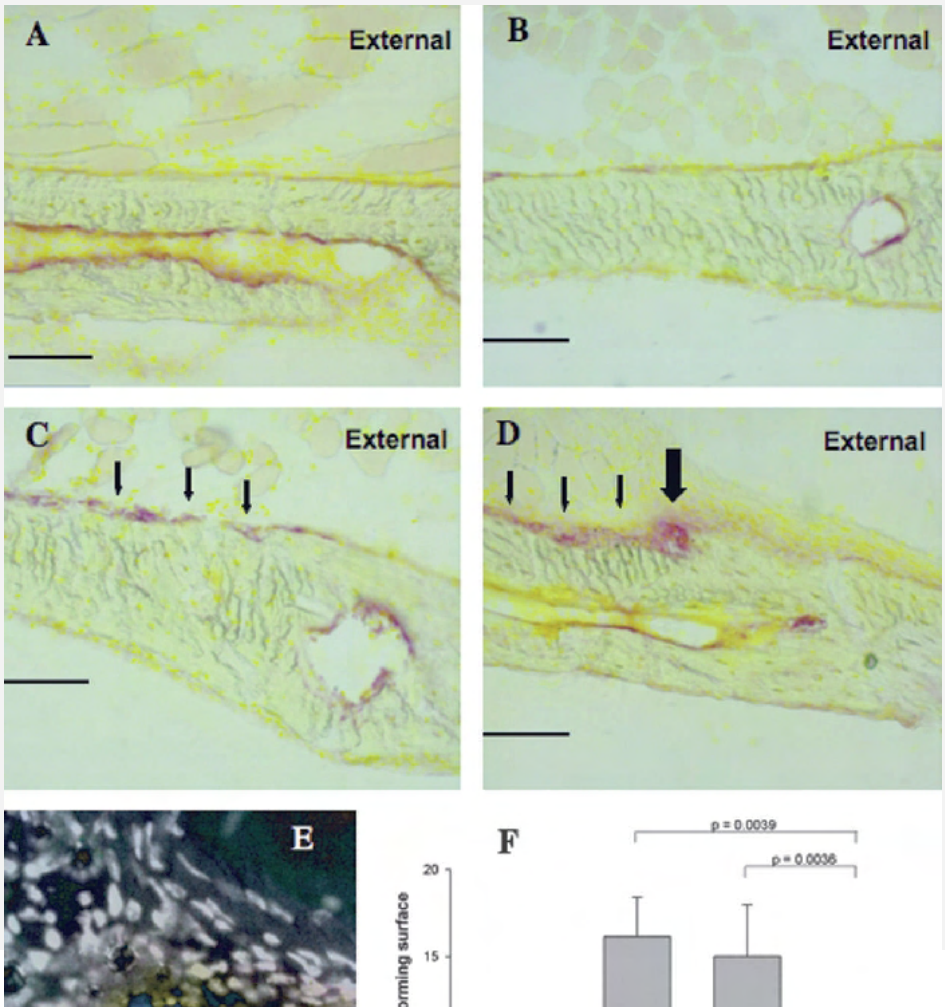


*Fig. 9.4.82c Dynamic histomorphometric analysis of femur midshaft showing increased cortical bone formation in KO mice. (A) Periosteal mineralizing surface (Ps. MS/BS). (B) Periosteal mineral apposition rate (Ps. MAR). (C) Periosteal bone formation rate (Ps. BFR/BS). (D) Endocortical mineralizing surface (Ec. MS/BS). (E) Endocortical mineral apposition rate (Ec. MAR). (F) Endocortical bone formation rate (Ec. BFR/BS). Values are mean±SE, n=10-12 per group. *p<0.05, **p<0.01, ***p<0.001 vs. sexmatched WT. Note that for WT males, sets of double labels were not detectable; therefore, Ps. MAR and Ps. BFR/BS equaled zero. Reproduced from J Bone Miner Res 2008;23:860-9 with permission of the American Society of Bone and Mineral Research.*

9.4.83 Apoptotic bodies convey activity capable of initiating osteoclastogenesis and localized bone destruction
Kogianni G, Mann V, Noble BS
J Bone Miner Res 2008;23:915-27

Osteocyte apoptosis co-localizes with osteoclastic bone resorption. Osteocyte apoptotic bodies (OABs) from MLO-Y4 osteocyte-like cell line and primary murine osteocytes and apoptotic bodies (ABs) from primary murine osteoblasts were introduced onto the right parietal bone of murine calvariae. The ability of primary murine and cell line-derived OABs to support osteoclastogenesis was examined in vitro in co-culture with murine bone marrow hematopoietic progenitors. OABs initiated osteoclastic resorption in vivo. Addition of OABs to mononuclear osteoclast precursors (OPs) in vitro resulted in the maintenance of OP cell numbers and an increase in the proportion and activity of TRACP+ cells. The osteoclastogenic capacity of OABs was independent of RANKL but dependent on the induction of TNF-α production by OP. Dying osteocytes target bone destruction through the distribution of OAB-associated signals.



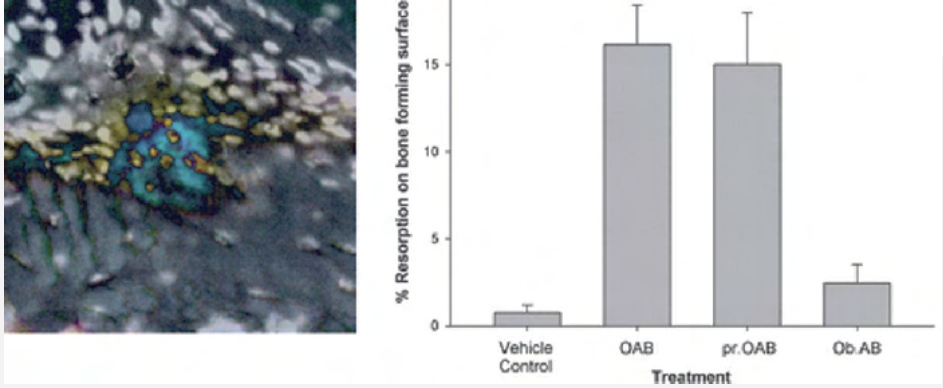


Fig. 9.4.83 Osteocyte ABs support osteoclastogenesis in vivo. Photomicrograph of TRACP stained calvariae sections after injection with (A) PBS vehicle control, (B) primary osteoblast apoptotic bodies (Ob.AB), (C) primary osteocyte apoptotic bodies (pr.OAB), or (D) MLO-Y4 osteocyte cell line apoptotic bodies (OAB). Sections were counterstained with DAPI to visualize cell nuclei, which appears as yellow signal. Bar=100 µm. (E) False colored image of an osteoclast, marked by the large arrow in D, showing multiple nuclei stained with DAPI. (F) The percentage of TRACP+ bone surface was measured across the formation side of calvariae after treatment. Reproduced from J Bone Miner Res 2008;23:915-27 with permission of the American Society of Bone and Mineral Research.

9.4.84 Oxygen tension regulates preosteocyte maturation and mineralization

Zahm AM, Bucaro MA, Srinivas V, Shapiro IM, Adams CS

Bone 2008;43:25-31

Volume 9, Issue 4, 2008

Systemic Factors

9.4.85 Calcitonin receptor plays a physiological role to protect against hypercalcemia in mice

Davey RA, Turner AG, McManus JF, Chiu WS, Tjahyono F, Moore AJ, Atkins GJ, Anderson PH, Ma C, Glatt V, MacLean HE, Vincent C, Bouxsein M, Morris HA, Findlay DM, Zajac JD

J Bone Miner Res 2008;23:1182-93

Data from genetically modified animal models suggest a possible role for calcitonin and calcitonin receptor (CTR) in controlling bone formation. In a global CTR knockout (KO) mouse model using the Cre/loxP system, in which the CTR is globally deleted by >94% but <100%, normal serum ultrafiltrable calcium levels and a mild increase in bone formation in males was observed. CTR plays a modest physiological role in the regulation of bone and calcium homeostasis in the basal state in mice. Furthermore, the peak in serum total calcium after calcitriol [1,25(OH)(2)D(3)]-induced hypercalcemia was greater in global CTRKOs than controls. These data provide evidence for a biological role of the CTR in regulating calcium homeostasis in states of calcium stress.

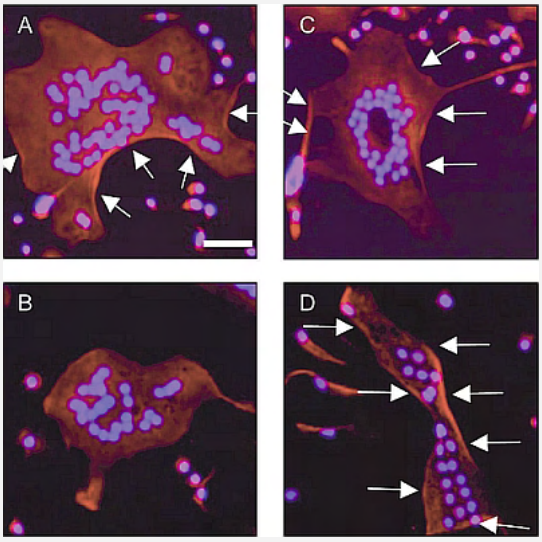
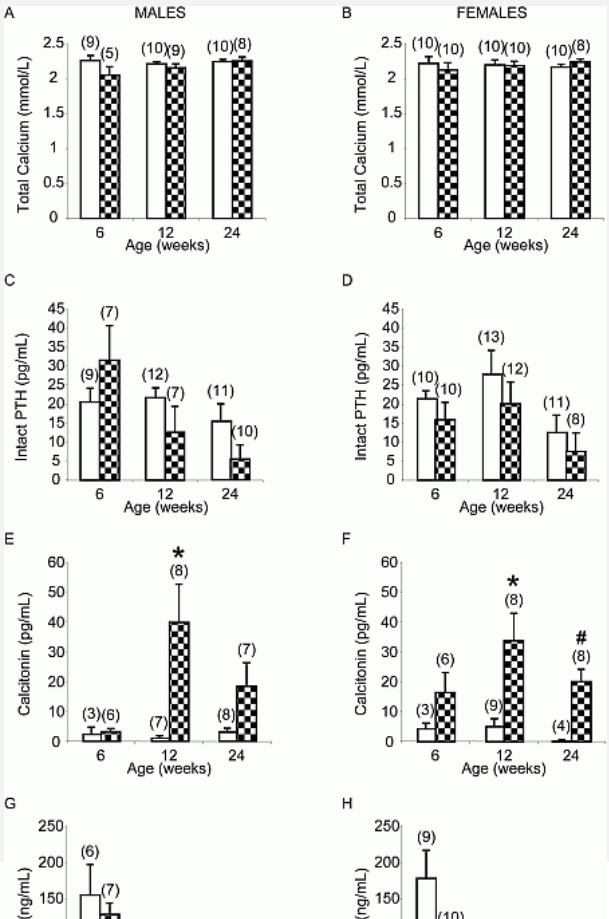


Fig. 9.4.85a Phalloidin staining of actin rings in osteoclast-like cells derived from the bone marrow of (A) control, (B) control treated for 30 min with 0.01 nM salmon calcitonin (sCT), (C) global CTRKO, and (D) global CTRKO treated for 30 min with 0.01 nM sCT. Arrows indicate actin ring. Nuclei of osteoclasts are counter-stained with DAPI. Scale bar represents 50 µm. Reproduced from J Bone Miner Res 2008;23:1182-93 with permission of the American Society of Bone and Mineral Research.



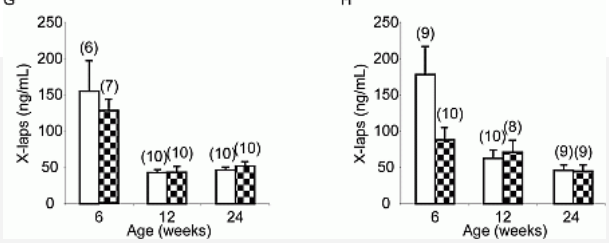


*Fig. 9.4.85b Serum biochemistry in control (white bars) and global CTRKOs (patterned bars): total serum calcium in (A) males and (B) females; intact PTH in (C) males and (D) females; calcitonin in (E) males and (F) females; and X-laps in (G) males and (H) females. Values are mean±SE; numbers in each group are shown in parentheses. *p<0.05, #p<0.005 vs. control at the same time point. Reproduced from J Bone Miner Res 2008;23:1182-93 with permission of the American Society of Bone and Mineral Research.*

9.4.86 Bone mineral density and bone turnover in relation to serum leptin, alpha-ketoglutarate and sex steroids in overweight and obese postmenopausal women

Filip R, Raszewski G

Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

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

Volume 9, Issue 4, 2008

Local Factors

9.4.87 Aromatase expression in osteoarthritic and osteoporotic bone
Hernandez JL, Garces CM, Sumillera M, Fernandez-Aldasoro EV, Garcia-Ibarbia C, Ortiz-Gomez JA, Arozamena J, Alonso MA, Riancho JA
Arthritis Rheum 2008;58:1696-700

In 104 patients with hip fracture (n=60) or primary hip OA (n=44), aromatase expression was determined in trabecular bone samples from the femoral neck and in osteoblast cultures grown by the primary explant technique (n=62), using real time reverse transcriptase-polymerase chain reaction. Aromatase RNA was detected in bone samples at levels similar to those found in adipose tissue. Transcript levels were lower in bone tissue samples obtained from patients with OA than in those obtained from patients with fracture (P=0.00001). Likewise, primary cultures of osteoblastcells from OA patients revealed lower aromatase expression than those of cells from fracture patients (P=0.012).

9.4.88 Identification of full-length dentin matrix protein 1 in dentin and bone
Huang B, Maciejewska I, Sun Y, Peng T, Qin D, Lu Y, Bonewald L, Butler WT, Feng J, Qin C
Calcif Tissue Int 2008;82:401-10

9.4.89 High levels of serum IL-18 promote cartilage loss through suppression of aggrecan synthesis
Inoue H, Hiraoka K, Hoshino T, Okamoto M, Iwanaga T, Zenmyo M, Shoda T, Aizawa H, Nagata K
Bone 2008;42:1102-10

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

Volume 9, Issue 4, 2008

Risk Factors

9.4.90 Vitamin D insufficiency: Disease or no disease?
Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Engelke JA, Shafer MM
J Bone Miner Res 2008;23:1052-60

Vitamin D insufficiency (VDI) rests on increases in fractional calcium absorption (FCA) when 25(OH)D increases above 30 ng/ml. Postmenopausal women with VDI [25(OH)D=16-24 ng/ml] and calcium intake ≤1100 mg daily underwent FCA studies before and after correction of VDI with ergocalciferol 50,000 IU/d for 15 days. Eighteen women completed the study; all but two had normal PTH. During the first and second FCA studies, their mean 25(OH)D was 22±4 and 64±21 ng/ml, respectively (p<0.001). Subjects' average FCA was 24±7% initially and 27±6% after vitamin D repletion (p=0.04). Thus, FCA increased by 3 ±1% with correction of VDI, this small change does not associate with lower fracture rates or consistently higher bone mass.

9.4.91 Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors
Neuhouser ML, Sorensen B, Hollis BW, Ambs A, Ulrich CM, McTiernan A, Bernstein L, Wayne S, Gilliland F, Baumgartner K, Baumgartner R, Ballard-Barbash R
Am J Clin Nutr 2008;88:133-9

In 790 breast cancer survivors, 597 (75.6%) had low serum 25(OH)D. The overall mean (±SD) was 24.8±10.4 ng/mL, but it was lower for African Americans (18.1±8.7 ng/mL) and Hispanics (22.1±9.2 ng/mL). Women with localized (n=424) or regional (n=182) breast cancer had lower serum 25(OH)D than did women with in situ disease (n=184) (P=0.05 and P=0.03, respectively). Stage of disease predicted serum 25(OH)D (P=0.02). In these breast cancer survivors, the prevalence of vitamin D insufficiency was high.

9.4.92 Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality
Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W
Arch Intern Med 2008;168:1340-9

In a prospective cohort study, 3258 consecutive male and female patients (mean [SD] age, 62 [10] years) scheduled for coronary angiography, during a median follow-up of 7.7 years, 737 (22.6%) died, including 463 deaths from cardiovascular causes. HRs for lower two 25-D quartiles (median, 7.6 and 13.3 ng/mL were higher for all-cause mortality (HR, 2.08;1.60-2.70; and HR, 1.53; 95% CI, 1.17-2.01; respectively) and for cardiovascular mortality (HR, 2.22; 1.57-3.13; and HR, 1.82; 1.29-2.58; respectively) compared with patients in the highest 25-hydroxyvitamin D quartile (median, 28.4 ng/mL). Similar results were obtained for patients in the lowest 1,25-D quartile.

9.4.93 Progression of vascular calcifications is associated with greater bone loss and increased bone fractures
Naves M, Rodriguez-Garcia M, Diaz-Lopez JB, Gomez-Alonso C, Cannata-Andia JB
Osteoporos Int 2008;19:1161-6

Men and women (n=624) aged 50 and over underwent two lateral X-rays of thoracic and lumbar spine and a DXA study at lumbar spine and hip, and were followed during 4 years. Abdominal aortic calcifications were classified as absent, mild-moderate and severe. There was a positive relationship between the prevalence of aortic calcifications and age. In both sexes, prevalent severe aortic calcifications were associated with prevalent fractures [odds ratio (OR)=1.93 (1.02-3.65)]. The association was stronger when only vertebral fracture was considered [OR=2.45 (1.23-4.87)]. In addition, progression of aortic calcifications showed a positive association with the rate of decline in BMD at lumbar spine. Aortic calcifications at baseline were positively associated with osteoporotic fractures. The progression of aortic calcifications was also positively associated with the rate of decline in BMD at lumbar spine.

9.4.94 Tibial bone geometry in chronic stroke patients: Influence of sex, cardiovascular health, and muscle mass
Pang MY, Ashe MC, Eng JJ
J Bone Miner Res 2008;23:1023-30

Fifty-five individuals with stroke were studied. In men, marrow cavity area on the paretic side was greater than the nonparetic side (p=0.011), whereas the total bone area showed no side-to-side difference (p=0.252). In women, total bone area on the paretic side was smaller than the nonparetic side (p = 0.003), whereas marrow area had no side-to-side difference. Peak oxygen consumption (r(2)=0.739, F(5,49)=22.693) and paretic leg lean mass (r(2)=0.802, F(6,48)=32.475) remained associated with tibial BSI. The geometry of the tibia in stroke patients showed sex-specific side-to-side differences. The results suggested that, whereas endosteal resorption was apparent in men, periosteal resorption was more predominant in women.

9.4.95 The presence of both an energy deficiency and estrogen deficiency exacerbate alterations of bone metabolism in exercising women
De Souza MJ, West SL, Jamal SA, Hawker GA, Gundberg CM, Williams NI
Bone 2008;43:140-8

In 44 exercising women, resting energy expenditure (REE) and urinary estrone and pregnanediol glucuronides (E1G, PdG) were measured. Volunteers were then categorized into: 1) Energy Replete+Estrogen Replete (EnR+E(2)R), (n=22); 2) Energy Replete+Estrogen Deficient (EnR+E(2)D), (n=7); 3) Energy Deficient+Estrogen Replete (EnD+E(2)R), (n=7); and 4) Energy Deficient+Estrogen Deficient (EnD+E(2)D), (n=8). By design, REE/FFM (p=0.028) and REE:pREE (p<0.001) were lower in the EnD vs. EnR group, and the E(2)D group had a lower REE:pREE (p=0.005) compared to the E(2)R group. The EnD+E(2)D group had suppressed PINP (p=0.034), and elevated U-CTX-I (p=0.052) and ghrelin (p=0.028) levels compared to the other groups.

These same women also had evidence of energy conservation, including TT(3) levels that were 29% lower (p=0.057) and ghrelin levels that were 44% higher (p=0.028) than that observed in the other groups. Energy deficiency was associated with suppressed osteocalcin, and TT(3) (p<0.05), whereas estrogen deficiency was associated with decreased E1G (p<0.02), and lower L2-L4 BMD (p=0.033). Leptin was significant in predicting markers of bone formation, but not markers of bone resorption. When the energy status of exercising women was adequate (replete), there were no apparent perturbations of bone formation or resorption, regardless of estrogen status. Estrogen deficiency in exercising women, in the presence of an energy deficiency, was associated with bone loss, suppressed bone formation and increased bone resorption.

9.4.96 Assessment of the 10-year probability of osteoporotic hip fracture combining clinical risk factors and heel bone ultrasound: The EPISEM prospective cohort of 12,958 elderly women
Hans D, Durosier C, Kanis JA, Johansson H, Schott-Pethelaz AM, Krieg MA
J Bone Miner Res 2008;23:1045-51

This study developed a hip screening tool that combines clinical risk factors (CRFs) and QUS at the heel to determine the 10-yr probability of hip fractures in elderly women. In 13,000 women 70 yr of age. Three hundred seven hip fractures were observed over a mean follow-up of 3.2 yr. In addition to SI, significant CRFs for hip fracture were body mass index, history of fracture, an impaired chair test, history of a recent fall, current cigarette smoking, and diabetes mellitus. The average GR for hip fracture was 2.10 per SD with the combined SI+CRF score compared with a GR of 1.77 with SI alone and of 1.52 with the CRF score alone. Thus, the use of CRFs enhanced the predictive value of SI alone. For example, in a woman 80 yr of age, the presence of two to four CRFs increased the probability of hip fracture from 16.9% to 26.6% and from 52.6% to 70.5% for SI Z-scores of +2 and -3, respectively.

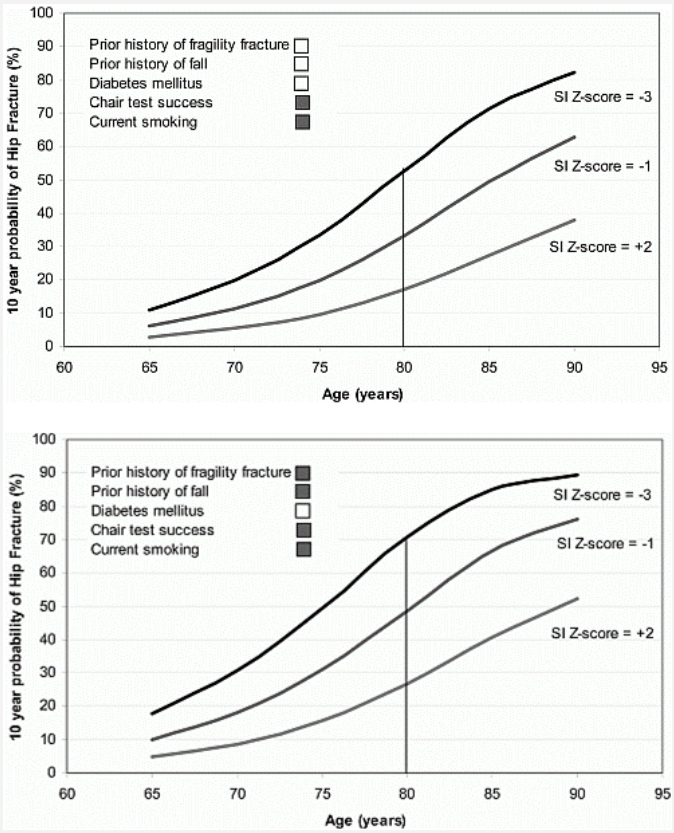

Fig. 9.4.96 Ten-year probability of hip fracture for a given BMI of 26 kg/m2, at different stiffness index Z-score, and the presence of two clinical risk factors (top panel) or four clinical risk factors (bottom panel). The shadowed squares means the presence of this specific CRF. Reproduced from J Bone Miner Res 2008;23:1045-51 with permission of the American Society of Bone and Mineral Research.

9.4.97 Association between functional capacity tests and fractures: An eight-year prospective population-based cohort study
Karkkainen M, Rikkonen T, Kroger H, Sirola J, Tuppurainen M, Salovaara K, Arokoski J, Jurvelin J, Honkanen R, Alhava E
Osteoporos Int 2008;19:1203-10

2928 postmenopausal women took part in the functional capacity and muscle strength tests. The duration of fracture follow-up varied from 6.43 to 9.86 (mean 8.37) years and the first fracture was the end-point event for the statistical analyses. A total of 261 endpoint fractures occurred. In multivariate analysis the inability to stand-on-one-foot for 10 seconds increased the risk of hip fracture (hazard ratio with 95% CI) 9.11-fold (1.98-42.00). Decreased grip strength associated with 1.05-fold (1.01-1.09) increased risk of hip fractures. Low leg extension strength associated with 1.02-fold (1.00-1.03) higher risk for all fractures. The self-assessed ability to walk less than 100 meters at baseline increased the risk of ankle 2.36-fold (1.10-5.08), hip 11.57-fold (2.73-49.15) and clinical vertebral fractures 3.85-fold (1.45-10.22). According to these results the standing-on-one-foot less than 10 s, grip strength and a question about ability to walk less than 100 m may help to predict postmenopausal fractures.

9.4.98 The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15-years
Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J, Silverberg SJ
J Clin Endocrinol Metab 2008;[Epub ahead of print]

116 patients (25 men, 91 women); 99 (85%) were asymptomatic. 59 (51%) underwent parathyroidectomy and 57 were followed without surgery. Lumbar spine BMD remained stable for 15 yrs. BMD started to fall at cortical sites before 10 years, decreasing by 10 % at the femoral neck, and 35% at the distal radius in the patients observed for 15 years. 37% of asymptomatic patients showed disease progression at any time point over the 15 years. Meeting surgical criteria at baseline did

not predict who would have progressive disease. BMD increases in patients who underwent surgery were sustained for 15 years. Parathyroidectomy led to normalization of biochemical indices and sustained increases in BMD. Without surgery, PHPT progressed in one-third of individuals; meeting surgical criteria at the outset did not predict this progression.

9.4.99 Hip and other osteoporotic fractures increase the risk of subsequent fractures in nursing home residents
Lyles KW, Schenck AP, Colon-Emeric CS
Osteoporos Int 2008;19:1225-33

Medicare enrollees aged 50 and older in a nursing home in North Carolina in 2000 (n=30,655) were identified and hospitalization claims in the preceding 4 years showed hip fracture (n=7257) or other fracture (n=663) cases. We followed participants from nursing home entry until the end of 2002 using Medicare hospital claims to determine which participants were hospitalized with a subsequent fracture (n=3381). Among residents with no recent fracture history, 6.8% had a hospital claim for a subsequent fracture, while 15.1% of those with a prior non-hip fracture and 23.9% of participants with a prior hip fracture sustained subsequent fractures. Persons with prior hip fractures are at three times higher risk (HR=2.99, 95% CI: 2.78, 3.21) and those hospitalized with other non-hip fractures are at 1.8 times higher risk of subsequent fractures (HR=1.84, 95% CI: 1.50, 2.25). Nursing home residents hospitalized with a prior osteoporotic fracture are at increased risk of a fracture.

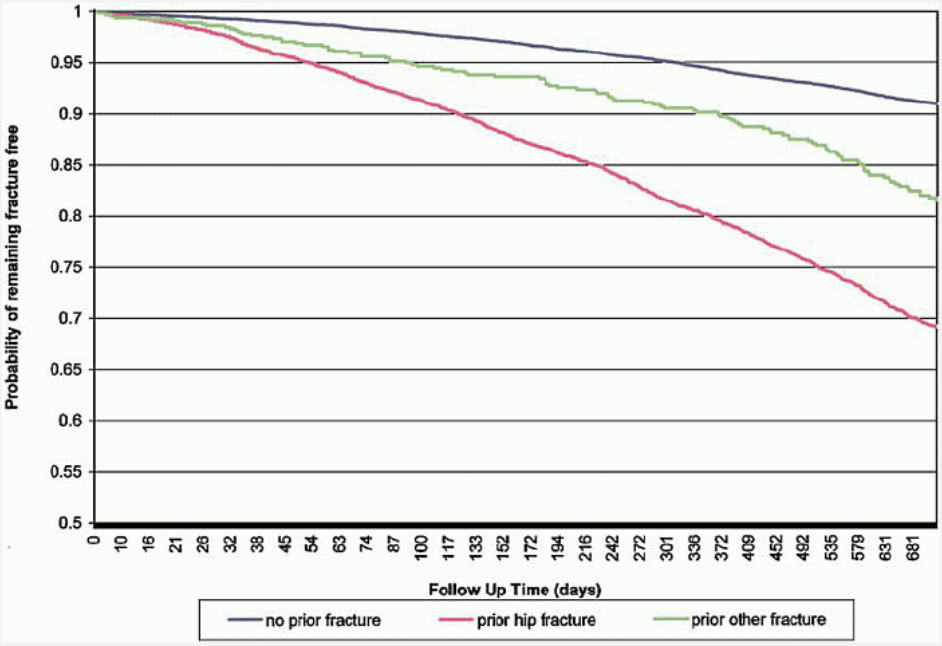

Fig. 9.4.99 Estimate of time to fracture for North Carolina Medicare enrollees admitted to a nursing home in 2000, by prior fracture status. Reproduced from Osteoporos Int 2008;19:1225-33 with permission from Springer.

9.4.100 Bone mineral metabolism and its relationship to kidney disease in a residential care home population: A cross-sectional study
Carter JL, O'Riordan SE, Eaglestone GL, Delaney MP, Lamb EJ
Nephrol Dial Transplant 2008;[Epub ahead of print]

In 188 residents not receiving vitamin D/calcium [mean age 85 (range 68- 100) years, 75% female] and in 52 residents receiving vitamin D/calcium, in the former, median PTH increased with declining GFR (P<0.0001), particularly as GFR (mL/min/1.73 m(2)) fell below 45. PTH was suppressed by increasing 25-D, but not 1,25-D (P>0.05) concentration. Nearly all (92%) had 25-D deficiency or insufficiency and this was uninfluenced by kidney function (P>0.05). Concentration of 1,25- D declined with worsening renal function but 1,25-D deficiency was prevalent at all stages of kidney disease, including amongst residents receiving vitamin D/calcium supplementation. Vitamin D deficiency and secondary hyperparathyroidism are common irrespective of renal function. However, as GFR falls below 45, the prevalence of secondary hyperparathyroidism and 1,25-D deficiency increases.

9.4.101 Isoform of fibronectin mediates bone loss in patients with primary biliary cirrhosis by suppressing bone formation
Kawelke N, Bentmann A, Hackl N, Hager HD, Feick P, Geursen A, Singer MV, Nakchbandi IA
J Bone Miner Res 2008;23:1278-86

Production of fibronectins during liver disease may result in decreased osteoblast-mediated mineralization. In patients with primary biliary cirrhosis, the oncofetal domain of fibronectin correlated with the decrease in osteocalcin, (r=-0.57, p<0.05). In vitro, amniotic fluid fibronectin (aFN) containing mainly the oncofetal domain and EIIIA domain resulted in decreased osteoblast-mediated mineralization in human osteoblasts (69% decrease at 100 µg/ml; p<0.01) and mouse osteoblasts (71% decrease; p<0.05). Removing the EIIIA domain from aFN similarly suppressed mineralization by osteoblasts (78% decrease; p<0.05). Injection of labeled aFN in mice showed that it infiltrates the bone, and its administration over 10 days resulted in decreased trabecular BMD (17% drop; p<0.05), mineralizing surface (30% drop; p<0.005), and number of osteoblasts (45% drop; p<0.05).

9.4.102 Uptake of postprandial lipoproteins into bone in vivo: Impact on osteoblast function
Niemeier A, Niedzielska D, Secer R, Schilling A, Merkel M, Enrich C, Rensen PC, Heeren J
Bone 2008;43:230-7

As a model for the postprandial state, chylomicron remnants (CR) were injected intravenously into mice. Next to the liver and compared to other organs, bone appeared to be the second most important organ for the clearance of radiolabeled CR particles from the circulation in vivo. In addition, uptake of radiolabeled CR by primary murine osteoblasts and hepatocytes was quantified to be in a similar range in vitro. A complementary approach with fluorescently labeled CR and immunohistochemical staining for apoE proved that intact CR particles were taken up into bone and liver. Electron

microscopy revealed CR uptake into sinusoidal endothelial cells, macrophages and osteoblasts. The relative amount of radiolabeled CR uptake into femoral cortical bone, representing predominantly osteoblasts, and bone marrow, representing predominantly non-osteoblast cells, was within the same range. Injection of vitamin K(1)-enriched CR resulted in an increase of the degree of osteocalcin carboxylation in vivo while total osteocalcin remained unaffected, so osteoblasts process CR in vivo. Bone is involved in the postprandial lipoprotein metabolism in mice. Osteoblasts participate in CR clearance from the circulation, which has a direct impact on the secretory function of osteoblasts.

9.4.103 Predictors of bone density in ambulatory patients on antiepileptic drugs
El-Hajj Fuleihan G, Dib L, Yamout B, Sawaya R, Mikati MA
Bone 2008;43:149-55

In patients with epilepsy, 137 adults mean age of 31 years, on therapy for a mean of 11.7 years, and 88 children mean age of 13 years, on therapy for an average of 4.7 years, hypovitaminosis D was common. BMD was reduced in adults but not children by 0.3-0.6 SD. Duration of treatment, but not vitamin D levels, was negatively correlated with BMD at the hip in adults. Bone density was reduced and was most severely reduced at the spine and hip with the use of enzyme-inducing drugs. Polytherapy in children and duration of therapy and enzyme-inducing drugs in adults were independent predictors of BMD.

9.4.104 Significance of serum TRACP in rheumatoid arthritis
Janckila AJ, Neustadt DH, Yam LT
J Bone Miner Res 2008;23:1287-95

Serum TRACP 5a protein is increased in about one-third of rheumatoid arthritis (RA) sera. 118 patients, 50 with RA (25 with nodules), 26 with osteoarthritis (OA), and 42 with other rheumatic diseases. 26 healthy adults served as controls. Mean TRACP 5a protein was elevated only in RA. TRACP 5a protein correlated only with IgM-RF in RA. Among RA patients, mean TRACP 5a protein and IgM RF were higher in nodule formers. In contrast, TRACP 5b activity was slightly elevated in RA and correlated with BALP, ICTP, and YKL-40 but not with IgM-RF or CRP. Mean TRACP 5b activity was no different in RA patients with or without nodules. TRACP 5a protein may be a measure of systemic inflammatory macrophage burden and disease severity. TRACP 5b activity is a marker for osteoclast number and perhaps local or systemic bone destruction.

9.4.105 Caloric restriction decreases cortical bone mass but spares trabecular bone in the mouse skeleton: Implications for the regulation of bone mass by body weight
Hamrick MW, Ding K, Ponnala S, Ferrari SL, Isales CM
J Bone Miner Res 2008;23:870-8

Caloric restriction (CR) results in a decline in lean and fat mass, percent body fat, serum leptin, and serum IGF-1. Whole body BMC and BMD did not differ between the CR and controls. Femur BMC, BMD, cortical thickness, and fracture strength decreased in CR mice, but trabecular bone volume fraction in the femur did not change with food restriction. Vertebral cortical thickness also decreased with caloric restriction; spine BMC, BMD, and trabecular bone volume fraction were increased. Consistent with the opposite effects of leptin on cortical and cancellous bone, trabecular bone mass is spared during food restriction.

9.4.106 Influence of high and low protein intakes on age-related bone loss in rats submitted to adequate or restricted energy conditions
Mardon J, Habauzit V, Trzeciakiewicz A, Davicco MJ, Lebecque P, Mercier S, Tressol JC, Horcajada MN, Demigne C, Coxam V
Calcif Tissue Int 2008;82:373-82

In 16-month old male rats, controls were fed a normal-protein content (13%, C-NP) or a high-protein content (26%) (C-HP). The other groups received a 40% protein/energy-restricted diet (PER-NP and PER-HP) or a normal protein/energy-restricted diet (ER-NP and ER-HP). After 5 months, protein intake (13% or 26%) did not modulate calcium retention or bone status in those rats, although a low-grade metabolic acidosis was induced with the HP diet. Both restrictions (PER and ER) decreased femoral bone mineral density and fracture load. Plasma osteocalcin and urinary deoxypyridinoline levels were lowered, suggesting a decrease in bone turnover in the PER and ER groups. Circulating insulin-like growth factor-I levels were also lowered by dietary restrictions, together with calcium retention. Both energy and protein deficiencies may contribute to age-related bone loss.

9.4.107 Short-term effect of ovariectomy on osteoprogenitors in the healing rat mandibular incisor extraction socket
Shoji K, Basso N, Elsubeihi ES, Heersche JN
Osteoporos Int 2008;19:1193-201

6-mo old rats were ovariectomized (n=8) and control rats were left intact (n=8). Two weeks post-OVX, the right mandibular incisor was extracted. Four weeks post-extraction, the basal mandibular bone between the 1st and 3rd molar in the healing extraction socket was used to determine the number of fibroblastic progenitors (CFU-F), alkaline phosphatase-positive fibroblastic progenitors (AP-positive CFU-F), Dex-dependent osteoprogenitors (CFU-O Dex) and Prog-dependent osteoprogenitors (CFU-O Prog) using colony assays (n=5). Osteocalcin mRNA expression was evaluated using in situ hybridization (n=3). Data were analyzed using two-way ANOVA or Student's t-test. OVX increased the percentage of AP-positive CFU-F in both mandible and femur. The number of CFU-O was increased only in femur. Osteocalcin mRNA expression in regenerating mandible was not statistically different between control and OVX animals. OVX on osteoprogenitors is either smaller or develops later in mandible relative to femur.

9.4.108 Natural history and risk factors for bone loss in postmenopausal Caucasian women: A 15-year follow-up population-based study
Zhai G, Hart DJ, Valdes AM, Kato BS, Richards JB, Hakim A, Spector TD
Osteoporos Int 2008;19:1211-7

9.4.109 Impact of systematic implementation of a clinical case finding strategy on diagnosis and therapy of postmenopausal osteoporosis
Geusens P, Dumitrescu B, van Geel T, van Helden S, Vanhoof J, Dinant GJ
J Bone Miner Res 2008;23:812-8

9.4.110 Clinical performance of osteoporosis risk assessment tools in women aged 67 years and older
Gourlay ML, Powers JM, Lui LY, Ensrud KE
Osteoporos Int 2008;19:1175-83

9.4.111 Correlates of bone mineral density among postmenopausal women of African Caribbean ancestry: Tobago women's health study
Hill DD, Cauley JA, Bunker CH, Baker CE, Patrick AL, Beckles GL, Wheeler VW, Zmuda JM
Bone 2008;43:156-61

9.4.112 Secondary contributors to bone loss in osteoporosis related hip fractures
Edwards BJ, Langman CB, Bunta AD, Vicuna M, Favus M
Osteoporos Int 2008;19:991-9

9.4.113 Vitamin D, parathyroid hormone 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) 2008;[Epub ahead of print]

9.4.114 Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans
Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, Wagenknecht LE, Bowden DW, Norris JM
J Clin Endocrinol Metab 2008;[Epub ahead of print]

9.4.115 Risk factors for decreased bone density and effects of HIV on bone in the elderly
Jones S, Restrepo D, Kasowitz A, Korenstein D, Wallenstein S, Schneider A, Keller MJ
Osteoporos Int 2008;19:913-8

9.4.116 Relationship between mandibular inferior cortex and general bone metabolism in older adults
Deguchi T, Yoshihara A, Hanada N, Miyazaki H
Osteoporos Int 2008;19:935-40

9.4.117 Prevalence of pre-stroke low bone mineral density and vertebral fracture in first stroke patients
Kim HW, Kang E, Im S, Ko YJ, Im SA, Lee JI
Bone 2008;43:183-6

9.4.118 Peptide YY (PYY) levels and bone mineral density (BMD) in women with anorexia nervosa
Utz AL, Lawson EA, Misra M, Mickley D, Gleysteen S, Herzog DB, Klibanski A, Miller KK
Bone 2008;43:135-9

9.4.119 Urban tropospheric ozone increases the prevalence of vitamin D deficiency among Belgian postmenopausal women with outdoor activities during summer
Manicourt DH, Devogelaer JP
J Clin Endocrinol Metab 2008;[Epub ahead of print]

9.4.120 Quantitative ultrasound detects bone impairment after bone marrow transplantation in children and adolescents affected by hematological diseases
Di Iorgi N, Muratori T, Secco A, Napoli F, Fratangeli N, De Terlizzi F, Giorgiani G, Locatelli F, Maghnie M
Bone 2008;43:177-82

9.4.121 The influence of gluten free diet on quantitative ultrasound of proximal phalanxes in children and adolescents with type 1 diabetes mellitus and celiac disease
Valerio G, Spadaro R, Iafusco D, Lombardi F, Del Puente A, Esposito A, De Terlizzi F, Prisco F, Troncone R, Franzese A
Bone 2008;43:322-6

9.4.122 Fracture prevalence and relationship to endocrinopathy in iron overloaded patients with sickle cell disease and thalassemia
Fung EB, Harmatz PR, Milet M, Coates TD, Thompson AA, Ranalli M, Mignaca R, Scher C, Giardina P, Robertson S, Neumayr L, Vichinsky EP
Bone 2008;43:162-8

9.4.123 Bone mineral density and body composition in men with systemic lupus erythematosus: A case control study
Mok CC, Ying SK, To CH, Ma KM
Bone 2008;43:327-31

9.4.124 Skeletal differences in bone mineral area and content before and after cure of endogenous Cushing's syndrome
Futo L, Toke J, Patocs A, Szappanos A, Varga I, Glaz E, Tulassay Z, Racz K, Toth M
Osteoporos Int 2008;19:941-9

9.4.125 The association of Parkinson's disease with bone mineral density and fracture in older women
Schneider JL, Fink HA, Ewing SK, Ensrud KE, Cummings SR
Osteoporos Int 2008;19:1093-7

9.4.126 Iodothyronine deiodinase enzyme activities in bone
Williams AJ, Robson H, Kester MH, van Leeuwen JP, Shalet SM, Visser TJ, Williams GR
Bone 2008;43:126-34

9.4.127 Effects of spinal cord injury and hindlimb immobilization on sublesional and supralesional bones in young growing rats
Liu D, Zhao CQ, Li H, Jiang SD, Jiang LS, Dai LY
Bone 2008;43:119-25

9.4.128 Protective effect of green tea polyphenols on bone loss in middle-aged female rats
Shen CL, Wang P, Guerrieri J, Yeh JK, Wang JS
Osteoporos Int 2008;19:979-90

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

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Corticosteroid Therapy

9.4.129 Glucocorticoid excess in mice results in early activation of osteoclastogenesis and adipogenesis and prolonged suppression of osteogenesis: A longitudinal study of gene expression in bone tissue from glucocorticoid-treated mice

Yao W, Cheng Z, Busse C, Pham A, Nakamura MC, Lane NE

Arthritis Rheum 2008;58:1674-86

Long bones from mice exposed to glucocorticoid (GC) excess were collected after 0, 7, 28, and 56 days of treatment. Bone loss in this animal model was confirmed by changes in bone turnover markers and architecture. GC excess induced an early upregulation of genes involved in osteoclast activation, function, and adipogenesis, which peaked on day 7. The expression of genes associated with osteoclast cytoskeletal reorganization and genes associated with matrix degradation peaked on day 28. On day 28 and day 56, the expression of genes associated with osteoblast activation and maturation was decreased from baseline, while the expression of Wnt antagonists was increased. In addition, the expression of genes expressed in osteocytes associated with bone mineralization was higher at the later time points, day 28 and day 56.

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

Volume 9, Issue 4, 2008

Falls

9.4.130 Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly
Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, Yoshida H
J Bone Miner Res 2008;23:1309-17

2957 persons (950 men and 2007 women) 65-92 yr of age participated in mass health examinations. Mean 25(OH)D was lower in women than in men ($p<0.001$). Women showed a decline of 25(OH)D with increased age ($p<0.001$). There was also a difference in the prevalence of 25(OH)D insufficiency [25(OH)D level <20 ng/ml] between the sexes ($p<0.001$). The rate of falls was significantly higher in the lowest quartile of 25(OH)D level in women ($p=0.02$) and in women with 25(OH)D insufficiency ($p=0.001$). Women also showed declines in all three fall-related physical performance tests. Multiple logistic regression analysis showed independent associations between 25(OH)D and experience of falls in women only ($p=0.01$). Low 25(OH)D level was associated with a high prevalence of falls in Japanese elderly women.

9.4.131 Vitamin D receptor polymorphisms and falls among older adults living in the community: Results from the iISIRENTE study
Onder G, Capoluongo E, Danese P, Settanni S, Russo A, Concolino P, Bernabei R, Landi F
J Bone Miner Res 2008;23:1031-6

9.4.132 Fall-related self-efficacy, not balance and mobility performance, is related to accidental falls in chronic stroke survivors with low bone mineral density
Pang MY, Eng JJ
Osteoporos Int 2008;19:919-27

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

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Treatment

9.4.133 Osteoporosis medication use in nursing home patients with fractures in 1 US state
Parikh S, Mogun H, Avorn J, Solomon DH
Arch Intern Med 2008;168:1111-5

Of the 4430 eligible postfracture patients, 11.5% were prescribed an osteoporosis medication. There was a progressive increase in use from 1.6% in 1995 to 18.7% in 2001 but no increases in 2001-2004. Patient characteristics associated with osteoporosis medication use included a history of osteoporosis medication use in the prior 12 months (HR, 19.5; 95% CI, 16.0-23.7) and female sex (HR, 1.57; 95% CI, 1.13-2.21). A history of falls or fracture was not a significant factor. Calcitonin was the most commonly used osteoporosis medication (56%).

9.4.134 Osteoporosis treatment and fracture incidence: The ICARO longitudinal study
Adami S, Isaia G, Luisetto G, Minisola S, Sinigaglia L, Silvestri S, Agnusdei D, Gentilella R, Nuti R
Osteoporos Int 2008;19:1219-23

The study includes 862 women with severe postmenopausal osteoporosis. 92 of these patients (10.7%) were defined as having ICR (9.5%/year) during therapy with antiresorptive drugs (alendronate, risedronate, and raloxifene) for at least one year. The ICR patients were comparable to patients who did not sustain clinical fractures. Those with ICR were older (p=0.032) and more frequently had multiple vertebral deformities (p=0.013). The incidence of ICR during treatment with antiresorptive agents among patients with severe postmenopausal osteoporosis in a routine setting is higher than that observed in randomized clinical trials.

9.4.135 Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial
Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML, Spector TD, Brixen K, Goemaere S, Cormier C, Balogh A, Delmas PD, Meunier PJ
Arthritis Rheum 2008;58:1687-95

5,091 postmenopausal women with osteoporosis were randomized to strontium ranelate at 2 g/day or placebo for 5 years. The main efficacy criterion was the incidence of nonvertebral fractures. In addition, incidence of hip fractures was assessed, by post hoc analysis, in the subset of 1,128 patients who were at high risk of fractures (age 74 years or older with lumbar spine and femoral neck BMD T-scores -2.4 or less). The incidence of new vertebral fractures was assessed in the 3,646 patients in whom spinal radiography (nonmandatory) was performed. Of the 5,091 patients, 2,714 (53%) completed the study up to 5 years. The risk of nonvertebral fracture was reduced by 15% in the strontium ranelate group (RR 0.85, 0.73-0.99). The risk of hip fracture was decreased by 43% (0.57, 0.33-0.97), and the risk of vertebral fracture was decreased by 24% (0.76 [95% CI, 0.65-0.88]) in the strontium ranelate group. After 5 years, the safety profile of strontium ranelate remained unchanged compared with the 3-year findings.

9.4.136 No difference between strontium ranelate and calcium/vitamin D on bone turnover markers in women with established osteoporosis previously treated with teriparatide: A randomized controlled trial
Anastasilakis AD, Goulis DG, Polyzos SA, Gerou S, Ballaouri I, Efstathiadou Z, Kita M, Avramidis A
Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

Twenty-two postmenopausal women (aged 65.7±1.7 years) with osteoporosis treated with TPTD 20 μg daily for 18 months were randomly assigned to SR n=11 or calcium and vitamin D (n=11). Serum P1NP, CTx and total ALP increased after TPTD and decreased at the end of the study in both groups, with no difference between them. SR following TPTD acts predominantly as an anti-resorptive with no evidence of additional anabolic action and is not more effective than Ca/vitamin D in effects on turnover markers.

9.4.137 Monthly dosing of 75 mg risedronate on 2 consecutive days a month: Efficacy and safety results
Delmas PD, Benhamou CL, Man Z, Tlustochowicz W, Matzkin E, Eusebio R, Zanchetta J, Olszynski WP, Recker RR, McClung MR
Osteoporos Int 2008;19:1039-45

Postmenopausal women with osteoporosis (n=1229) were randomly assigned to double-blind treatment with 75 mg risedronate on two consecutive days each month (2CDM), or 5 mg daily. Risedronate 75 mg 2CDM was non-inferior to 5 mg daily (treatment difference 0.21; 95% CI -0.19 to 0.62). Mean percent change in LS-BMD was 3.4%±0.16 and 3.6%±0.15 respectively. Mean percent changes in BMD and BTMs were significant and similar for both treatment groups. New vertebral fractures occurred in 1% of subjects with either treatment. Both treatments were generally well tolerated and safe.

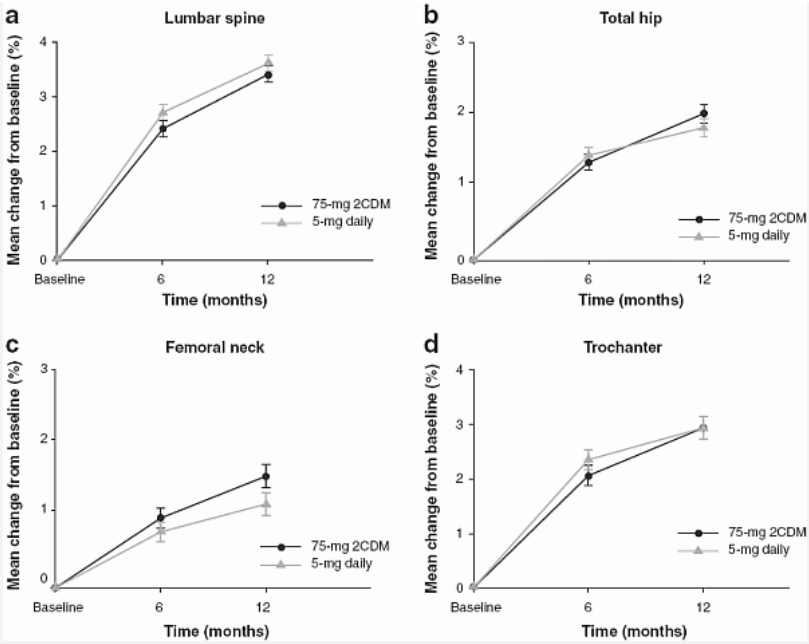


Fig. 9.4.137a Mean percent change in bone mineral density of the lumbar spine, total hip, femoral neck, and trochanter 2CDM=two consecutive days each month. Reproduced from Osteoporos Int 2008;19:1039-45 with permission from Springer.

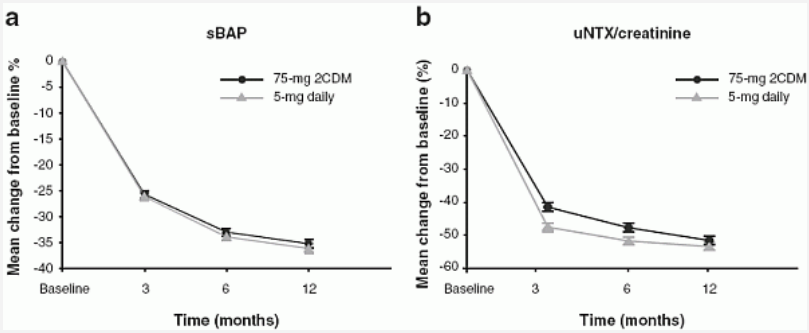


Fig. 9.4.137b Mean percent change from baseline in bone turnover markers 2CDM=two consecutive days each month, sBAP=bone-specific alkaline phosphatase, uNTX=urinary type 1 collagen N-telopeptide. Reproduced from Osteoporos Int 2008;19:1039-45 with permission from Springer.

9.4.138 Effect of risedronate on hip structural geometry: A 1-year, double-blind trial in chemotherapy-induced postmenopausal women

van Londen GJ, Perera S, Vujevich KT, Sereika SM, Bhattacharya R, Greenspan SL
Bone 2008;43:274-8

This 1 year interim, secondary analysis of the Risedronate's Effect on Bone loss in Breast CAncer Study (REBBeCA Study) examined hip structure analysis (HSA), i.e., changes in the bone cross-sectional area (bone CSA), section modulus (SM), cortical thickness (CT) and buckling ratio (BR), in a double-blind trial of 87 newly postmenopausal, nonmetastatic breast cancer patients, randomized to risedronate, 35 mg once weekly (RIS) vs. placebo (PBO). After 12 months, intertrochanteric parameters demonstrated improvement (RIS vs. PBO) from baseline in bone CSA (mean±SD: 4.25±6.29 vs. 0.60±5.99%), SM (3.97±6.40 vs. 0.80±7.08%), and CT (5.20±6.98 vs. 1.13±6.87%). Similar improvements were observed at the femoral shaft [bone CSA: 2.24±5.74 vs. -0.78±5.73%; SM: 1.62±6.23 vs. -1.39±7.06%; CT: 3.79±7.84 vs. -0.17±7.90% (all p-values <0.05, RIS vs. PBO, except SM p =0.0568)]. At both sites, the BR had decreases consistent with improved strength.

9.4.139 Effects of intravenous zoledronate on bone turnover and BMD persist for at least 24 months

Bolland MJ, Grey AB, Horne AM, Briggs SE, Thomas MG, Ellis-Pegler RB, Callon KE, Gamble GD, Reid IR
J Bone Miner Res 2008;23:1304-8

33 HIV-infected men completed a trial of 4 mg annual zoledronate (n=17) or placebo (n=16) and were studied for 12 mo, off treatment. Bone turnover markers were suppressed at 24 and 36 mo (12 and 24 mo after the second annual dose of zoledronate, respectively). There were no significant within-group changes in urine N-telopeptide, serum C-telopeptide, and osteocalcin between 24 and 36 mo and at each time point, each of the turnover markers was lower in the zoledronate group. There were also no between-group differences in the changes in BMD at each site between 24 and 36 mo (p>0.5), and at each time point, BMD at each site was significantly higher in the zoledronate group. Zoledronate could be administered less frequently than annually.

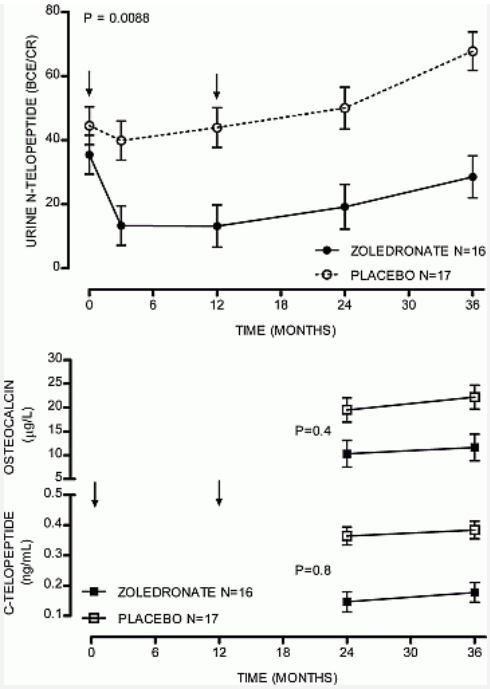


Fig. 9.4.139a Effect of two annual doses of 4 mg zoledronate or placebo (indicated by arrows) on urine N-telopeptide, osteocalcin, and serum C-telopeptide in HIV-infected men. Data are mean (SE). p values are for the time-treatment interaction. The units of urine N-telopeptide/creatinine are nanomolar bone collagen equivalents (BCEs)/mmoles urine creatinine (CR). The normal range for men for urine N-telopeptide is 3-51 nM BCE/CR, for osteocalcin is 14-46 µg/liter, and for serum C-telopeptide is 0.10-0.50 ng/ml. Reproduced from J Bone Miner Res 2008;23:1304-8 with permission of the American Society of Bone and Mineral Research.

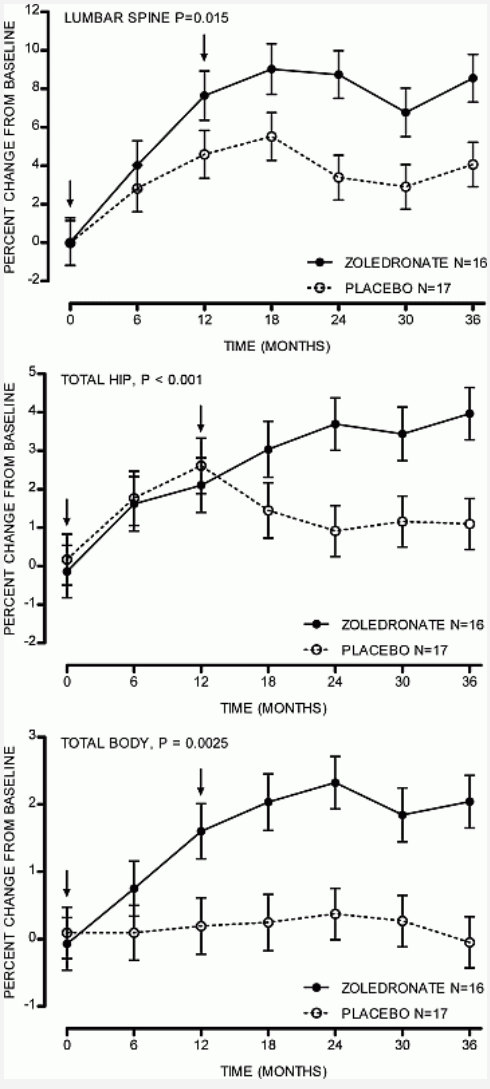


Fig. 9.4.139b The effect of two annual doses of 4 mg zoledronate or placebo (indicated by arrows) on BMD at the lumbar spine, total hip, and total body in HIV-infected men. BMDs are expressed as mean (SE) percent of initial values. p values are for the time-treatment interaction. Reproduced from J Bone Miner Res 2008;23:1304-8 with permission of the American Society of Bone and Mineral Research.

9.4.140 Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women

Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P, Eriksen EF, Miller PD
Kidney Int 2008;[Epub ahead of print]

The renal effects of zoledronic acid were assessed in osteoporotic postmenopausal women from 27 countries who received three annual infusions of zoledronic acid or a placebo in a randomized, double-blind trial. Serum creatinine, estimated creatinine clearance and urinary protein were measured before and after at least one infusion in a predefined renal safety cohort of 5035 compared to 7714 patients whose parameters were measured annually. More transient pre- to post-infusion increases in serum creatinine occurred in zoledronic acid than placebo-treated patients with significant elevations, relative to pre-infusion, only in the second year. All 31 zoledronic acid and 8 of 10 patients on placebo recovered their pre-infusion serum creatinine value within 12 months. No differences in mean changes in serum creatinine, estimated creatinine clearance or adverse renal events were found. Transient changes in renal function occur following an annual zoledronic acid infusion but, in the long term, renal function was not different from control patients.

9.4.141 Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw
Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F, Peters E, Hanley DA, Chaudry SR, Dempster DW, Glorieux FH, Neville AJ, Talwar RM, Clokie CM, Al Mardini M, Paul T, Khosla S, Josse RG, Sutherland S, Lam DK, Carmichael RP, Blanas N, Kendler D, Pe
J Rheumatol 2008;35:1391-7

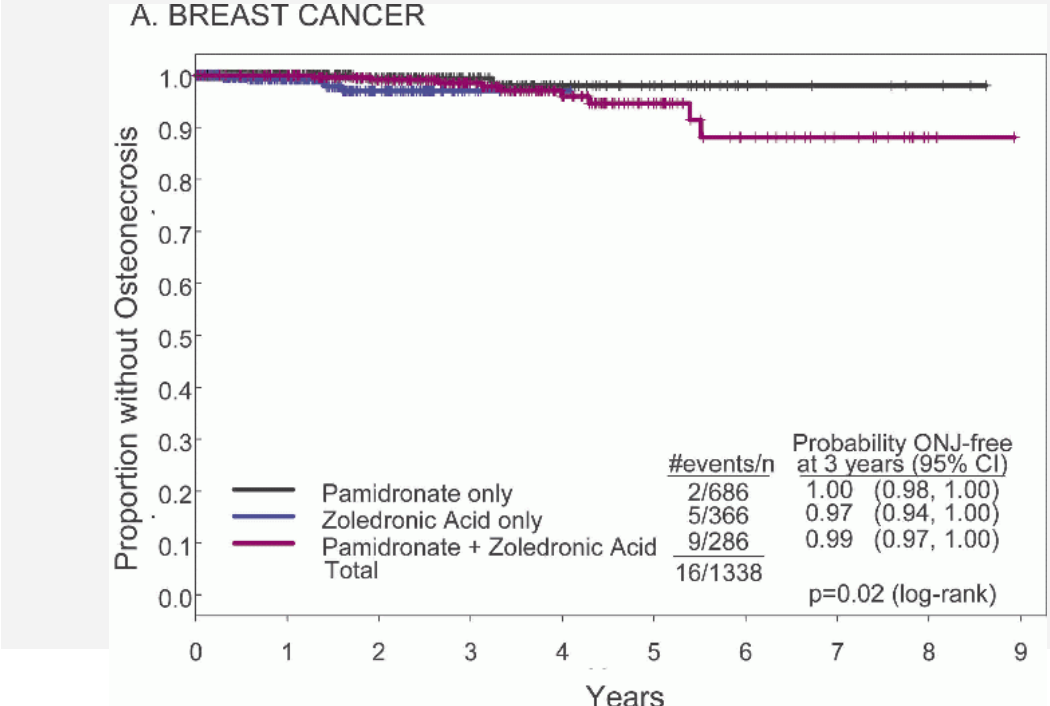
In all oncology patients, a dental examination including radiographs should be completed prior to the initiation of intravenous bisphosphonate therapy. In this population, any invasive dental procedure is ideally completed prior to the initiation of high-dose bisphosphonate therapy. Non-urgent procedures are preferably delayed for 3 to 6 months following interruption of bisphosphonate therapy. Osteoporosis patients receiving oral or intravenous bisphosphonates do not require a dental examination prior to initiating therapy in the presence of appropriate dental care and good oral hygiene. Stopping smoking, limiting alcohol intake, and maintaining good oral hygiene should be emphasized for all patients receiving bisphosphonate therapy. Individuals with established osteonecrosis of the jaw are most appropriately managed with supportive care including pain control, treatment of secondary infection, removal of necrotic debris, and mobile sequestrate. Aggressive debridement is contraindicated.

9.4.142 Factors associated with osteonecrosis of the jaw among bisphosphonate users
Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS
Am J Med 2008;121:475-83

A systematic review search strategy was used to identify cases of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer. Ninety-nine cases of osteonecrosis of the jaw were identified among patients who were prescribed a bisphosphonate for an indication other than cancer. These cases included 85 osteoporosis patients, 10 patients with Paget's disease, 2 patients with rheumatoid arthritis, 1 patient with diabetes, and 1 patient with maxillary fibrous dysplasia. The mean age was 69.4 years, 87.3% were female, and 83.3% werereceiving oral, but not intravenous, bisphosphonates. Of the 63 patients reporting dental care information, 88.9% had a dental procedure before the onset of osteonecrosis of the jaw. Of all cases providing medical information, 71% were taking at least one medication that affects bone turnover in addition to the bisphosphonate, and 81.3% reported additional underlying health conditions. The case details suggest a multiplicity of factors associated with this condition.

9.4.143 Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates
Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel R, Hortobagyi GN
J Bone Miner Res 2008;23:826-36

Retrospective analysis of 4019 patients treated with intravenous bisphosphonates between 1996 and 2004 revealed 16/1338 patients with breast cancer (1.2%) and 13/548 patients with myeloma (2.4%) developed ONJ. The median dose and duration of treatment with pamidronate or zoledronic acid were higher in patients with ONJ ($p<0.0001$). Zoledronic acid was associated with a hazards ratio (HR)=15.01 (2.41-93.48), treatment with pamidronate followed by zoledronic acid (HR, 4.00, 0.86-18.70), and dental extractions (HR, 53.19,18.20-155.46) as risks for ONJ in breast cancer. In multiple myeloma, dental extractions (HR, 9.78, 3.07-31.14) and osteoporosis (HR, 6.11,1.56-23.98) were risk factors while controlling for bisphosphonate therapy. 13/29 patients were followed for a median of 17.1 mo (range, 7-67 mo); lesions healed in 3 patients during this period.



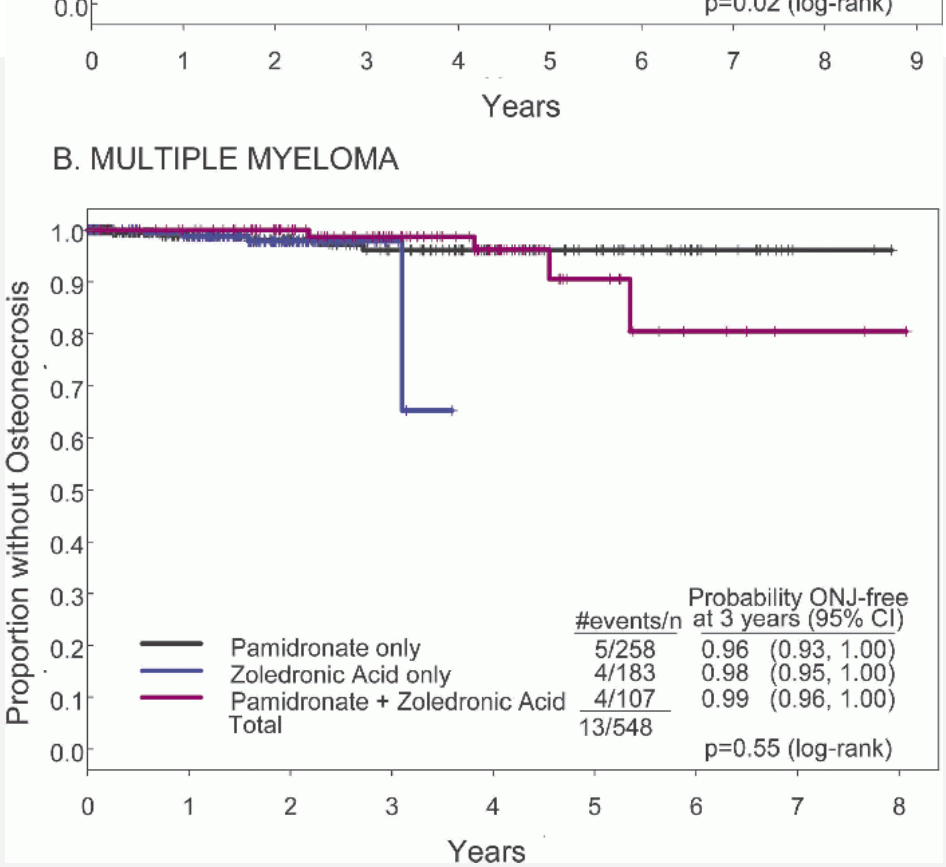


Fig. 9.4.143 Kaplan-Meier estimates of the proportion of patients free of ONJ over time according to type of bisphosphonate received. The Kaplan-Meier method was used to estimate the number of patients free of ONJ at 3 and 5 yr of bisphosphonate treatment. (A) Kaplan-Meier curve in patients with breast cancer. (B) Same analysis in patients with multiple myeloma. Black line, patients treated with pamidronate; blue line, patients treated with zoledronic acid; red line, patients treated with both pamidronate and zoledronic acid. In patients with breast cancer, the probability of being ONJ-free at 3 yr was 99.5% (95% CI: 98.4-100%) in the pamidronate only group, 97% (95% CI: 94.3-99.8%) in the zoledronic acid group, and 98.6% (95% CI: 96.9-100%) in patients treated with pamidronate followed by zoledronic acid. The comparable values for 5 yr were 98% (95% CI: 95.1-100%), inadequate data for zoledronic acid, and 94.6% (95% CI: 90.5-98.9%). In patients with multiple myeloma, the probability of being ONJ-free at 3 yr was 96% (95% CI: 92.7-99.6%) in the pamidronate group, 97.8% (95% CI: 95.4-100%) in the zoledronic acid group, and 98.7% (95% CI: 96.2-100%) in patients treated with both. The comparable data for 5 yr is 96.1% (95% CI: 92.7-99.6%), inadequate for zoledronic acid, and 90.6% (95% CI: 79.4-100%). Time to ONJ differed significantly between the bisphosphonates treatment groups. Reproduced from J Bone Miner Res 2008;23:826-36 with permission of the American Society of Bone and Mineral Research.

9.4.144 Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial
Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, Liu Y, San Martin J, For The Amg 162 Bone Loss Study G Bone 2008;43:222-9

Denosumab is a fully human monoclonal antibody inhibits RANKL, a mediator of osteoclast formation, function, and survival, decreases bone turnover and increases BMD. Postmenopausal women with a spine T-score of -1.8 to -4.0 or proximal femur T-score of -1.8 to -3.5 were randomized to denosumab every 3 months (Q3M; 6, 14, or 30 mg) or every 6 months (Q6M; 14, 60, 100, or 210 mg); placebo; or open-label oral alendronate weekly. After 24 months, patients receiving denosumab either continued at 60 mg Q6M for an additional 24 months, discontinued therapy, or discontinued for 12 months then re-initiated denosumab (60 mg Q6M) for 12 months. The placebo cohort was maintained. Alendronate-treated patients discontinued alendronate and were followed. Overall, 262/412 (64%) patients completed 48 months. Continuous treatment increased BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0% to 6.1%). BTM were consistently suppressed over 48 months. Discontinuation was associated with a BMD decrease of 6.6% at the spine and 5.3% at the total hip within the first 12 months of discontinuation. Retreatment increased spine BMD by 9.0% from original baseline. BTMs increased on discontinuation and decreased with retreatment. The effects on bone turnover were fully reversible with discontinuation and restored with subsequent retreatment.

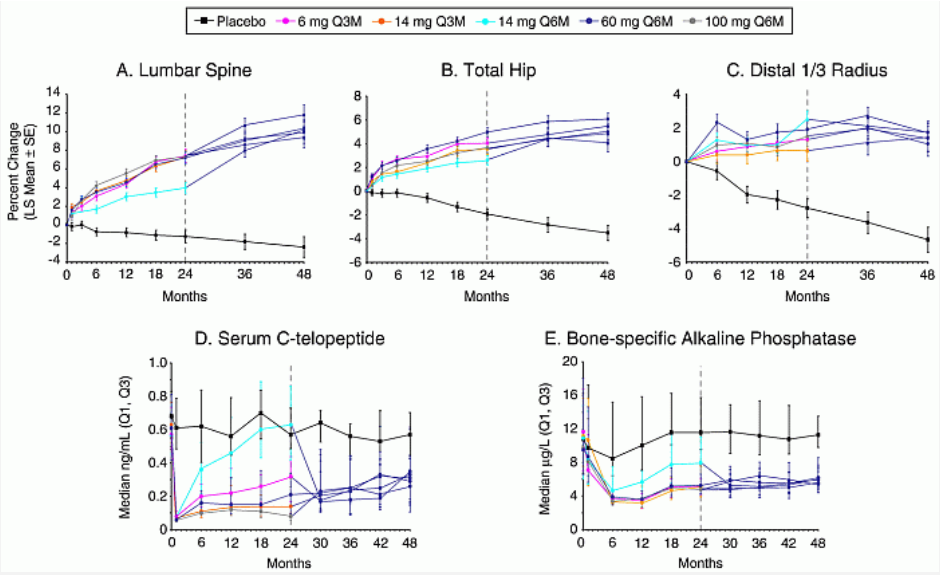


Fig. 9.4.144a Percentage change in bone mineral density (BMD) and actual values of biochemical markers of bone turnover (BTM) in patients who continued denosumab treatment for 48 months: (A) lumbar spine; (B) total hip; (C) distal 1/3 radius; (D) serum C-telopeptide; (E) bone-specific alkaline phosphatase. BMD values are shown as percentage change from baseline (least square mean±standard error), while BTM levels are shown as absolute values (median with interquartile range) at the end of each dosing cycle. The dashed line at month 24 indicates the time at which patients were reallocated to the 60 mg Q6M dose. Reproduced from Bone, 43:222-229, Copyright (2008), with permission from Elsevier.

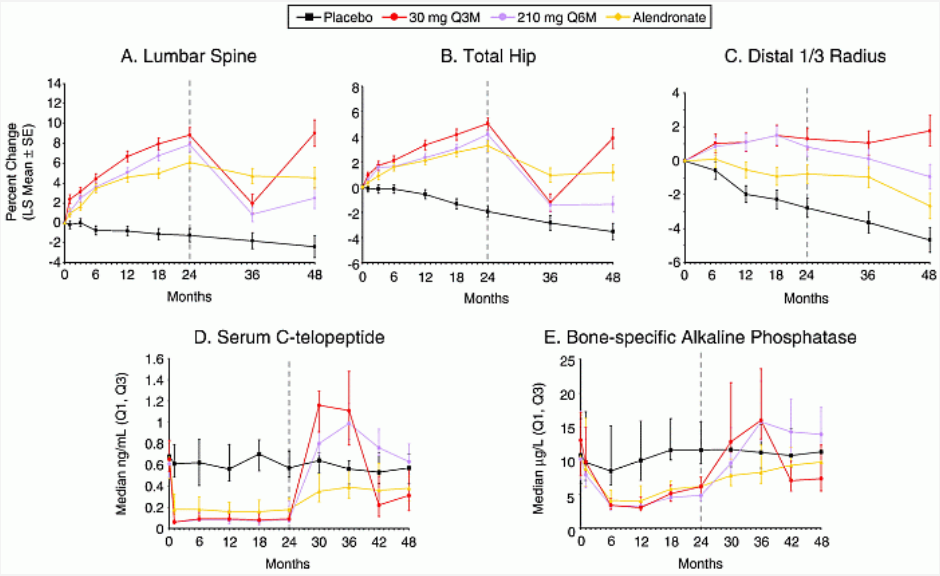


Fig. 9.4.144b Percentage change in bone mineral density (BMD) and actual values of biochemical markers of bone turnover (BTM) in patients who discontinued denosumab treatment for the last 24 months (210 mg Q6M), were re-treated with denosumab 60 mg Q6M at month 36 (30 mg Q3M), or discontinued alendronate treatment: (A) lumbar spine; (B) total hip; (C) distal 1/3 radius; (D) serum C-telopeptide; (E) bone-specific alkaline phosphatase. BMD values are shown as percentage change from baseline (least square mean±standard error), while BTM levels are shown as absolute values (median with interquartile range) at the end of each dosing cycle. The dashed line at month 24 indicates the time at which dosing was reallocated. Reproduced from Bone, 43:222-229, Copyright (2008), with permission from Elsevier.

9.4.145 Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women

Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA

Osteoporos Int 2008;19:1153-60

Both tibolone is a selective tissue estrogenic activity regulator (STEAR), and raloxifene, a selective estrogen receptor modulator (SERM). A double-blind, randomized trial was conducted in osteopenic postmenopausal women aged 60-79 years to compare the effects of tibolone 1.25 mg/day to raloxifene 60 mg/day on BMD. 308 subjects were allocated to treatment. Both treatments increased spine BMD, however the increase was larger after tibolone than raloxifene (at year 1: 2.2% versus 1.2%, p<0.01 and at year 2: 3.8% versus 2.1%, p<0.001). After 2 years, the increase in total hip BMD in the tibolone group was larger than in the raloxifene group (p<0.05). Both treatments reduced type I collagen C-telopeptides and osteocalcin levels.

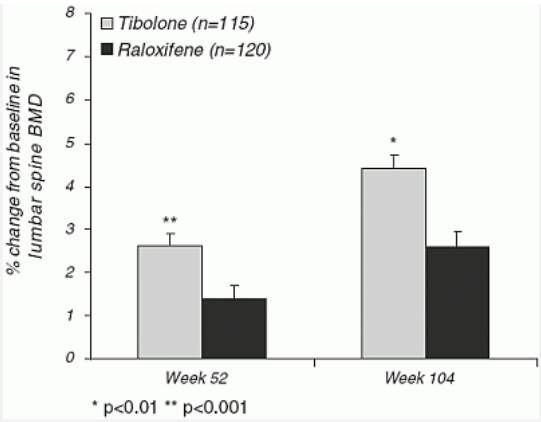


*Fig. 9.4.145a Percentage change from baseline in mean lumbar spine BMD (±SEM) with tibolone and raloxifene after 1 and 2 years (ITT population). *p<0.01 vs. raloxifene. **p<0.001 vs. raloxifene. Reproduced from Osteoporos Int 2008;19:1153-60 with permission from Springer.*

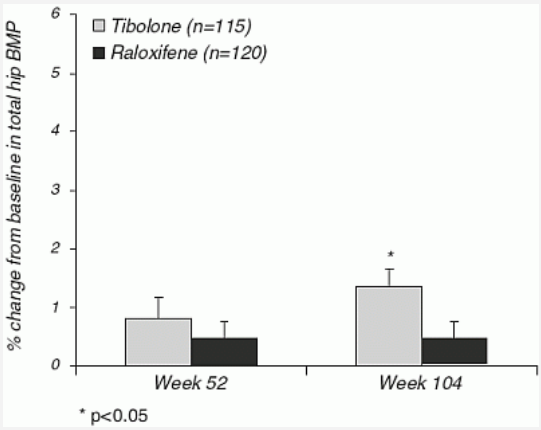


*Fig. 9.4.145b Percentage change from baseline in mean total hip BMD (±SEM) with tibolone and raloxifene after 1 and 2 years (ITT population). *p<0.05 vs. raloxifene. Reproduced from Osteoporos Int 2008;19:1153-60 with permission from Springer.*

9.4.146 Effect of tamoxifen and aromatase inhibitors on the risk of fractures in women with breast cancer
Vestergaard P, Rejnmark L, Mosekilde L
Calcif Tissue Int 2008;82:334-40

64,548 fracture cases and 193,641 age- and gender-matched controls were studied. Use of tamoxifen was not associated with any change in the risk of fracture. A decreasing relative risk of fractures was seen with increasing dose, although the risk never declined significantly below that in nonusers. An increased risk of hip fractures was seen, but the increase was limited to patients who had used low average doses (<20 mg of tamoxifen/day) and were prior users (i.e., had not used tamoxifen within the last year). Aromatase inhibitors were associated with increases in overall risk of fractures and risk of hip fractures.

9.4.147 Exogenous PTH and endogenous 1,25-dihydroxyvitamin D are complementary in inducing an anabolic effect on bone
Samadfam R, Xia Q, Miao D, Hendy GN, Goltzman D
J Bone Miner Res 2008;23:1257-66

3-mo old wildtype mice were injected once daily (40 µg/kg) or infused continuously (120 µg/kg/d) with PTH(1-34) for up to one month. Infused PTH reduced BMD, increased the bone resorption marker TRACP-5b, and raised serum calcium but did not increase serum 1,25(OH)(2)D. Injected PTH increased serum 1,25(OH)(2)D and BMD, raised the bone formation marker osteocalcin more than did infused PTH, and did not produce sustained hypercalcemia as did PTH infusion. 3-mo old 1 alpha(OH) ase(-/-) mice, were injected with PTH(1-34) (40 µg/kg) either once daily or three times daily for 1 mo. In 1 alpha(OH)ase(-/-) mice, baseline bone volume (BV/TV) and bone formation (BFR/BS) were lower than in wildtype. PTH intermittently increased BV/TV and BFR/BS in a dose-dependent manner, but the increases were always less than in wildtype. PTH continuously resorbs bone without raising endogenous 1,25(OH)(2)D. Intermittently PTH can increase bone accrual in the absence of 1,25(OH)(2)D, but 1,25(OH)(2)D complements this PTH action.

9.4.148 Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration
Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, Pollack S, Yeh JK
Am J Clin Nutr 2008;87:1952-8

To determine the intake of vitamin D(3) needed to raise serum 25(OH)D to >75 nmol/L, in 6-mo, prospective, randomized, double-blinded, double-dummy, placebo-controlled study of vitamin D(3) supplementation in 138 subjects, almost all active subjects attained concentrations of 25(OH)D >75 nmol/L, and no subjects exceeded 220 nmol/L. The mean (±SD) slope at 9 wk was 0.66±0.35 (nmol/L)/(µg/d) and did not differ between blacks and whites. The mean daily dose was 86 µg (3440 IU). The use of computer simulations to obtain the most participants within the range of 75-220 nmol/L predicted an optimal daily dose of 115 µg/d (4600 IU). No hypercalcemia or hypercalciuria was observed. Projection of the dose-response curves suggests a dose of 95 µg/d (3800 IU) for those above a 25(OH)D threshold of 55 nmol/L and a dose of 125 µg/d (5000 IU) for those below that threshold.

9.4.149 Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients

Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R
J Clin Endocrinol Metab 2008;[Epub ahead of print]

To determine whether the same cumulative dose of vitamin D3 produces different effects if given daily, weekly or monthly, women, age 81±8 yr (±SD, n=48), who had surgery for hip fracture were randomized to vitamin D3 supplementation at 1,500 IU daily, or 10,500 IU once weekly, or 45,000 IU once every 28 days. Initially, serum 25(OH)D for daily, weekly and monthly groups were, respectively, 15.13±6.9, 15.7±10.1, and 16.2±10.1 ng/mL. By day 7, these had risen in all the groups ($p<0.001$). On the first day after the monthly dose, both 25(OH)D and 1,25(OH)D increased ($p<0.012$) whereas these did not change on the day after daily or weekly doses. After 2 months, serum 25(OH)D with daily, weekly and monthly dosing were respectively, 33.2±8.5, 29.2±8.9, 37.1±10.3 ng/mL. Supplementation with vitamin D can be achieved equally well with daily, weekly or monthly dosing.

9.4.150 Short and long term variations in serum calciotrophic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly
Romagnoli E, Mascia ML, Cipriani C, Fassino V, Mazzei F, D'Erasmo E, Carnevale V, Scillitani A, Minisola S
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Thirty-two female patients (age 66-97 years), with vitamin D deficiency were randomized to a single dose of 300,000 IU of ergocalciferol or cholecalciferol by oral (os) or intramuscular (im) route. 25(OH)D increased at day 3 only when vitamins were given orally. The 30-day basal difference in serum 25(OH)D was greater after cholecalciferol oral (47.8±7.3 ng/ml) compared with other forms (D3 im: 15.9±11.3; D2 os:17.3±4.7; D2 im: 5±4.4; all $p<0.001$). The AUC of the serum 25(OH)D against time (AUC60) was: D3 os: 3193±759 ng x d/mL vs. D2 os: 1820±512, $p<0.001$; D3 im: 1361±492 vs. D2 im 728±195, $p<0.01$. At 60 days, cholecalciferol lowers PTH. Cholecalciferol is almost twice as potent as ergocalciferol in raising serum 25(OH)D, when administered either by mouth or im. 25(OH)D plays a role in modulating serum PTH.

9.4.151 Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency
Zhu K, Bruce D, Austin N, Devine A, Ebeling PR, Prince RL
J Bone Miner Res 2008;23:1343-8

302 elderly women (age, 77.2±4.6 yr) with serum 25(OH)D <60 nM participated in a 1-yr randomized, double-blind, placebo-controlled trial. All subjects received 1000 mg calcium citrate per day with either 1000 IU ergocalciferol (vitamin D(2)) or identical placebo (control). At baseline, calcium intake was 1100 mg/d, and 25(OH)D was 44.3±12.9 nM; this increased in the vitamin D group by 34% but not the control group after 1 year (59.8±13.8 versus 45.0±13.3 nM, $p<0.001$). Total hip and total body BMD increased, and procollagen type I intact N-terminal propeptide (PINP) decreased with no difference between the treatment groups (hip BMD change: vitamin D, +0.5%; control, +0.2%; total body BMD change: vitamin D, +0.4%; control, +0.4%; PINP change: vitamin D, -3.9%; placebo, -2.8%). Although the fasting plasma and urine calcium increased in both groups equally, there was no detectable change in serum PTH. The increase in 25(OH)D had no extra effect on active fractional intestinal calcium absorption, which fell equally in both groups (vitamin D, -17.4%; control, -14.8%). In patients with a baseline calcium intake of 1100 mg/d and vitamin D insufficiency, vitamin D(2) 1000 IU for one year has no extra beneficial effect on bone structure, bone formation markers, or intestinal calcium absorption over an additional 1000 mg of calcium.

9.4.152 Severely suppressed bone turnover and atypical skeletal fragility
Visekruna M, Wilson D, McKiernan FE
J Clin Endocrinol Metab 2008;[Epub ahead of print]

Atypical skeletal fragility in three subjects after long term, combined antiremodeling therapy experienced spontaneous or minimal trauma "chalk-stick" type metadiaphyseal femoral fractures on long term bisphosphonate. All three subjects had concomitant circumstances (endogenous estrogen) or medications (glucocorticoids, hormone replacement therapy, raloxifene). Biochemical markers of bone turnover were low or in the low premenopausal range. Double tetracycline labeled bone biopsy showed low activation frequency in one subject and limited single tetracycline label in a second consistent with severely suppressed bone turnover.

9.4.153 Effect of calcium supplementation on hip fractures
Reid IR, Bolland MJ, Grey A
Osteoporos Int 2008;19:1119-23

In 5,500 women involved in trials of calcium monotherapy adverse trends in numbers of hip fractures (relative risk 1.50, 95% CI 1.06-2.12). Until there are further trial results to clarify this area, the present findings suggest that reliance on high calcium intakes to reduce the risk of hip fracture in older women is not appropriate.

9.4.154 The remodeling transient and the calcium economy
Aloia JF, Arunabh-Talwar S, Pollack S, Yeh JK
Osteoporos Int 2008;19:1001-9

Calcium and vitamin D in 208 postmenopausal African-American women where the remodeling transient was considered a priori in the study design. Both groups (calcium alone vs. calcium + 20 µg (800 IU) vitamin D(3)) were ensured a calcium intake in excess of 1200 mg/day. There were no differences between the two groups in changes in BMD over time. These BMD changes were therefore interpreted to reflect increased calcium intake in both groups but not any influence of vitamin D. A transient increase in BMD was observed during the first year of study, followed by a decline. The remodeling period was 9 months, which is similar to histomorphometric estimates. It is problematic to draw conclusions concerning interventions that influence the calcium economy without considering the remodeling transient in study design. Studies of agents that effect bone remodeling must be carried out for at least two remodeling cycles and appropriate techniques must be used in data analysis.

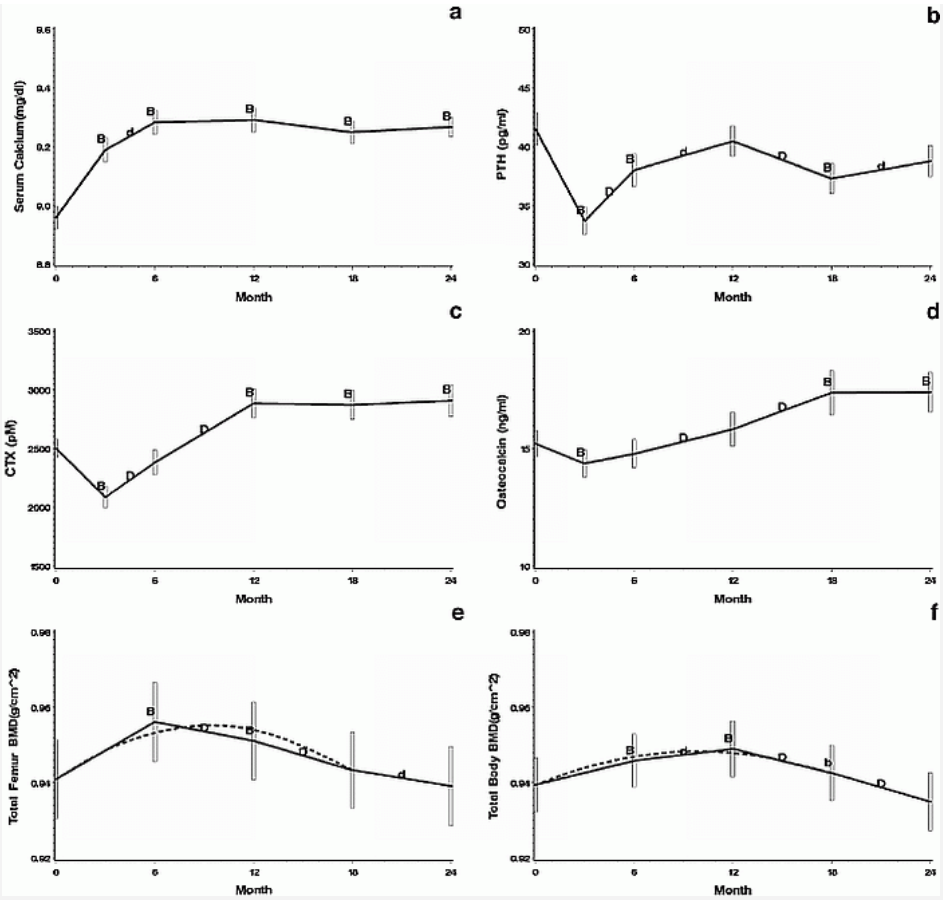


Fig. 9.4.154a Concomitant changes with calcium supplementation: Absolute values (±2 SEM). Panel (1a): Serum calcium, Panel (1b): PTH, Panel (1c): CTX, Panel (1d): Osteocalcin, Panel (1e): Total femur BMD, Panel (1f): total body BMD, B: significantly different from baseline, p<0.002, b: significantly different from baseline, p<0.05, D: significantly different from preceding period, p<0.002, d: significantly different from preceding period, p<0.05, The dashed line in Panels 1e and 1f represent the quadratic model fitted to the data over 18 months. Reproduced from Osteoporos Int 2008;19:1001-9 with permission from Springer.

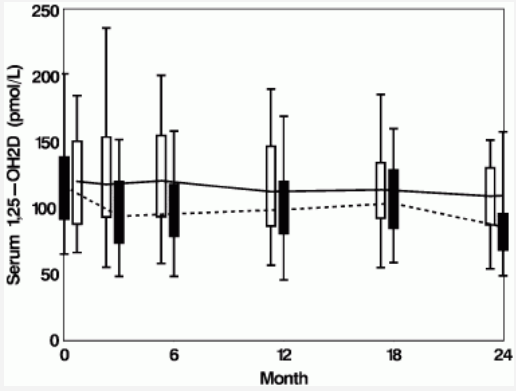


Fig. 9.4.154b Initial and sustained changes in 1,25OHD2D in the calcium only group (dashed lines) are not experienced by the vitamin D + calcium group (solid line). p<0.01 group comparisons at each line point; p<0.01 for all comparisons with baseline for the calcium group but not for the vitamin D + calcium group. Reproduced from Osteoporos Int 2008;19:1001-9 with permission from Springer.

9.4.155 Effect of soft shell hip protectors on pressure distribution to the hip during sideways falls

Laing AC, Robinovitch SN

Osteoporos Int 2008;19:1067-75

15 women participated in "pelvis release experiments," which safely simulate the impact stage of a sideways fall. During the trials, we measured total impact force and mean pressure over the greater trochanter with the participant unpadded, and while wearing two commercially available soft shell protectors. Mean pressure over the greater trochanter was reduced by 76% by a 14-mm thick horseshoe-shaped protector and by 73% by a 16-mm thick continuous protector. Total force was reduced by 9% by the horseshoe and by 19% by the continuous protector.

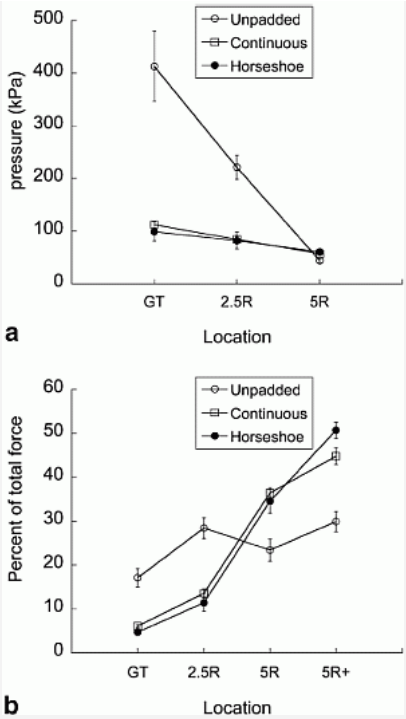


Fig. 9.4.155 Effect of hip protectors on a the pressure and b the percentage of total force applied to various hip locations. Both hip protectors caused a dramatic reduction in pressure over the GT, and redistribution of force to a region at least 2.5 cm outside the GT. Error bars show standard errors. Reproduced from Osteoporos Int 2008;19:1067-75 with permission from Springer.

9.4.156 Effect of tumor necrosis factor alpha inhibition on bone density and turnover markers in patients with rheumatoid arthritis and spondyloarthropathy

Barnabe C, Hanley DA

Semin Arthritis Rheum 2008;[Epub ahead of print]

In rheumatoid arthritis, 4 studies (238 patients) showed a stabilization or increase of BMD at the spine (up to 2.8%) or hip (up to 13.1%), with only 1 negative study in 48 patients (decline of 3.2% at the spine and 2.7% at the hip). In spondyloarthopathies, 3 studies (75 patients) all demonstrated an increase in BMD at the lumbar spine (3.2-3.6%) and at the hip (1.8-2.2%). Changes in markers of bone formation and bone resorption were heterogeneous but in general represented a modest increase in formation and decline in resorption. In general, anti-TNF alpha therapy has a beneficial effect on bone density and bone turnover markers.

9.4.157 Alendronate reduces bone toughness of ribs without significantly increasing microdamage accumulation in dogs following 3 years of daily treatment

Allen MR, Reinwald S, Burr DB

Calcif Tissue Int 2008;82:354-60

Reduced bone toughness has been consistently documented in vertebrae of animals treated with a wide range of bisphosphonate doses. To evaluate changes in bone toughness and various other tissue-level properties of the rib following 3 years of bisphosphonate with doses at and above those used to treat osteoporosis skeletally mature intact beagle dogs were treated daily for 3 years with vehicle (VEH), alendronate 0.2 mg/kg (ALN0.2), or alendronate 1.0 mg/kg (ALN1.0). The lower ALN dose approximates, on a mg/kg basis, that used for treatment of postmenopausal osteoporosis, with the higher dose being five times higher. Toughness was lower with ALN1.0 (-33%) but not ALN0.2 (-19%) compared to VEH, while neither ultimate stress nor modulus differed among the groups. Bone density, geometry, and structural biomechanical properties were similar among the three groups. There was no difference in overall microdamage accumulation among the groups. Intracortical bone formation rate was lower than VEH in both ALN groups (-69% to -90%). Rib cortical bone experiences reductions in turnover following bisphosphonate treatment, it is only in animals treated with doses above those used to treat osteoporosis that toughness is compromised.

9.4.158 Intratrabecular tunneling increases trabecular number throughout the skeleton of ovariectomized rhesus monkeys treated with parathyroid hormone 1-84

Miller MA, Bare SP, Recker RR, Smith SY, Fox J

Bone 2008;42:1175-83

Daily human parathyroid hormone (PTH) 1-84 for 16 months increases trabecular bone volume (BV/TV), number (Tb.N) and connectivity at lumbar vertebra-3 (L3) and thoracic vertebra-10. Intratrabecular tunneling at L3 and on trabecular bone at the proximal femur, distal radius and iliac crest is observed. At L3, tunneling frequency was low in control sham and OVX animals (approximately 0.05/mm(2)) but increased in PTH(1-84)-treated animals (0.27, 0.49 and 0.95/mm(2) with the 5, 10 and 25 μg/kg doses, respectively). Very similar tunneling frequencies were observed at all skeletal sites in all groups. PTH(1-84) increased Tb.N, as well as BV/TV and bone formation rate at all sites. A modest but significant increase in trabecular thickness occurred only at the iliac crest. This phenomenon provides an explanation for the PTH(1-84)-induced increase in Tb.N observed in OVX monkeys.

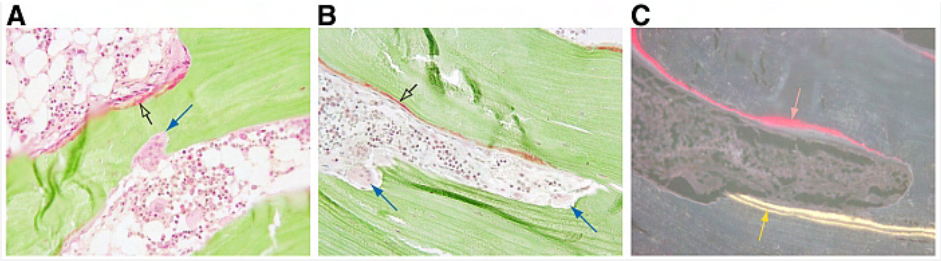


Fig. 9.4.158a Intratrabecular tunneling as a mechanism responsible for increased trabecular number at multiple skeletal locations in OVX rhesus monkeys treated daily with vehicle or PTH(1–84) for 16 months. Dynamic intratrabecular tunneling was defined as remodeling that is longitudinally orientated in the lamellae of bone at a nonnodal location. The images show Goldner's stained sections (panels A, B) and a serial unstained section viewed under uv light (panel C) from the iliac crest. Shown is (A) the possible initiation of a tunneling event and (B) intratrabecular tunneling created by osteoclasts (blue arrows) and followed by osteoid (open arrows) and boneforming osteoblasts. Panel C shows fluorochrome labels, oxytetracycline (yellow arrow), and xylenol orange (red arrow) which were given 10 months and 2 weeks, respectively, prior to bone collection and illustrate actively mineralizing surfaces. Note the osteoclastic resorption of the double oxytetracycline label given at month 6. Reproduced from Bone, 42:1175-83, Copyright (2008), with permission from Elsevier.

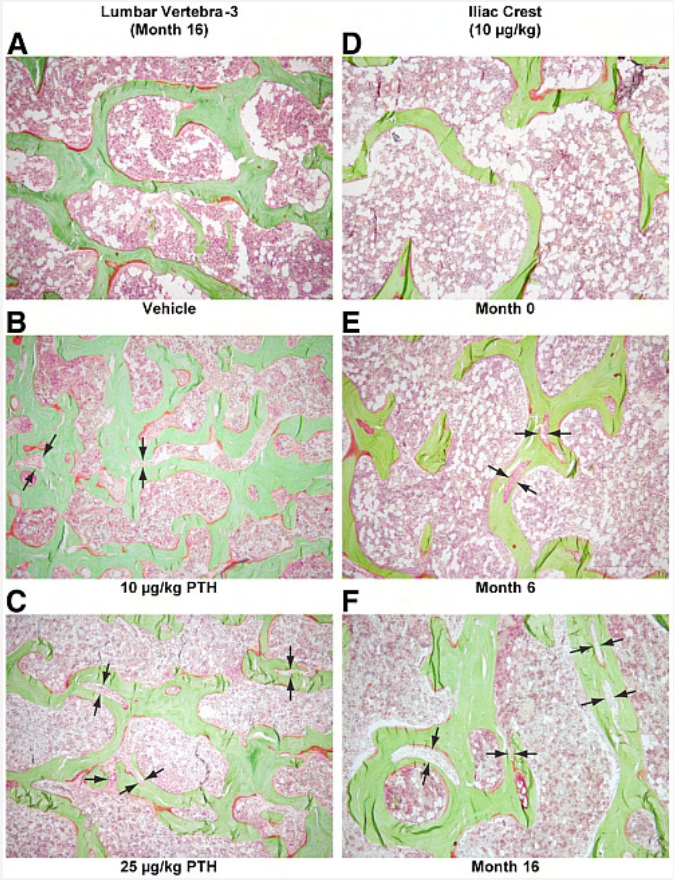


Fig. 9.4.158b Dose- and time-dependent increase in the frequency of intratrabecular tunneling at L3 and iliac crest of OVX rhesus monkeys treated daily with vehicle or PTH (1-84) for 16 months. Panels A, B, and C show examples of intratrabecular tunneling at L3 of animals receiving vehicle or PTH(1-84) at 10 or 25 µg/kg, respectively. Note the dose-related increases in tunneling (black arrows) with the 10 and 25 µg/kg doses. Panels D, E, and F illustrate the progressive increase in the frequency of intratrabecular tunneling (black arrows) in the iliac crest at months 6 and 16, respectively, with the 10 µg/kg dose. Reproduced from Bone, 42:1175-83, Copyright (2008), with permission from Elsevier.

9.4.159 Accentuated osteoclastic response to parathyroid hormone undermines bone mass acquisition in osteonectin-null mice

Machado do Reis L, Kessler CB, Adams DJ, Lorenzo J, Jorgetti V, Delany AM

Bone 2008;43:264-73

Osteonectin is the most abundant non-collagenous protein in bone. In its absence, mice develop low turnover osteopenia, particularly of trabecular bone. 10-week old female wild type, osteonectin-haploinsufficient, and osteonectin-null mice (C57Bl/6 genetic background) were given 80 µg/kg body weight/day PTH(1-34) for 4 weeks. The trabecular connectivity density decreased, the osteoclastic response was accentuatedm eroded surface and osteoclast number were higher as was endosteal area. PTH induced the formation of more osteoclast-like cells in marrow. PTH in osteonectin-null bone marrow cells expressed more RANKL mRNA. However, the ratio of RANKL:OPG mRNA was lower in PTH treated osteonectin-null cultures. Mice had a similar osteoblastic response to PTH. Increased expression of RANKL in response to PTH could contribute to the accentuated osteoclastic response in osteonectin(-/-) mice.

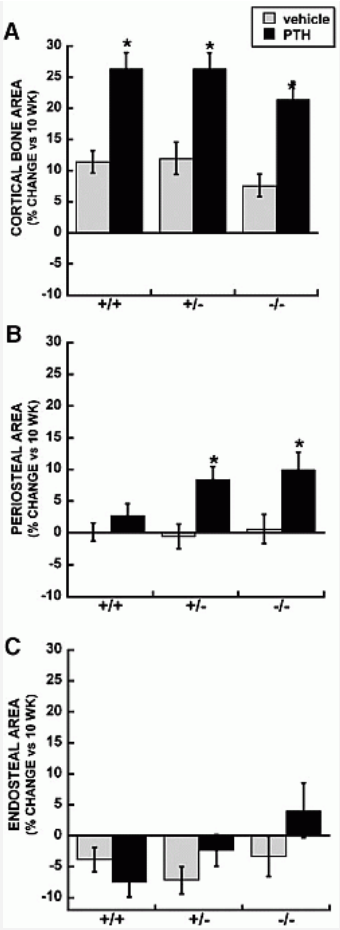


*Fig. 9.4.159 Cortical bone parameters in femur of vehicle and PTH treated wild type, osteonectin+/- and osteonectin-/- mice. Percent change (vs. 10-week baseline) in A. Bone area; B. Periosteal area; C. Endosteal area. *=significantly different from corresponding vehicle treated, p≤0.02. Reproduced from Bone, 43:264-73, Copyright (2008), with permission from Elsevier.*

9.4.160 Intermittent Fugu parathyroid hormone 1 (1-34) is an anabolic bone agent in young male rats and osteopenic ovariectomized rats
McManus JF, Davey RA, Maclean HE, Doust EA, Chiu WS, Sims NA, Bouxsein ML, Glatt V, Zajac JD, Danks JA
Bone 2008;42:1164-74

Fish Fugu parathyroid hormone 1 (fPth1) has hPTH-like biological activity in vitro despite fPth1(1-34) sharing 53% identity with hPTH (1-34). Young male rats were injected intermittently for 30 days with fPth1 [30 μg-1000 μg/kg body weight (b.w.), (30fPth1-1000fPth1)] or hPTH [30 μg-100 μg/kg b.w. (30hPTH-100hPTH)]. In proximal tibiae at low doses, the fPth1 correlated with trabecular bone volume/total volume (TbBV/TV) while hPTH increased TbBV/TV, trabecular thickness (TbTh) and trabecular number (TbN). 500fPth1 and 1000fPth1 increased TbBV/TV, TbTh, TbN, mineral apposition rate (MAR) and bone formation rate/bone surface (BFR/BS) with a concomitant decrease in osteoclast surface and number. OVX osteopenic rats and sham operated (SHAM) rats were injected intermittently with 500 microg/kg b.w. of fPth1 (500fPth1) for 11 weeks. 500fPth1 increased TbBV/TV (151%) and TbTh (96%) in the proximal tibiae due to increased bone formation as assessed by BFR/BS (490%) and MAR (131%). The effect was restoration of TbBV/TV to SHAM levels without any effect on bone resorption. 500fPth1 also increased TbBV/TV and TbTh in the vertebrae (L6) and cortical thickness in the mid-femora increasing bone strength at these sites. fPth1 was similarly effective in SHAM rats.

9.4.161 Onion decreases the ovariectomy-induced osteopenia in young adult rats
Huang TH, Muhlbauer RC, Tang CH, Chen HI, Chang GL, Huang YW, Lai YT, Lin HS, Yang WT, Yang RS
Bone 2008;42:1154-63

Sixty-four female Wistar rats (14-week-old) with sham operations or ovariectomy were assigned to CON, sham-operated; OVX; ALN, ovariectomized with alendronate (1 mg/kg/day, p.o.); and 3% ON, 7% ON and 14% ON, ovariectomized rats fed with diets containing 3%, 7% and 14% (wt/wt) onion powder, respectively. Alendronate and all three onion-enriched diets decreased serum calcium level ($p<0.05$). Both 14% ON group and the ALN group even showed similarly lower level of serum osteocalcin ($p<0.05$). The histomorphometric analysis showed that ovariectomy markedly decrease bone trabeculae. The ALN and 14% ON rats were 80% and 46% higher, respectively, in BV/TV than the OVX rats ($p<0.05$), and the rats fed with onion enriched food showed a lesser ovariectomy-induced bone loss in a dose-dependent manner. Additionally, both ALN and 14% ON groups had significantly more trabecular number, less separated trabeculae, and fewer osteoclasts ($p<0.05$), but the protective efficacy from the 14% onion-enriched diet was slightly inferior to that of alendronate. Ovariectomy also significantly decreased tissue weight and biomechanical strength in the OVX group ($p<0.05$). The ALN and 14% ON groups equivalently showed a lesser decrease in tissue weight, though the difference was not significant. On the other hand, both the ALN and 14% ON groups represented similar biomaterial properties of femurs, and both reduced the ovariectomy-induced decrease in bending load and bending energy ($p<0.05$).

9.4.162 Strontium ranelate promotes osteoblastic cell replication through at least two different mechanisms
Caverzasio J
Bone 2008;42:1131-6

Signaling involved in strontium ranelate-induced replication were investigated in preosteoblastic MC3T3-E1 and pluripotent mesenchymal C3H10T1/2 cells and were compared with calcium chloride as Ca(2+). In MC3T3-E1 cells, strontium

ranelate but not CaCl(2) dose-dependently increased cell number whereas similar effects were observed for both cations in C3H10T1/2 cells. Immunoblot analysis indicated that activation of ERK, PKC and PKD by strontium ranelate in MC3T3-E1 cells was delayed compared with CaCl(2). Onset of signaling by strontium ranelate was detected after one or several hours whereas CaCl(2) had a maximal effect already after 5 min exposure. In C3H10T1/2 cells, strontium ranelate induced two types of signaling, a rapid effect and a delayed response. In addition to activation of ERK, PKC and PKD, strontium ranelate and CaCl(2) also transiently activated p38 in C3H10T1/2 cells. Functional analysis with specific inhibitors indicated that cell replication induced by strontium ranelate involves a PKC/PKD pathway in MC3T3-E1 cells and p38 in C3H10T1/2 cells. In both cell types, inhibition of the ERK pathway decreased basal cell replication but not the strontium ranelate response. Strontium ranelate increases the replication of cells of the osteoblastic lineage and may interact with the CaSR and trigger mitogenic signals such as p38 in C3H10T1/2 cells. The delayed activation of several signaling pathways in both cell lines, however, suggests the release of an autocrine growth factor by strontium ranelate that represents another potential mechanism for inducing osteoblastic cell replication.

9.4.163 The effects of bisphosphonates on osteoblasts in vitro
Naidu A, Dechow PC, Spears R, Wright JM, Kessler HP, Opperman LA
Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:829-37

Primary rat osteoblasts were cultured in normal media or media containing increasing concentrations of alendronate and zoledronate. Enzyme-linked immunoabsorbent assays (ELISAs) were used to measure interleukin (IL)-6, transforming growth factor (TGF) beta1, and receptor activator of nuclear factor kappaB ligand (RANKL) expression in supernatants after 24, 48, and 72 h. Live and necrotic cell numbers were assessed with trypan blue assays. As drug concentrations increased, cell viability decreased. The ELISAs revealed increases in TGF-beta1 in treatment groups, but no significant change in RANKL or IL-6. High concentrations of alendronate and zoledronate were cytotoxic, decreasing cell viability at 72 h. Transforming growth factor beta1 increased even as viability decreased, suggesting a mechanism for bisphosphonate action. These data suggest that lower concentrations of bisphosphonates may have therapeutic benefits without the cytotoxic effects which may result in osteonecrosis.

9.4.164 Stimulation of osteogenic differentiation and inhibition of adipogenic differentiation in bone marrow stromal cells by alendronate via ERK and JNK activation
Fu L, Tang T, Miao Y, Zhang S, Qu Z, Dai K
Bone 2008;43:40-7

Bone marrow stromal cells (BMSCs) from ovariectomized SD rats were studied. Alendronate increased the mRNA level of bone morphogenetic protein-2, runt-related transcription factor 2, osteopontin, bone sialoprotein, and alkaline phosphatase activity after osteogenic induction and decreased the mRNA of peroxisome proliferator activated receptor gamma 2 and total droplet number indicated by Oil Red O staining after adipogenic induction. The MAPK-specific inhibitors, PD98059 and SP600125, but not the p38-specific inhibitor, blocked the alendronate-induced regulation of BMSC differentiation. Analysis of BMSCs induced in the presence of alendronate revealed an immediate increase in ERK and JNK phosphorylation. Alendronate acts on BMSCs to stimulate osteogenic differentiation and inhibit adipogenic differentiation in a dose-dependent manner via activating ERK and JNK.

9.4.165 Trends in HRT and anti-osteoporosis medication prescribing in a European population after the WHI study
Huot L, Couris CM, Tainturier V, Jaglal S, Colin C, Schott AM
Osteoporos Int 2008;19:1047-54

9.4.166 Effects of teriparatide on serum calcium in postmenopausal women with osteoporosis previously treated with raloxifene or alendronate
Wermers RA, Recknor CP, Cosman F, Xie L, Glass EV, Krege JH
Osteoporos Int 2008;19:1055-65

9.4.167 Effect of long-term treatment with risedronate on arterial compliance in osteoporotic patients with cardiovascular risk factors
Luckish A, Cernes R, Boaz M, Gavish D, Matas Z, Fux A, Shargorodsky M
Bone 2008;43:279-83

9.4.168 Patients' preferences for osteoporosis drug treatment: A discrete choice experiment
de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW
Osteoporos Int 2008;19:1029-37

9.4.169 Consequences of lifetime isolated growth hormone (GH) deficiency and effects of short-term GH treatment on bone in adults with a mutation in the GHRH-receptor gene
de Paula FJ, Gois-Junior MB, Aguiar-Oliveira MH, de APF, Oliveira CR, Pereira RM, Farias CT, Vicente TA, Salvatori R
Clin Endocrinol (Oxf) 2008;[Epub ahead of print]

9.4.170 25-hydroxylation of vitamin D3: Relation to circulating vitamin D3 under various input conditions
Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW
Am J Clin Nutr 2008;87:1738-42

9.4.171 Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula
Rutten S, Nolte PA, Korstjens CM, van Duin MA, Klein-Nulend J
Bone 2008;43:348-54

9.4.172 Treatment of collagen-induced arthritis with an anti-osteopontin monoclonal antibody through promotion of apoptosis of both murine and human activated T cells
Fan K, Dai J, Wang H, Wei H, Cao Z, Hou S, Qian W, Wang H, Li B, Zhao J, Xu H, Yang C, Guo Y

Arthritis Rheum 2008;58:2041-52

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

Volume 9, Issue 4, 2008

Exercise

9.4.173 Impact exercise increases BMC during growth: an 8-year longitudinal study
Gunter K, Baxter-Jones AD, Mirwald RL, Almstedt H, Fuchs RK, Durski S, Snow C
J Bone Miner Res 2008;23:986-93

BMC of the hip over 8 yr in prepubertal children who participated in a 7-mo jumping intervention compared with controls who participated in a stretching program (N=57; jumpers=33, controls=24; 47% of the original participants). After 7 mo, those children that completed high-impact jumping exercises had 3.6% more BMC at the hip than control subjects ($p<0.05$) and 1.4% more BMC at the hip after nearly 8 yr ($p<0.05$).

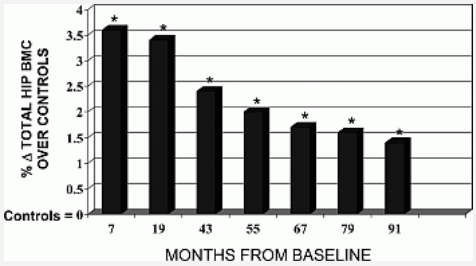


*Fig. 9.4.173 Jumping intervention effect on △total hip BMC after 8 yr. Percent change in total hip BMC in jumpers above that of controls after 7 mo of exercise training, 1 yr of detraining (19 mo), and 4–8 yr of detraining (43-91 mo). The intervention participants had 3.6% greater bone mass than controls immediately after the intervention and 1.4% greater bone mass at the total hip than controls after 8 yr. *Results are adjusted for baseline age, △Ht, △Wt, maturity, and sports participation and are significant at each of the seven measurement intervals ($p<0.05$). Reproduced from J Bone Miner Res 2008;23:986-93 with permission of the American Society of Bone and Mineral Research.*

9.4.174 Eight months of regular in-school jumping improves indices of bone strength in adolescent boys and Girls: the POWER PE study
Weeks BK, Young CM, Beck BR
J Bone Miner Res 2008;23:1002-11

During 8 mo, randomized, controlled, 99 adolescents (46 boys, 53 girls), mean age of 13.8±0.4 yr performed 10 min of jumping in place of regular physical education (PE). Controls performed usual PE warm-ups. Boys in the intervention group experienced improvements in calcaneal BUA (+5.0%) and fat mass (-10.5%), whereas controls did not (+1.4% and -0.8%, respectively). Girls improved FN BMC (+13.9%) and lumbar spine (LS) BMAD (+5.2%) more than controls (+4.9% and +1.5%, respectively). Between-group comparisons showed effects only for whole body (WB) BMC (+10.6% versus +6.3%) for boys. Boys in the intervention group gained more lean tissue mass, trochanter (TR) BMC, LS BMC, and WB BMC and lost more fat mass than girls in the intervention group ($p<0.05$). Ten minutes of jumping activity twice a week for 8 mo during adolescence seems to improve bone accrual in a sex-specific manner.

9.4.175 Vigorous physical activity increases fracture risk in children irrespective of bone mass: A prospective study of the independent risk factors for fractures in healthy children
Clark EM, Ness AR, Tobias JH
J Bone Miner Res 2008;23:1012-22

Children from the Avon Longitudinal Study of Parents and Children have been followed from birth to 11 yrs. Maternal self-reported data have been collected contemporaneously on early life factors, diet, puberty, and physical activity. These were linked to reported fractures between 9 and 11 yr of age. Multivariable logistic regression techniques were used to assess whether these potential determinants were independent of, or worked through, estimated volumetric BMD or estimated bone size relative to body size measured by total body DXA scan at 9.9 yr of age. 2692 children had full data. 193 (7.2%) reported at least one fracture over the 2-yr period. Children who reported daily or more episodes of vigorous physical activity had double the fracture risk compared with those children who reported less than four episodes per week (OR, 2.06; 95% CI, 1.21-1.76). No other independent determinants of fracture risk in healthy children were found. The higher bone mass associated with increased physical activity does not compensate for the risk caused by increased exposure to injuries.

9.4.176 Positive effects of exercise on falls and fracture risk in osteopenic women
Hourigan SR, Nitz JC, Brauer SG, O'Neill S, Wong J, Richardson CA
Osteoporos Int 2008;19:1077-86

98 community-dwelling osteopenic women aged 41-78 years were randomized into either a control (receiving no intervention), or exercise group (two one-hour exercise sessions per week for 20 weeks with a trained physiotherapist). 98 women (mean age 62.01 years, SD 8.9 years) enrolled. The mean number of classes attended for the 42 participants in the exercise group who completed the program was 28.2 of a possible 40 classes (71%). At the completion of the trial the intervention group showed better performances in balance (unilateral and bilateral stance sway measures, lateral reach, timed up and go and step test) ($p < 0.05$) with positive training effects reflecting improvements of between 10% to 71%. Similarly there were gains in strength of the hip muscles (abductors, adductors, and external rotators), quadriceps and trunk extensors with training effects between 9% and 23%. Specific workstation exercises can improve balance and strength in osteopenic women.

9.4.177 High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury

Frotzler A, Coupaud S, Perret C, Kakebeeke TH, Hunt KJ, Donaldson Nde N, Eser P
Bone 2008;43:169-76

Functional electrical stimulation (FES) induced high-volume cycle training can partially reverse the loss of bone substance in the legs after chronic complete SCI. Eleven participants with motor-sensory complete SCI (mean age 41.9±7.5 years; 11.0±7.1 years post injury) performed on average 3.7±0.6 FES-cycling sessions per week, of 58±5 min each, over 12 months at each individual's highest power output. After 12 months trabecular and total BMD as well as total cross-sectional area in the distal femoral epiphysis increased by 14.4±21.1%, 7.0±10.8% and 1.2±1.5%, respectively. Bone parameters in the femoral shaft showed small decreases, with a reduction of 0.4±0.4% in cortical BMD, 1.8±3.0% in bone mineral content, and 1.5±2.1% in cortical thickness. No changes were found in any of the measured bone parameters in the tibia. Muscle CSA at the thigh increased by 35.5±18.3%, while fat CSA at the shank decreased by 16.7±12.3%.

9.4.178 Mechanical loading enhances the anabolic effects of intermittent parathyroid hormone (1-34) on trabecular and cortical bone in mice
Sugiyama T, Saxon LK, Zaman G, Moustafa A, Sunters A, Price JS, Lanyon LE
Bone 2008;43:238-48

Female C57BL/6 mice from 13 to 19 weeks of age were given daily PTH (1-34) (20, 40 or 80 μg/kg/day). For three alternate days per week during the last two weeks of this treatment, the tibiae and ulnae on one side were subjected to a single period of dynamic axial loading (40 cycles at 10 Hz, 10-second, between each cycle). Two levels of peak load were used; one sufficient to engender an osteogenic response, and the other insufficient to do so. In the tibia, loading at a level sufficient by itself to stimulate osteogenesis produced an osteogenic response in the low-dose iPTH (1-34)-treated trabecular bone and in the proximal and middle cortical bone treated with all doses of iPTH (1-34). In the ulna, loading at a level that did not stimulate osteogenesis was osteogenic at the distal site with 80 μg/kg/day iPTH. At both levels of loading, there were synergistic effects in cortical bone volume of the proximal tibia and distal ulna between loading and high-dose iPTH from increases in endosteal and periosteal bone formation. No woven bone was induced by iPTH (1-34), whereas the combination of iPTH (1-34) and the "sufficient" level of loading stimulated woven bone formation on endosteal and periosteal surfaces of the proximal cortex in the tibiae.

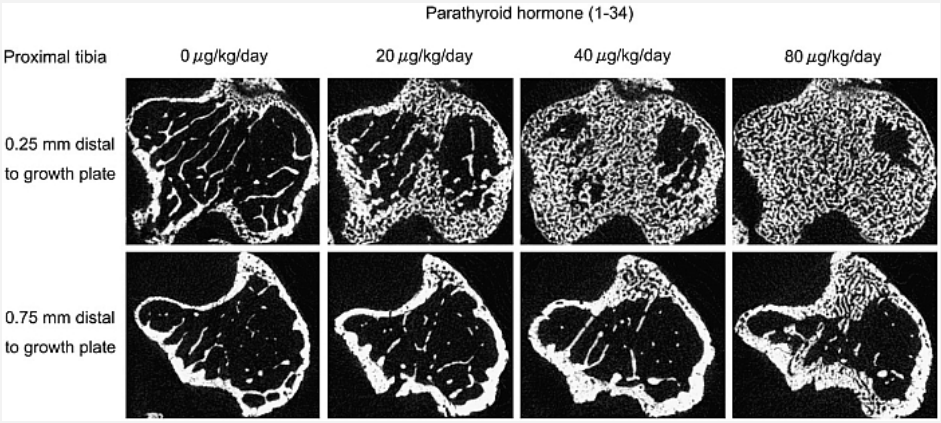


Fig. 9.4.178a Representative transverse μCT images of the trabecular bone in 17 week old female C57BL/6 mice treated with 4-weeks of intermittent parathyroid hormone (1-34). Reproduced from Bone, 43:238-48, Copyright (2008), with permission from Elsevier.

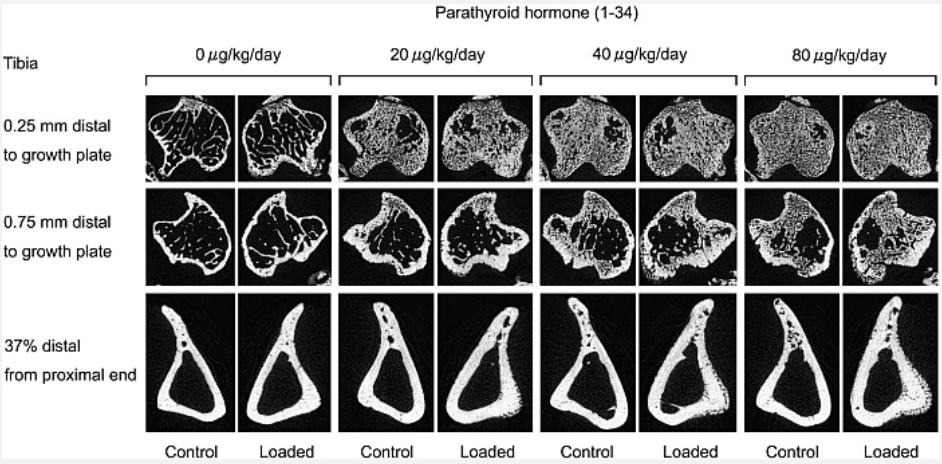


Fig. 9.4.178b Representative transverse μCT images of the trabecular and cortical bone in 19 week old female C57BL/6 mice treated with 6-weeks of intermittent parathyroid hormone (1-34) and 2-weeks of mechanical loading. Level of peak load: sufficient to engender an osteogenic response. Reproduced from Bone, 43:238-48, Copyright (2008), with permission from Elsevier.

9.4.179 Attenuated response to in vivo mechanical loading in mice with conditional osteoblast ablation of the connexin43 gene (Gja1)
Grimston SK, Brodt MD, Silva MJ, Civitelli R
J Bone Miner Res 2008;23:879-86

Gap junctional intercellular communication is mediated by connexin43 (Cx43) and plays a role in bone cell response to mechanical stimulation. Genetic deficiency of the Cx43 gene (Gja1) in 4-month-old female mice with a conditional Gja1 ablation in osteoblasts (ColCre;Gja1−/flox), wildtype (Gja1+/flox) and heterozygotes (Gja1−/flox) were subjected to a three-point bending. ColCre;Gja1−/flox mice had thinner cortices, larger tibial diaphysial marrow area and total cross-sectional area. These mice needed 40% more force to generate the required endocortical strain. In Gja1+/flox mice, loading produced double labels at the endocortical surface, whereas single labels were seen in ColCre;Gja1−/flox mice and mineral apposition rate and bone

formation rate were lower (54.8% and 50.2%, respectively) in ColCre;Gja1−/flox relative to Gja1+/flox mice. Intermediate values were found in Gja1−/flox mice. Cx43 plays a role in adaptive responses to physical stimuli.

9.4.180 Trabecular bone microarchitecture in female collegiate gymnasts
Modlesky CM, Majumdar S, Dudley GA
Osteoporos Int 2008;19:1011-8

9.4.181 Transmission of vertical whole body vibration to the human body
Kiiski J, Heinonen A, Jarvinen TL, Kannus P, Sievanen H
J Bone Miner Res 2008;23:1318-25

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

Volume 9, Issue 4, 2008

Men

9.4.182 Physical performance and risk of hip fractures in older men
Mannen Cawthon P, Fullman RL, Marshall L, Mackey DC, Fink HA, Cauley JA, Cummings SR, Orwoll ES, Ensrud KE
J Bone Miner Res 2008;23:1037-44

In 5902 men ≥65 yr of age followed averaged 5.3 yr; 77 incident hip fractures were confirmed. Poor physical performance was associated with an increased risk of hip fracture. In particular, repeated chair stand performance was strongly related to hip fracture risk. Men unable to complete this exam were much more likely to experience a hip fracture than men in the fastest quartile (multivariate hazard ratio [MHR]: 8.15; 95% CI: 2.65, 25.03). Men with the worst performance (weakest/slowest quartile or unable) on at least three exams had an increased risk of hip fracture compared with men with higher functioning (MHR: 3.14, 95% CI: 1.46, 6.73). Nearly two thirds of the hip fractures (N=49, 64%) occurred in men with poor performance on at least three exams.

9.4.183 Treatment of symptomatic androgen deficiency: Results from the Boston Area Community Health Survey
Hall SA, Araujo AB, Esche GR, Williams RE, Clark RV, Travison TG, McKinlay JB
Arch Intern Med 2008;168:1070-6

Data were available for 1486 Boston Area Community Health Survey participants (mean age, 46.4 years; age range, 30-79 years). A total of 5.5% (95% CI, 3.5-8.5) men met the criteria for having untreated, symptomatic androgen deficiency (AD), and 0.8% (95% CI, 0.4-1.4) met the criteria for having treated AD. Considering all cases, the proportion treated was 12.2%, so 87.8% of 97 men in with AD were not receiving treatment despite adequate access to care. The reasons for this are unknown but could be due to unrecognized AD or unwillingness to prescribe testosterone therapy.

9.4.184 Proximal femoral structure and the prediction of hip fracture in men: A large prospective study using QCT
Black DM, Bouxsein ML, Marshall LM, Cummings SR, Lang TF, Cauley JA, Ensrud KE, Nielson CM, Orwoll ES
J Bone Miner Res 2008;23:1326-33

Baseline QCT scans of the hip were obtained in 3347 men ≥65 yr of age followed for 5.5 yr. 42 men sustained incident hip fractures (2.3/1000 person-years). Multivariable analyses showed a lower percent cortical volume (hazard ratio [HR] per SD decrease: 3.2; 95% CI: 2.2-4.6), smaller minimal cross-sectional area (HR: 1.6; 95% CI: 1.2-2.1), and lower trabecular BMD (HR: 1.7; 95% CI: 1.2-2.4) were independently related to increased hip fracture risk. Femoral neck areal BMD was also related to hip fracture risk (HR: 4.1; 95% CI: 2.7-6.4). Percent cortical volume and minimum cross-sectional area remained predictors of hip fracture risk after adjustment for areal BMD, but overall prediction was not improved by adding QCT parameters to DXA.

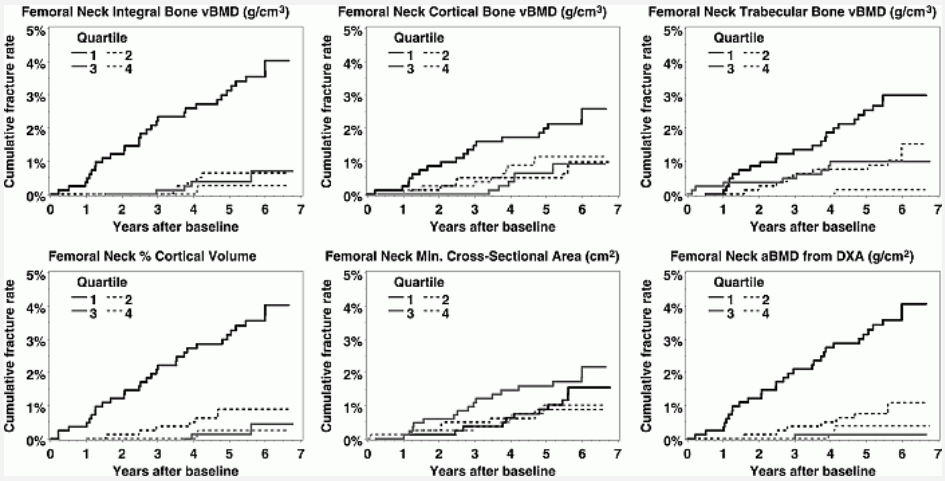


Fig. 9.4.184 Relationship of quartile of structure and density to hip fracture risk, unadjusted. Reproduced from J Bone Miner Res 2008;23:1326-33 with permission of the American Society of Bone and Mineral Research.

9.4.185 Computer-based screening of chest X-rays for vertebral compression fractures as an osteoporosis index in men
Nakai Y, Noth R, Wexler J, Volpp B, Tsodikov A, Swislocki A
Bone 2008;42:1214-8

26,994 chest X-ray (CXR) examinations were performed on 18,069 patients. 22,494 (83.3% of the total) CXR examinations were done in 14,561 men ≥50 years of age. 780 CXR reports (3.5%) encompassing 664 men (4.5%) contained at least one key phrase suggesting osteoporosis. Three years later, 495 of these 664 men were still living. 99 of these (20%) had been diagnosed with osteoporosis, 72 (15%) had a DXA scan, and 89 (18%) had ever been prescribed a bisphosphonate. Overall, only 126 (25%) men had chart documentation indicating some recognition by the provider of the abnormality reported on CXR.

9.4.186 Link between obstructive sleep apnea and increased bone resorption in men
Tomiyama H, Okazaki R, Inoue D, Ochiai H, Shiina K, Takata Y, Hashimoto H, Yamashina A
Osteoporos Int 2008;19:1185-92

A cross-sectional and prospective study was conducted in 50 consecutive male subjects visiting a sleep clinic and 15 age-

matched control subjects without OSA. Plasma concentrations of IL-1beta, IL-6, TNF-alpha, 3-nitrotyrosine, osteocalcin, bone-specific alkaline phosphatase (BAP), and urinary concentrations of cross-linked C-terminal telopeptide of type I collagen (CTX) were examined before and after 3 months' CPAP in subjects with OSA. The plasma levels of the cytokines as well as the urinary CTX levels were higher in subjects with severe OSA than in those with mild OSA or control subjects. Significant decrease of the urinary excretion of CTX (before: 211±107 vs. after: 128±59 mug/mmol/creatinine; p<0.01) as well as of the plasma levels of the cytokines was observed following 3 months' CPAP.

9.4.187 25-hydroxyvitamin D and risk of myocardial infarction in men: A prospective study
Giovannucci E, Liu Y, Hollis BW, Rimm EB
Arch Intern Med 2008;168:1174-80

A nested case-control study in 18,225 men aged 40-75 years free of cardiovascular disease at blood collection. During 10 years, 454 developed nonfatal myocardial infarction (MI) or fatal coronary heart disease, controls (n=900) were selected in a 2:1 ratio and matched for age, date of blood collection, and smoking status. After adjustment, men deficient in 25(OH)D (≤15 ng/ml) were at increased risk for MI (relative risk [RR], 2.42; 1.53-3.84). After additional adjustment, this relationship remained (RR, 2.09; 1.24-3.54). Low levels of 25(OH)D are associated with higher risk of myocardial infarction.

9.4.188 Vitamin D-binding protein gene microsatellite polymorphism influences BMD and risk of fractures in men
Al-Oanzi ZH, Tuck SP, Mastana SS, Summers GD, Cook DB, Francis RM, Datta HK
Osteoporos Int 2008;19:951-60

Intra-intronic variable tandem (TAAA)n-Alu repeat expansion in the DBP gene in 170 men was investigated. The predominant DBP-Alu genotype in the control subjects was 10/10 (frequency 0.421), whereas the frequency of this genotype in men with osteoporosis was 0.089. DBP-Alu alleles *10, *8 and *9, respectively, were the three commonest in both healthy subjects and men with osteoporosis. Allele *10 was associated with a lower risk of osteoporosis (OR 0.39, 95% CI 0.25-0.64; p<0.0005), as was allele *11 (OR 0.09, 95% CI 0.01-0.67; p<0.007). Logistic regression gave similar results, showing that individuals with genotype 10/10 and 19-20 repeats (genotypes 9/10, 9/11, 10/10) are protected from fracture or osteoporosis. Overall, there was a relationship between DBP Alu genotype and BMD, suggesting that DBP-Alu genotype may influence fracture risk.

9.4.189 An evaluation of osteoporosis screening tools for the osteoporotic fractures in men (MrOS) study
Lynn HS, Woo J, Leung PC, Barrett-Connor EL, Nevitt MC, Cauley JA, Adler RA, Orwoll ES
Osteoporos Int 2008;19:1087-92

9.4.190 A high activity index of stearoyl-CoA desaturase is associated with increased risk of fracture in men
Melhus H, Riserus U, Warensjo E, Wernroth L, Jensevik K, Berglund L, Vessby B, Michaelsson K
Osteoporos Int 2008;19:929-34

9.4.191 Osteonectin/SPARC polymorphisms in Caucasian men with idiopathic osteoporosis
Delany AM, McMahon DJ, Powell JS, Greenberg DA, Kurland ES
Osteoporos Int 2008;19:969-78

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

Volume 9, Issue 4, 2008

Reviews

General

9.4.192 How can bone turnover modify bone strength independent of bone mass?
Hernandez CJ
Bone 2008;42:1014-20

9.4.193 Model structure and control of bone remodeling: A theoretical study
Pivonka P, Zimak J, Smith DW, Gardiner BS, Dunstan CR, Sims NA, John Martin T, Mundy GR
Bone 2008;43:249-63

9.4.194 Vitamin D and health: Perspectives from mice and man
Bouillon R, Bischoff-Ferrari H, Willett W
J Bone Miner Res 2008;23:974-9

9.4.195 Leptin and the sympathetic connection of fat to bone
Hamrick MW, Ferrari SL
Osteoporos Int 2008;19:905-12

9.4.196 The pathogenesis of the bone disease of multiple myeloma
Edwards CM, Zhuang J, Mundy GR
Bone 2008;42:1007-13

9.4.197 Ephs and ephrins: A new way for bone cells to communicate
Lorenzo J
J Bone Miner Res 2008;23:1168-9

9.4.198 Genetics of the musculoskeletal system: A pleiotropic approach
Karasik D, Kiel DP
J Bone Miner Res 2008;23:788-802

Morbidity/Mortality

9.4.199 Back pain in osteoporotic vertebral fractures
Francis RM, Aspray TJ, Hide G, Sutcliffe AM, Wilkinson P
Osteoporos Int 2008;19:895-903

Local Factors

9.4.200 Matrix metalloproteinases and bone
Krane SM, Inada M
Bone 2008;43:7-18

Risk Factors

9.4.201 Misconceptions - Vitamin D insufficiency causes malabsorption of calcium
Need AG, Nordin BE
Bone 2008;42:1021-4

9.4.202 Diabetes and fragility fractures - A burgeoning epidemic?
Epstein S, Leroith D
Bone 2008;43:3-6

Treatment

9.4.203 A revised clinician's guide to the prevention and treatment of osteoporosis
Dawson-Hughes B
J Clin Endocrinol Metab 2008;93:2463-5

9.4.204 Regulatory pathways revealing new approaches to the development of anabolic drugs for osteoporosis
Martin TJ, Sims NA, Ng KW
Osteoporos Int 2008;19:1125-38

9.4.205 On the interpretation of rat carcinogenicity studies for human PTH(1-34) and human PTH(1-84)
Tashjian AH, Goltzman D
J Bone Miner Res 2008;23:803-11

9.4.206 NICE continues to muddy the waters of osteoporosis
Kanis JA, Compston JE
Osteoporos Int 2008;19:1105-7

9.4.207 Considerations for development of surrogate endpoints for antifracture efficacy of new treatments in osteoporosis: A perspective
Bouxsein ML, Delmas PD
J Bone Miner Res 2008;23:1155-67

Progress in
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Summaries and Critical Analyses of the Current Literature
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Volume 9, Issue 4, 2008

Invest in Your Bones Campaign

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.