PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 1

Ego Seeman

Editor

Volume 13, Issue 1

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By Ego Seeman Fri, 01/18/2013 - 10:30

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Subtrochanteric Fractures

Most persons at risk for fracture are not treated, even when they have a prevalent fracture. Indeed, fewer women and men are being treated despite efforts to establish capture the fracture programs. One reason may be concern about the occurrence of atypical subtrochanteric fractures. The risk of subtrochanteric fractures needs to be kept in perspective because stopping treatment to avert rare events may result in more fractures. Stopping treatment results in an increase in the intensity of remodelling to its pretreatment state eventually. As each remodelling event removes more bone than it deposits, structural decay will recur increasing fracture risk.

Dell et al identified all femur fractures from January 1, 2007 until December 31, 2011 in 1,835,116 patients older than 45 enrolled in the Healthy Bones Program at Kaiser Southern California. Among these, 188,814 patients used bisphosphonates. Of 142 patients with atypical fractures 128 had bisphosphonate exposure. The age-adjusted incidence per 100,000 persons per year for atypical fracture with exposure from 0.1-1.9 years was 1.78, and 113.1 with exposure from 8-9.9 years (~1/1000 patients). (1)

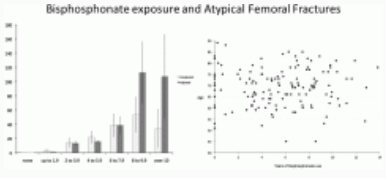


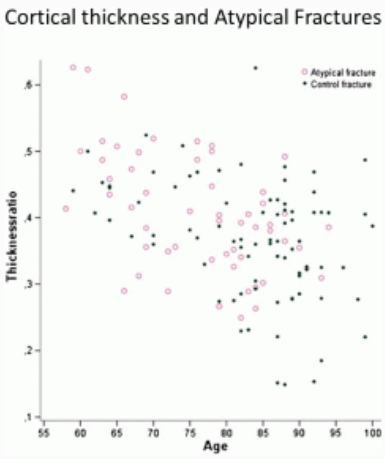
Figure 1. Left panel: Incidence of atypical femoral fractures age adjusted (darker bar) and unadjusted by duration of bisphosphonate exposure (±95% CI). Right panel: Age at fracture versus duration of bisphosphonate exposure. Reproduced from J Bone Miner Res 2012;27:2544-50 with permission of the American Society of Bone and Mineral Research.

Patients with subtrochanteric fractures are reported to have thicker cortices. While tenting is seen

in the vicinity of the cortical fracture, there is no basis for the cortices to be thicker; bisphosphonates do not increase endocortical or periosteal apposition. Bisphosphonates reduce remodelling intensity so that bone matrix that would have been resorbed undergoes more complete secondary mineralization which produces greater photon attenuation. Bone edges are more readily detected by including edge voxels that now attenuate photons above the level designated by the thresholding as being a 'bone'. This results is an apparent thicker cortex. Similar problems arise measuring trabecular density. Claims that bisphosphonates or strontium ranelate increase trabecular number have no basis. Existing trabeculae that are more fully mineralized or contain strontium, which has twice the atomic number of calcium, attenuate photons making it seem like trabecular number or thickness has increased.

Koeppen et al report that in 59 women with an atypical fracture, femoral cortical thickness index (thickness/femoral diameter) was not increased compared with the 218 patients with ordinary fractures. There was no difference in cortical thickness between patients with or without bisphosphonate treatment or between the ipsilateral and contralateral femurs in patients with an atypical fracture. (2)

Figure 2. Cortical thickness as a function of age. There is no difference in cortical thickness in cases with atypical fracture relative to controls. Reproduced from Osteoporos Int 2012;23:2893-6 with permission from Springer.

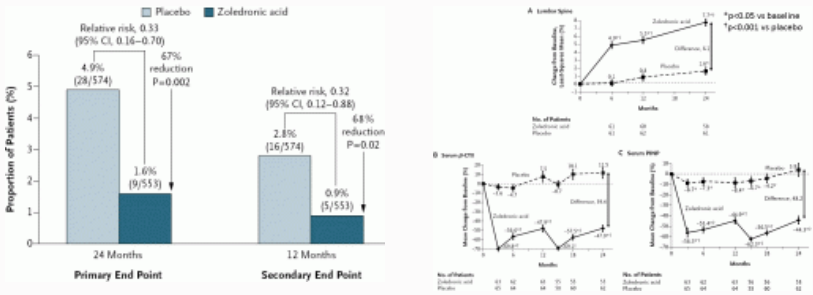


Osteosarcoma and PTH Administration

Andrews et al report that at the 7th year of the 15-year Osteosarcoma Surveillance Study, 1448 cases were identified; 549 patients or proxies were interviewed. Age of those interviewed was 61 years, 46% were female, 86% were white, and 77% were alive when the case was reported to the study investigators. There were no patients with osteosarcoma who received teriparatide. (3)

Zoledronic Acid and Vertebral Fracture Risk Reduction in Men

There are very few randomized placebo controlled trials examining the antifracture efficacy of any drug in men. Most of the studies are small, brief in duration and so the credibility of the studies is not strong. This has changed. **Boonen et al** report that 1199 men aged 50-85 years with primary or hypogonadism-associated osteoporosis received an intravenous infusion of zoledronic acid (5 mg) or placebo at baseline and at 12 months. After 24 months the incidence of any new morphometric vertebral fracture was 1.6% compared with 4.9% in controls; a 67% risk reduction (RR 0.33; 95% CI 0.16-0.70). BMD was higher and bone turnover markers were lower in treated patients. Results were similar in men with low serum levels of total testosterone. The zoledronic acid and placebo groups did not differ with respect to the incidence of death (2.6% and 2.9%, respectively) or serious adverse events (25.3% and 25.2%). There was no detectable group differences in nonvertebral or hip fracture risk. (4)



Figures 3-4. Incidence of vertebral fractures at 12 and 24 months in men treated with zoledronic acid and controls. Changes in BMD and bone remodeling markers. From N Engl J Med, Steven Boonen, Jean-Yves Reginster, Jean-Marc Kaufman, et al., Fracture Risk and Zoledronic Acid Therapy in Men with Osteoporosis, Volume 367, Page 1714. Copyright © (2012) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Beta Blockage as a Protective Factor

Exposure to β-blockers (BBs) is associated with lower fracture rates. In 501,924 Korean patients (≥65 years, 65% female), the incidence of fractures per 1000 person-years in users (17.2 men,

30.5 women) was lower than in nonusers (29.3 and 48.2 per for men and women, respectively. Non-BB users had an increased risk (95% CI) of all fracture [aHR 1.56 (1.42-1.72) in men and 1.44 (1.36-1.51) in women] and hip fracture [aHR 2.17 (1.45-3.24) in men and 1.61 (1.31-1.98) in women] after adjustment. The risk of all fractures in users of α-blockers, calcium channel blockers, diuretics, and renin-angiotensin-aldosterone system blockers were higher compared to BB users (1.72, 1.77, 1.58, 1.29 in men; 2.11, 1.50, 1.46, 1.22 in women, respectively). Compared to non-BBs, β1 selective BBs showed a lower risk of fracture (39% for men and 33% for women) after adjustment. Nonselective BBs were not protective. (5)

The Osteocyte:
Conductor of remodeling symphony for two

Discussions of bone remodelling as a classical duet for osteoclasts and osteoblasts are no longer appropriate. This insight, reported by Frost in the middle of the last century is not wrong, but it is incomplete. The osteocyte is a third player, not as a third fiddle, but rather the conductor initiating the first movement of this orchestral concert. Osteocyte apoptosis initiates osteoclastic bone resorption following fatigue-induced microdamage in vivo. However, apoptotic osteocytes may not be the signal for damage repair.

Kennedy et al report that ulnae from female Sprague Dawley rats were loaded to a single fatigue level. Osteoclast expression of RANKL, OPG, VEGF genes associated with osteoclastogenesis and apoptosis were assessed. Osteocyte apoptotic (caspase 3-positive) cells were highest in the damage region and declined to control levels within several hundred microns of microdamage. Cells expressing RANKL or VEGF peaked between 100-300 μm from the damage site, then returned to control levels beyond this distance. Osteocytes in nonfatigued control bones expressed OPG. OPG staining was reduced in osteocytes immediately surrounding microdamage. (6)

Osteocyte apoptosis triggers remodeling response to microdamage, the neighbouring nonapoptotic osteocytes are the source of pro-osteoclastogenic signals. The apoptotic and osteoclast-signalling osteocyte populations are localized in a spatially and temporally restricted pattern consistent with the targeted nature of this remodelling response.

*Figure 5. Gene expression of osteoclastogenic factors: RANKL, OPG, VEGF and M-CSF from osteocyte enriched segment of rat ulnar cortex at 3 and 7 days after fatigue loading (*p<0.001). Reproduced from Bone, 50:1115-22, Copyright (2012), with permission from Elsevier.*

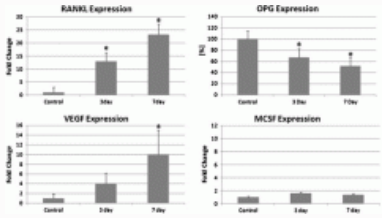
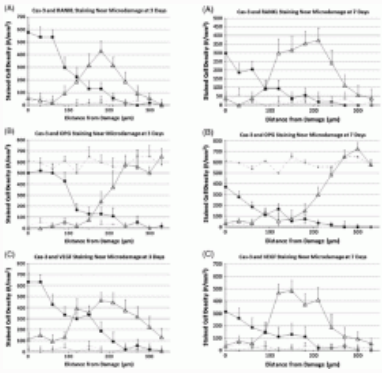


*Figure 6. Left panel: Distance distribution showing expression of (A) Cas-3 and RANKL (B) Cas-3 and OPG (C) Cas-3 and VEGF in osteocytes as a function of distance from the damage region 3 days (left panels) and 7 days (right panels) after fatigue loading. (*p<0.01). Reproduced from Bone, 50:1115-22, Copyright (2012), with permission from Elsevier.*



Vitamin D: A little surprise

Vitamin D has been in fashion for some time, it has a cult following, a bit like The Rocky Horror Show which plays at midnight and you better bring a raincoat. Excess blood as a cause of everything and bloodletting as a cure for everything were in the same league up to the mid-1970s. Leach farming was a big business and farmers did not declare a conflict of interest.

The first recent surprise was the randomized double blind trail from Sanders et al suggesting that large doses of vitamin D increase fracture risk. Now that can't be correct surely, this doesn't 'fit' with our preconceived ideas, it doesn't make sense so it must be wrong (7). Recall Galileo's words to his student, "be most worried when the data fits your hypothesis."

Another little surprise is here. **Rossini et al** report that 37 elderly subjects (mean age 75 years) were randomized to a single oral bolus of 600,000, 300,000, or 100,000 IU vitamin D3. Twenty-four subjects served as controls. With 600,000 IU, a significant increase of sCTX was observed at day 1 and was sustained for 2 months. The changes in sCTX with smaller doses were less and reached significance only within the first 3 days with the 300,000 IU dose. BAP remained unchanged in patients given 300,000 and 600,000 IU. No relevant changes in markers were observed in controls. In patients given 100,000 IU sCTX rose by 15-23%. Vitamin D bolus exceeding 100,000 IU may be associated with acute increases of sCTX. (8) Is this the beginning of the end; probably not. Does more work need to be done? Of course.

PTH1-34 Reduces Vertebral and Nonvertebral Fractures But what of hip fractures?

A 12-month, phase III, randomized, multicenter, double-blind, placebo-controlled trial with BMD as a primary endpoint was conducted in Japanese subjects. A meta-analysis was carried out in 3 studies in which fracture data were available from prospectively scheduled spinal radiographs. Odds ratios (95% CI) were 0.29 (0.20, 0.43) for vertebral fracture and 0.53 (0.32, 0.86) for nonvertebral fracture. There was also a consistent effect of teriparatide to increase BMD. Furthermore, teriparatide-mediated increases in spine BMD accounted for 25–32% of the reduction in vertebral fracture risk in the combined Caucasian and Japanese patients. (9)

The Burden of Nonvertebral Fractures

The incidence of hip, spine, major NHNV (pelvis/leg, shoulder/arm) and minor NHNV (wrist/hand, ankle/foot, rib/clavicle) fractures was assessed among women in GLOW. Health-related quality of life (HRQoL) was analysed using the EuroQol EQ-5D tool and the SF-36 health survey. Among 50,461 women, there were 1822 fractures (57% minor NHNV, 26% major NHNV, 10% spine, 7% hip) over one year. Spine fractures had the greatest detrimental effect on EQ-5D summary scores, followed by major NHNV and hip fractures. The number of women with mobility problems increased most for those with major NHNV and spine fractures (both +8%); spine fractures were associated with the largest increases in problems with selfcare (+11%), activities (+14%), and pain/discomfort (+12%). Decreases in physical function and health status were greatest for those with spine or hip fractures. EQ-5D reduction was greatest for spine fractures, followed by hip and major/minor NHNV. Statistically significant reductions in SF-36 physical function were found for spine fractures, and were borderline significant for major NHNV fractures. NHNV fractures have a detrimental effect on HRQoL. (10)

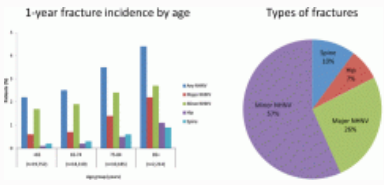


Figure 7. Left panel: 1-year incidence of fractures in GLOW by age group. Right panel: Distribution of incident fracture types. Major NHNV pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow; minor NHNV wrist, hand, ankle, foot, rib, and clavicle. Reproduced from Osteoporos Int 2012;23:2863-71 with permission from Springer.

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By Ego Seeman Thu, 02/21/2013 - 08:34

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Bone Remodelling Compartments

Bone remodelling is the removal of damaged mineralized bone matrix and replacement by a volume of new matrix by the cells of the BMU. For remodelling to occur, the need for it must first be signalled from the damage or from nearby cells. These signals, whatever their nature, must then reach a point upon the endosteal (internal) surface of bone – one or more of the intracortical (Haversian), endocortical or trabecular components of this surface because initiation of remodelling always occurs upon a surface. At this point upon the bone surface, a bone remodelling compartment (BRC) is formed (1). The flattened osteoblasts that form the endosteal lining cells are modified to produce local factors participating in recruitment of vascular structures, and collagenase, which removes a collagen layer to then form the roof of this BRC (2).

Hematopoietic precursor cells of the osteoclast lineage and mesenchymal precursors of the osteoblast lineage are recruited from the marrow, circulation and locally. They differentiate to become mature bone resorbing osteoclasts and bone forming osteoblasts within this compartment, from which osteoclasts excavate a tunnel within cortical bone or a trench upon the endocortical surface or trabecular surface. Osteoblasts follow from 'behind', 'zipping up' the excavated canal or trench with newly deposited osteoid from the cement line inwards leaving what will be the new Haversian canal in cortical osteons.

Provided equal volumes of bone are resorbed and formed by each BMU, there is no net loss of bone. As age advances, the volume of bone formed by each BMU decreases producing a negative BMU balance, the single necessary and sufficient morphological abnormality responsible for structural deterioration (3). One of the mechanisms that may contribute to this is a change in the roof of the BRC.

Kristensen et al report iliac crest biopsies from normal individuals showed the BRC canopy

consists of CD56 positive osteoblasts in association with increased numbers of capillaries, putative osteoblast progenitors and proliferative cells in a region within 50 µm of the canopy surface and highest above eroded surfaces (4). Between 51-100 µm, capillary densities were less. The close proximity between BRC canopies and capillaries support the existence of an osteogenic vascular interface in cancellous bone. Initiation of remodelling may occur with approximation of vasculature and endosteal surfaces allowing capillary BRC canopy interactions to provide a gateway for access of the osteoclast and mesenchymal precursors of the osteoblast into the BRCs.

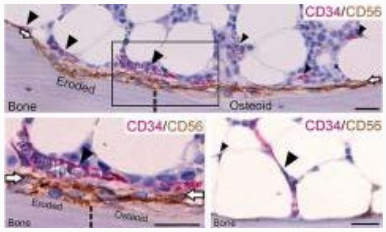

Figure 1. Relation between bone surface and prevalence of capillaries. CD34+ capillaries and CD56+ OB-lineage cells. (top) Frequent capillaries (arrowheads) are positioned next to a canopy-covered remodelling surface. The capillaries adjacent to the BRC canopy (large arrowheads) run parallel to it thereby offering a large interface between the two entities. (bottom left) Enlargement of the framed area in the upper picture illustrating contact between a BRC canopy (arrows) and a capillary (arrowhead). (bottom right) A capillary (large arrowhead) runs perpendicularly to the quiescent bone surface thereby offering only a small interface with the surface. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1760] with permission of the American Society of Bone and Mineral Research.

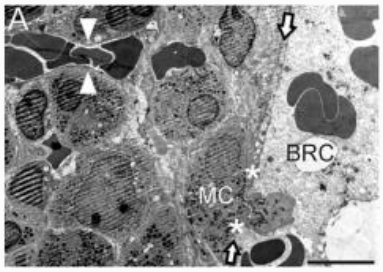

Figure 2. Electron microscopic analysis of the bone marrow bone matrix interface in areas where capillaries are close to BRC canopies. A marrow cell (MC) performs diapedesis (asterisks) through a BRC canopy (arrows) into the lumen of a BRC (BRC). A capillary (arrowheads) is situated close by. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1760] with permission of the American Society of Bone and Mineral Research.

Jensen et al report that viability of canopies determines the occurrence of the bone formation phase of remodelling (5). Canopies are present in early stage of the remodelling cycle, but their absence was associated with reduced bone formation surfaces. In healthy individuals and in patients with endogenous Cushing's syndrome (CS), ~100% canopy coverage above resorbing osteoclasts is observed, but only about 76% above bone forming surfaces.

The authors suggest that canopies are associated with the early stage of the remodelling cycle but may disappear later. In control and two-thirds of the CS patients, a decline in canopy coverage occurred when bone formation was initiated. In the remaining third of the CS patients, the prevalence of canopies decreased before bone formation and coincided with less bone forming surface. The authors suggest bone restitution is compromised in the absence of canopies. BRC canopies could be targets for treatment.

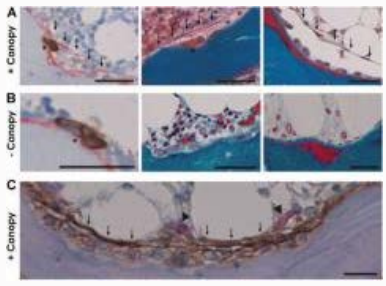

Figure 3. BRC canopy in patients with CS. (A, left) Immunohistochemical stainings show NCAM-positive BRC canopy cells (red, arrows) separating a bone surface – TRACP-positive osteoclast (brown, asterisk) from the bone marrow. (B, left) Remodelling surfaces, as identified here through a TRACP-positive osteoclast (brown, asterix) are not covered by a BRC canopy. Similarly, when staining with Masson-Goldner Trichome, BRC canopies (arrows) covering eroded (A, middle) or osteoid (A, right) bone surfaces can be detected on some occasions, but not on others (B, middle, right). (C) CD34-positive capillaries (red, arrowheads) are observed in close proximity to NCAM-positive BRC canopy cells (brown, arrows). Scale bars: 50 µm. Reproduced from J Bone Miner Res 2012;27:770-80 with permission of the American Society of Bone and Mineral Research.

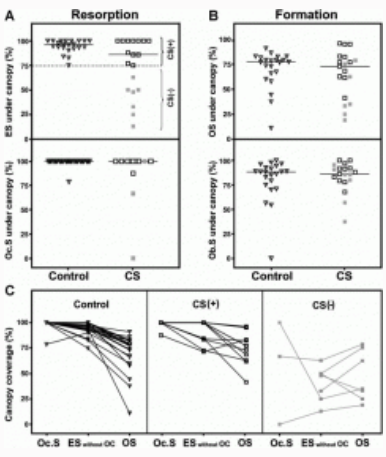

Figure 4. Prevalence of BRC canopies above eroded and bone-forming surfaces in controls and patients with CS. The prevalence of BRC canopies covering eroded (A) and bone-forming surfaces (B) was evaluated in 22 controls (triangles) and 19 patients with CS (squares). It was expressed as percentage of ES, Oc.S, OS, and Ob.S under canopy relative to total ES, Oc.S, OS, and Ob.S, respectively. The percentage of ES under BRC canopy was higher than 75% in all controls (median 96%), whereas the CS cohort showed values both above (open squares) and below (filled grey squares) 75% (A, upper graph). Therefore, our subsequent analysis considered separately these two CS subpopulations, indicated as (+) and (-), respectively. The prevalence of canopies at the successive stages of the remodelling cycle is

shown for each biopsy in three separate graphs corresponding to the controls, CS(+), and CS(-), respectively (C). The successive stages of the remodelling cycle were reflected by Oc.S, ES vacated by osteoclasts (reversal surface), and OS. Reproduced from J Bone Miner Res 2012;27:770-80 with permission of the American Society of Bone and Mineral Research.

Serum Vitamin D, Dietary Calcium Deficiency and Fracture Risk

Looker examined the relationship between serum 25(OH)D and risk of incident hip, spine, radius and humerus fractures in 4749 men and women ages 65 years and older from NHANES III, 1988 94 and NHANES 2000 2004 (6). There were 525 incident major osteoporotic fractures (287 hip). Serum 25(OH)D was a linear predictor of fracture and quadratic predictor of hip fracture in the total sample and among those with less than 10 years of follow up but not those with longer follow-up. The associations appeared to be independent of age. Major osteoporotic fracture risk was increased by 26 27% for each SD lower serum 25(OH)D among those with less than 10 years of follow up. The increase in risk for fracture seemed to occur when values of 25(OH)D were below 30 nmol/L. The question of whether 'insufficiency' in serum 25(OH)D is associated with adverse health outcomes remains.

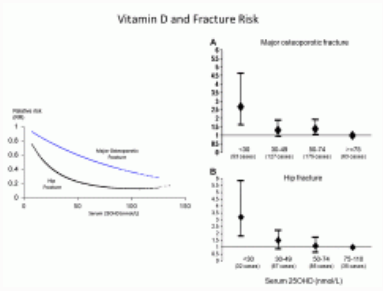

Figure 5. (left panel) Smoothed relative risk of major osteoporotic fracture or hip fracture by serum 25(OH)D value among persons with less than 10 years of follow-up, adjusted for age, sex, race/ethnicity, and survey. (right panel) Relative risk of major osteoporotic fracture or hip fracture by serum 25(OH)D category among persons with less than 10 years of follow-up, adjusted for age, sex, race/ethnicity and survey. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1828] with permission of the American Society of Bone and Mineral Research.

Joo et al divided 2567 men and 2,095 women ≥50 years of age from the 2009 2010 Korea National Health and Nutrition Examination Survey (KNHANES) into two groups according to dietary calcium quintiles (means: 154, 278, 400, 557 and 951 mg/d) and serum 25(OH)D <50, 50 75 and >75 nmol/L (7). Lower calcium intakes were associated with higher serum PTH and lower femoral neck BMD irrespective of serum 25(OH)D. Serum PTH was highest and femoral neck BMD was lowest in the group with a serum 25(OH)D <50 nmol/L. In this low intake population, calcium intake is a determinant of serum PTH and BMD irrespective of 25(OH)D.

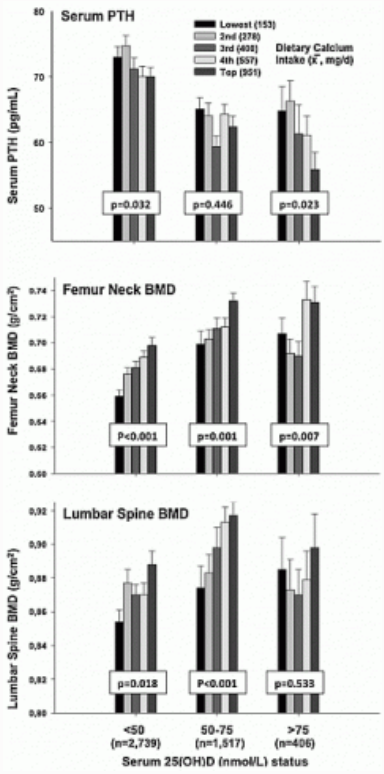

Figure 6. Adjusted mean serum PTH and BMDs according to serum 25(OH)D concentrations and dietary calcium intakes. Five bars represent quintiles of dietary calcium (Lowest ≤220 mg/d; second=220.1-331.3 mg/d; third=331.4-467.1 mg/d; forth=467.4-666.7 mg/d; top=667.6-1986.3 mg/d). P for trend (p) in same groups are from general lineal model in complex data analysis. Data are adjusted for age, sex, BMI, GFR, smoking, occupation, season, and physical activity. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1790] with permission of the American Society of Bone and Mineral Research.

Tissue Mineralization Density and Zoledronic Acid

Reducing remodelling intensity is the main action of antiresorptive agents like zoledronic acid. When remodelling intensity is reduced, there is more time available for bone deposited prior starting treatment to undergo secondary mineralization, a process which can take some years to reach completion (8). With protracted remodelling suppression, more and more of the bone matrix volume that would have been removed by high remodelling is not removed and undergoes this secondary mineralization. As a consequence, adjacent regions of bone become more fully and so homogeneously mineralized. This loss of heterogeneity in mineralization may not be a good thing because microcracks, in addition to not being removed because remodelling is

suppressed, may also be more liable to grow in size as resistance to crack propagation is less in homogeneously mineralized bone.

Misof et al report cancellous and cortical bone mineralization density distribution (BMDD) in biopsies using backscattered electron imaging (qBEI) in 82 patients receiving ZOL, yearly 5mg) and 70 controls (9). BMDD mean values for cancellous (Cn.) and cortical (Ct.) relative to controls were higher by +3.2% and +2.7% with increased percentages of high mineralized bone areas +64% +31%, lower heterogeneity of mineralization (Width -14%, -13%), and decreased percentages of low mineralized bone areas (-22%, -26%) (all p<0.001). Those with lower Cn.MS/BS, a measure of suppression of remodelling, had higher degree of bone matrix mineralization. There are no surprises here. The question is whether this is good or bad in terms of material strength.

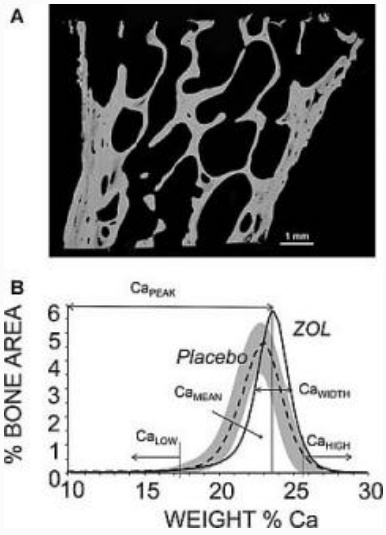

Figure 7. (A) Backscattered electron image of the cross-sectional area of one ZOL treated biopsy sample (the brighter in the image the higher the local calcium concentrations). (B) Grey level histogram (bone mineralization density distribution, BMDD) of trabecular bone with one example of the cancellous BMDD of the placebo treated (dashed line) and 95% CI of normal cancellous BMDD curves showing the average (CaMean) and the mode (the most frequent) Ca concentrations (CaPeak), the heterogeneity of mineralization (CaWidth), the percentages of low (primary) mineralized (CaLow) and highly mineralized bone areas (CaHigh). Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1780] with permission of the American Society of Bone and Mineral Research.

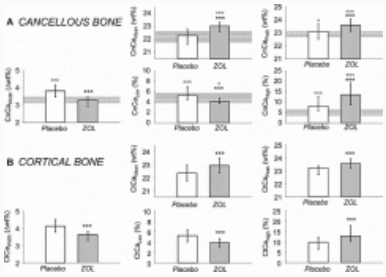

*Figure 8. Cancellous (A) and cortical (B) BMDD outcomes (white placebo, back-white patterned ZOL treated). The bars show mean (SD) or median (25th, 75th percentile). White dotted lines and grey areas in the background of (A) are revealing the mean/median and ±1 SD/interquartile range of the cancellous reference BMDD, cortical reference BMDD data are not available. ***p<0.001 vs. placebo. °° °p≤0.001, °p<0.05 vs. normal reference BMDD. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1780] with permission of the American Society of Bone and Mineral Research.*

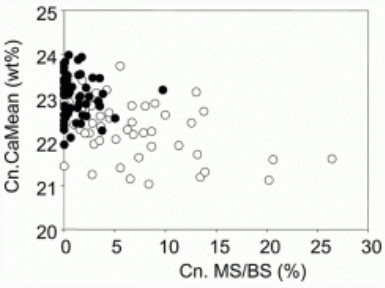

Figure 9. The average calcium concentration of cancellous bone (Cn.CaMean) vs. Cn. MS/BS. Full symbols ZOL, empty symbols placebo. Reproduced from J Bone Miner Res 2012;doi:[10.1002/jbmr.1780] with permission of the American Society of Bone and Mineral Research.

The Burden of Nonvertebral Fractures is Substantial

Nonvertebral fractures comprise about 80% of all fractures. This has been documented many times and should refocus thinking to extend beyond osteoporosis as a disease characterized by trabecular bone loss and vertebral fractures.

To assess direct medical resource utilization related to the treatment of nonvertebral osteoporotic fractures within 1 year postfracture, **Jean et al** evaluated a physician claims databases identified 15,327 women aged 50 years or older with incident nonvertebral fractures (10). The proportions of fractures treated by open reduction, closed reduction, immobilization or follow up by an orthopaedic surgeon (OS) were evaluated. The mean number of claims for consultation with an OS or other clinicians in inpatient and outpatient visits, the hospitalization rate and length of stay (LOS) were assessed.

Hip/femur fractures represented the highest rate of resource utilization since the majority of them required surgery (91.1%) and hospitalization (94.5%) with a mean LOS of 39.2 days. Other nonvertebral fracture types needed clinical care related to surgery (27.9%), follow up consultation with an OS (77.6%) and hospitalization (27.3% of total LOS). Pelvic fractures commanded high resource utilization due to the high hospitalization rate (67.4%) with mean LOS of 34.2 days. Age was associated with an increased number of visits to other physicians, hospitalization, and length of hospitalization (LOS), admissions to long term care (LTC), and

death.

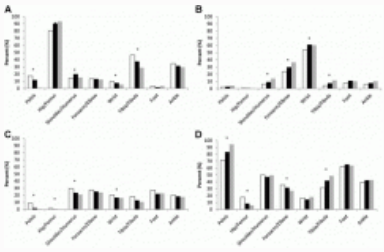

*Figure 10. Fracture treatments by age groups. (A) Open reduction. (B) Closed reduction. (C) Immobilization. (D) Conservative treatment. The white, dark and light grey bars represent, respectively, 50-64 years, 65-79 years and 80 years and older age groups. *Significant difference between age groups (chi-square test, p<0.05). Reproduced from J Bone Miner Res 2013;28:360-71 with permission of the American Society of Bone and Mineral Research.*

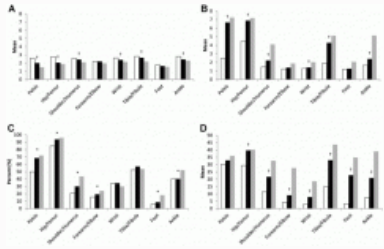

*Figure 11. Health resources utilization by age groups. (A) Orthopaedic surgeon visit. (B) Other physician visit. (C) Hospitalization. (D) Length of stay (days). *Significant difference between age groups (chi-square test, p<0.05). † Significant difference between age groups (Wilcoxon test, p<0.05). Reproduced from J Bone Miner Res 2013;28:360-71 with permission of the American Society of Bone and Mineral Research.*

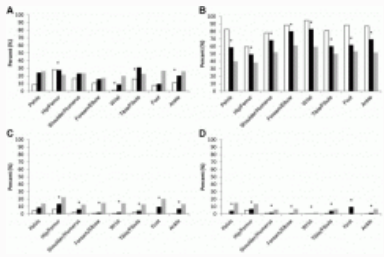

*Figure 12. Discharge destinations after hospitalization by age groups. (A) Rehabilitation or local community health services center. (B) Home. (C) Long-term care (D) inpatient death. *Significant difference between age groups (chi-square test, p<0.05). Reproduced from J Bone Miner Res 2013;28:360-71 with permission of the American Society of Bone and Mineral Research.*

Diabetes and Cortical Porosity

Diabetes and bone fragility is a challenging area of research. While early studies did not report associations with fracture, more recent research does seem to suggest that both types 1 and 2 diabetes are associated with increased fracture risk (11). Indeed, the risk for hip fracture in patients with type 1 diabetes is higher than in type 2. What is puzzling is the pathogenesis of bone fragility in diabetes. Patients with type 1 diabetes have deficits in BMD, but most patients with diabetes and fractures have modest deficits. This itself is not a surprise really because most patients with fractures have osteopenia, not osteoporosis. Patients with type 2 diabetes appear to have normal BMD. It is with interest that the study reported here is the first to suggest the morphological basis of fractures in diabetes might be, in part, increased cortical porosity.

Patsch et al studied 80 women; diabetics with (DMFx) and without fractures (DM), nondiabetics with (Fx) and without fractures (Co), and women with and without diabetes (12). At the ultradistal and distal tibia, diabetics with fractures had greater pore volume (+52.6%; +95.4%), relative porosity (+58.1%; +87.9%) and endocortical bone surface (+10.9%; +11.5%) than diabetics without fractures. At the distal radius, diabetics with fractures had 4.7 fold greater relative porosity than diabetics without fractures. At the ultradistal radius, pore volume was higher in diabetics with fractures than without (+67.8%). Diabetics with fractures also had larger trabecular heterogeneity (ultradistal radius; +36.8%), and lower total and cortical BMD (ultradistal tibia: 12.6%; 6.8%) than diabetics without fractures. Diabetics with fractures also exhibited greater deficits in stiffness, failure load and cortical load fraction at the ultradistal and distal tibia, and the distal radius.

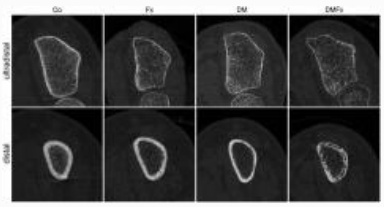

Figure 13. HR-pQCT images of the ultradistal (above) and distal (below) radius: mid-stack tomograms for the Co (left), Fx (left-center), DM (right-center), and DMFx (right) groups. Marked cortical porosity can be seen in DMFx (right). Reproduced from J Bone Miner Res 2013;28:313-24 with permission of the American Society of Bone and Mineral Research.

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OVERVIEW, VOL 13, ISSUE 3

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Editor

Volume 13, Issue 3

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By Ego Seeman Thu, 03/28/2013 - 11:53

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

T.S. Eliot
'Little Gidding', *The Waste Land*

Therapeutic Challenges
Are we there yet?

The contemporary history of osteoporosis began about 70 years ago with Fuller Albright reporting the common occurrence of vertebral fractures in postmenopausal women (1). Progress has been made during this short history, but there are many challenges for those blessed to continue this journey. What are these challenges?

How good are we at reducing the burden of fractures? Treatments reduce vertebral and hip fracture risk by ~50% (2). Is that 'success'? Nonhip and nonvertebral fractures comprise about 80% of all fractures – when seeing a patient concerned about fracture risk, the likelihood is that the patient will have a nonvertebral not vertebral fracture, yet only a small number of trials demonstrate nonvertebral fracture efficacy at all.

In the few studies of antiresorptives that do demonstrate any nonvertebral antifracture efficacy based on intent to treat analyses, only risedronate, zoledronic acid, denosumab and strontium ranelate achieve this level of evidence. However, among these studies, the risk reduction is ~20%. Post hoc analysis was required to detect a benefit of alendronate against nonvertebral fractures in the Fracture Intervention Trial (FIT 1 and 2). Is this 'success'? Why are the treatments

we use producing such modest benefits? Evidence of antifracture efficacy for any drug is fragmentary among >75 year olds, women with osteopenia (the origin of 60% of fractures), men, children, and *any* and all drugs after 3-4 years.

What is the cure? The negative BMU balance is *the* cause of bone loss and structural decay (3), effectively, the cause of 'osteoporosis', the word so often used loosely and interchangeably with 'fragility'. Each time a volume of bone is resorbed by the basic multicellular unit, less bone is deposited producing bone loss (4). In the presence of this negative balance, accelerated remodeling after menopause irreversibly removes bone from the intracortical, endocortical and trabecular components of the inner (endosteal) surface producing cortical porosity and thinning, trabecular thinning, perforation and loss of connectedness. By old age, half the mineralized bone volume has disappeared. Periosteal apposition continues in adulthood, but probably not after menopause, or minimally so. Each of these events – reduced formation by the BMU, increased resorption by the BMU, increased remodeling rate (more BMUs), reduced periosteal apposition – are targets for therapy.

Reducing the negative BMU balance can be achieved by reducing the volume of bone resorbed and by increasing the volume of bone formed. If BMU balance is corrected, remodeling, no matter what its intensity, will produce no permanent bone loss. Nevertheless, fragility can occur if remodeling is rapid because the excavated cavities form stress risers until they refill (5). If BMU balance is made less negative, bone loss will continue and erode the skeleton, albeit slowly, despite compliance with therapy. This continued slow loss of mineralized bone may not be detectable using bone densitometry because secondary mineralization of the larger volume of bone obscures the slow bone loss; total bone volume is decreasing, but the tissue density of the diminishing total bone volume is increasing, producing a net increase in BMD as determined using bone densitometry; this increase in bone density is not necessarily synonymous with increasing bone strength (6).

Reducing resorption depth results in smaller cortical osteons and trabecular hemiosteons with fewer lamellae, more interstitial bone (in relative and absolute terms) with higher tissue density, pentosidine collagen crosslinking and fewer osteocytes – features that may compromise material strength (7).

To restore structure, BMU balance must be made positive by increasing the volume of bone formed by the BMU. This may be achievable using exogenous PTH or treatment induced increases in endogenous PTH provided that resorption is not concurrently stimulated by PTH. This probably explains cortical bone loss occurring with ronacaleret, a calcium-sensing receptor antagonist that stimulates endogenous PTH secretion (8). This approach is probably also limited, as only ~15% of the endosteal surface is actively remodeling at any time. A more rationale target is the ~85% of the surface that is quiescent (9). About 30% of the anabolic effect of PTH is modeling based, 70% is remodeling based. The modeling effect may deposit bone upon either side of trabeculae making them thicker and more connected, upon the endocortical surface thickening the cortex and narrowing the medullary canal and upon Haversian canal surfaces reducing cortical porosity. Convincing evidence that intermittent PTH achieves all of these changes is lacking.

Completely stopping remodeling may compromise material strength (microdamage accumulation, secondary mineralization, pentosidine crosslinking), especially if baseline remodeling is low and tissue mineral density is high. If BMU balance is negative, reducing remodeling intensity is valuable as the rate of structural decay will diminish. Bisphosphonates reduce remodeling intensity by ~50% as assessed by remodeling markers, but probably not the negative BMU balance. The residual 50% remodeling with its negative BMU balance erodes bone despite treatment, particularly cortical bone (80% of the skeleton) as bisphosphonate with high matrix binding affinity does not penetrate deep cortical matrix so osteoclasts continue resorbing cortical bone (10). If BMU balance could be made positive, increasing remodeling rate would be desirable. Periosteal deposition is desirable biomechanically, but has not been convincingly demonstrated in humans

Thus, preventing and reversing bone fragility requires assessment of baseline material composition, microstructure, remodeling balance and intensity to allow reasoned choices. Single therapy may suffice in preventing structural decay. Reversing structural decay may require combined or sequential use of anabolic, antiresorptives and agents specifically designed to influence material strength. While some of these approaches have been tested, none has been designed based on abnormalities in baseline morphology, modeling and remodeling, none have fracture outcomes, and none have measured morphological changes with fracture outcomes in the same trial to then determine whether these morphological changes may serve as surrogates for fracture endpoints. The search for effective therapies and new targets is not over.

There are more things in heaven and earth, Horatio
Than are dreamt of in your philosophy.

W. Shakespeare
Hamlet (Act 1, scene 5)

Osteoclasts Regulate Bone Formation

Lotinun et al have published a real knockout (KO) (11). There are many lessons. If you think the clotting pathway is complicated, put on your safety belt and helmet. It is well appreciated now that osteoblast precursors produce RANKL which binds to its receptor RANK on osteoclast precursors facilitating differentiation into mature bone resorbing osteoclasts. What is less well appreciated is that osteoclasts participate in osteoblastogenesis and bone formation.

Cathepsin K is secreted by osteoclasts and degrades collagen during bone resorption. Global deletion of the gene encoding cathepsin (Ctsk) in mice decreases bone resorption producing more shallow resorption pits ex vitro. However, this KO is also associated with increases bone formation rate suggesting KO of this gene facilitates production of a factor or factors that facilitate bone formation.

The authors generated osteoclast-targeted Ctsk KO mice. This resulted in increased bone volume and BFR, increased osteoclast and osteoblast numbers. MicroCT showed an increase in femur cancellous bone volume, trabecular number, and connectivity density, with a concomitant decrease in trabecular separation. Deletion of Ctsk in osteoclasts also led to an increase in femoral total and cortical crosssectional area with no change in medullary area implying an increase in periosteal bone formation; a reasonable inference but not directed demonstrated using dynamic histomorphometry. (Deletion of Ctsk in osteoblasts did not affect bone resorption or BFR.)

It gets more interesting. What are the factors produced by osteoclasts that may contribute to bone formation when this gene is knocked out? Sphingosine kinase 1 (Sphk1) catalyzes the phosphorylation of sphingosine to sphingosine1phosphate (S1P), which promotes osteoblast differentiation and bone forming activity (12). Deletion of Ctsk in osteoclasts increases sphingosine kinase 1 (Sphk1) expression. Conditioned media from Ctsk-deficient osteoclasts contained elevated levels of S1P, increased alkaline phosphatase and mineralized nodules in osteoblast cultures. An S1P1,3 receptor antagonist inhibited these responses. Osteoblasts from mice with Ctsk-deficient osteoclasts had an increased RANKL/OPG ratio that increased osteoclast numbers.

Thus, cathepsin K inhibits expression the gene Sphk1 regulating synthesis of S1P. The authors infer that deletion of CTSK in osteoclasts enhances bone formation in vivo by increasing the generation of osteoclast-derived S1P. Thus, S1P appears to be a 'coupling' factor produced by osteoclasts, perhaps one of many. This paper is well worth reading, as is reference 12 cited here and referred to in the paper. I thank the authors for educating me.

Adhere and You Will be OK
But not necessarily because of what you adhere to

Medication adherence may be a surrogate for healthy behaviors and better outcomes. Several studies report that adherence to placebo leads to better outcomes than poor adherence to placebo. This is an important observation for several reasons. **Curtis et al** report that in 13,444 postmenopausal women observed for 106,066 person-years, high placebo adherence was associated with hip fracture [hazard ratio (HR), 0.50; 0.33-0.78], myocardial infarction (HR, 0.69; 95% CI 0.50-0.95), cancer death (HR, 0.60; 95% CI 0.43-0.82), and all-cause mortality (HR, 0.64; 95% CI 0.51-0.80) after adjustment for potential confounders (13). Women with low adherence to placebo were 20% more likely to have low adherence to statins and osteoporosis medications. This is a fascinating observation. Studies of drug trials in which compliance is poor often report subanalyses of adherers, and when there is an association with a better outcome the investigators infer the lower event rate is evidence of efficacy of the treatment. This is common in the study of calcium and vitamin D supplementation trials where failure of compliance is common.

Tibolone and Breast Cancer

Bundred et al report that in LIBERATE, a randomized, placebo-controlled, double-blind trial, tibolone (Livial) treatment was associated with increased risk of breast cancer recurrence; HR 1.40 (95% CI 1.14-1.70; P=0.001) (14). Women with surgically excised primary breast cancer within the last 5 years were assigned to tibolone, 2.5 mg daily, or placebo for 5 years. The BMD substudy evaluated 699 women. Women with normal BMD had increased breast cancer recurrence with tibolone, 22 (15.6%) of 141 compared with placebo, 11 (6.9%) of 159 (P=0.016), whereas no increased breast cancer recurrence was seen in women with low BMD; 15 (7.4%) of 204 taking tibolone vs. 13 (6.7%) of 195 taking placebo.

TSH and Bone Loss

Thyroid stimulating hormone receptor (Tshr) KO mice are osteopenic. To determine whether low TSH contributes to bone loss in hyperthyroidism, **Baliram et al** compared the wildtype (WT) and Tshr KO mice rendered hyperthyroid (implanted with T4 pellets) (15). Hyperthyroid mice lacking TSHR had greater bone loss than hyperthyroid WT mice suggesting that absence of TSH signaling contributes to bone loss.

Sympathetic Nervous System and Bone Loss

Farr et al report that in rodents, sympathetic activity reduces bone formation mediated by osteopontin (16). Sympathetic activity was assessed by microneurography at the peroneal nerve in 23 women aged 20-72 years (10 pre- and 13 postmenopausal). Sympathetic activity (bursts per 100 heart beats) was 2.4-fold higher in post- than premenopausal women. In the groups combined, sympathetic activity correlated inversely with trabecular bone volume fraction (r=-0.55, P<0.01) and thickness (r=-0.59, P<0.01), and with P1NP in postmenopausal women (r=-0.65, P=0.015), with a trend in premenopausal women (r=-0.58, P=0.082). Sympathetic activity negatively correlated with plasma osteopontin (r=-0.43, P=0.045), driven mainly by the correlation in postmenopausal women (r=-0.76, P=0.002).

Age at Menarche and Fracture Risk

Delayed menarche may associate with continued skeletal growth due to failure close the epiphyseal plates. In addition, there may be a reduction in cortical thickness due to reduced endocortical apposition which in turn may produce a larger medullary canal and lower areal BMD and total vBMD. The authors produce the first quantitative assessment of bone microstructure associated with later menarche.

Chevalley et al quantified the fracture risk and late menarcheal age (MENA) in 124 healthy girls between 7.9-20.4 years of age. Sixty-one fractures occurred in 42 subjects (17). At 20.4 years, subjects with fractures had lower radial diaphysis and metaphysis aBMD, lower distal radius trabecular vBMD and thickness, and reduced stiffness, failure load, and apparent modulus. OR for a 1-SD reduction in radial aBMD diaphysis 1.97 and metaphysis 1.97 and distal radius trabecular vBMD 1.89, thickness 1.97, stiffness 2.02, failure load 2.00, and apparent modulus 1.79. MENA occurred at a later age in subjects with fractures. For MENA 1 SD (1.2 yr) later, the increase of fracture risk was 2.1 (P=0.002). Low trabecular vBMD and thickness in the distal radius are associated with reduced bone strength and increased fracture risk during growth.

Accelerated Bone Loss in Men is an Independent Risk Factor for Nonspine Fractures

Bone fragility in men remains a neglected area of research and nonspine fractures remain the most common fracture in the community. **Cawthorn et al** assessed the role of bone loss as an independent risk factor for fracture (18). High remodeling may produce bone fragility by producing stress risers; excavated cavities concentrate stress and predispose to microcracking.

BMD was assessed during 4.6 years for 4470 men aged ≥65 years in MrOS. BMD change was 'accelerated' (≤-0.034 g/cm^2), 'expected' (0 and -0.034 g/cm^2), or 'maintained' (≥). 371 (8.3%) men experienced at least one nonspine fracture, 78 (1.7%) hip fractures. Men with accelerated femoral neck BMD loss had an increased risk of nonspine fracture HR=2.0; 95% 1.4-2.8; nonspine/nonhip fracture HR=1.6; 95% CI 1.1-2.3; and hip fracture HR=6.3; 95% CI 2.7-14.8 compared with men who maintained BMD. Adjustment for the final BMD attenuated the risk relationship between rates of loss and fracture. Accelerated bone loss is an independent risk factor for hip and other nonspine fractures in men.

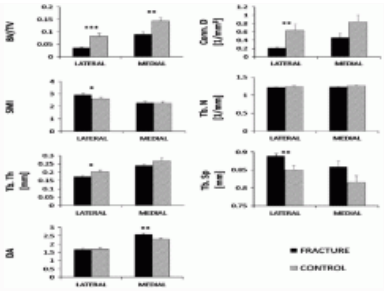
There is More than One Way to Form Bone with Leptin

It is held that, at least in mice, leptin, acts through a hypothalamic relay to decrease bone formation. **Turner et al** report that leptin acts through peripheral pathways to increase osteoblast number and activity (19). Leptin receptor-deficient db/db, leptin-deficient ob/ob, and ob/ob mice were treated with leptin and had hypothalamic leptin gene therapy. Decreases in bone growth, osteoblast-perimeter and bone formation rate were observed in ob/ob mice and increased in ob/ob mice following subcutaneous leptin. Hypothalamic leptin gene therapy increased osteoblast-perimeter in ob/ob mice. In spite of normal osteoclast-lined bone perimeter, db/db mice exhibited a mild generalized osteopetrotic-like phenotype and reduced turnover markers. WT mice engrafted with db/db bone marrow (BM) are not capable of directly responding to leptin and did not differ in energy homeostasis from untreated WT mice or WT mice engrafted with WT BM, indicating that central leptin signaling was not disturbed by BM transplant. Bone formation in WT mice engrafted with WT BM did not differ from WT mice, whereas bone formation in WT mice engrafted with db/db cells did not differ from the low rates observed in untreated db/db mice, indicating that leptin acting peripherally increases bone mass.

The Achilles' Heel of the Femoral Neck

The superior cortex of the femoral neck is thin and liable to undergo more rapid bone loss (20). **Milovanovic et al** extend these observations to suggest that trabecular morphology in this region is also severely compromised (21). The investigators analyzed the trabecular bone microarchitecture in the inferomedial and superolateral subregions of the femoral neck in 29 Caucasian female cadavers (15 with hip fracture: age 79.5 years; and 14 without hip fractures: age 74.1 years). The fracture group had lower bone volume fraction (6.3 vs. 11.2%), connectivity density (0.33 vs. 0.74/mm^3) and higher separation (0.87 vs. 0.83 mm). The superolateral neck had greater deficits in most parameters in the fracture group; lower trabecular bone volume fraction (3.6 vs. 8.2%), connectivity (0.21 vs. 0.63/mm^3), more rod like trabeculae (SMI: 2.94 vs. 2.62), higher separation and the thinned trabeculae (Tb.Sp: 0.89 vs. 0.85 mm; Tb.Th: 0.17 vs. 0.20 mm).

*Figure 1. Comparison of microarchitectural parameters between the fracture and nonfracture (control) group for the superolateral and inferomedial neck: bone volume fraction (BV/TV), connectivity density (Conn.D), structural model index (SMI), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), degree of anisotropy (DA). Bars indicate SE. (*p≤0.05, **p≤0.01,*



****p≤0.001). Reproduced from Bone, 50:63-8, Copyright (2012), with permission from Elsevier.*

Regional Variation in Cortical Porosity

Kazakia et al characterized the spatial variability in cortical geometry and microstructure using HR-pQCT scans of 92 females and 54 males, 20-78 years (22). Cortical porosity (Ct.Po) displayed the greatest regional variations. Differences in Ct.Po were most pronounced in the anterior quadrant of the radius (36% lower in women) and the posterior quadrant of the tibia (27% lower in women). Comparing elderly to young women, differences in Ct.Po were most pronounced in the lateral quadrant of the radius (328% higher in elderly women) and the anterior quadrant of the tibia (433% higher in elderly women). Comparing elderly to young men, the most pronounced age differences were found in the anterior radius (205% higher in elderly men) and the anterior tibia (190% higher in elderly men). All subregional Ct.Po differences provided greater sensitivity to gender and age effects than those based on the global means. Regional analysis may be important in studies of disease and therapeutic effects.

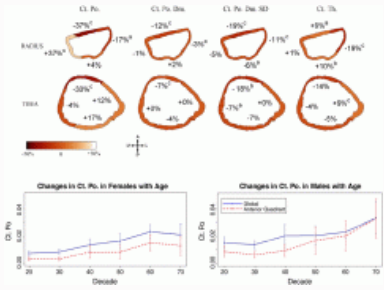


Figure 2. Upper: The mean percent difference from the global mean in cortical indices in each subregion in the distal radius (N=140, top) and tibia (N=145, bottom). Significant regional variation was detected in cortical porosity (Ct.Po), mean pore diameter (Ct.Po.Dm), heterogeneity of pore diameter (Ct.Po.Dm.SD), and cortical thickness (Ct.Th). Significant differences from global mean [a]p<0.05, [b]p<0.01, [c]p<0.001. Lower: Changes in Ct.Po with age for males (right) and females (left) globally (blue) and in the anterior quadrant of the radius (red). Women show comparable increases across quadrants in porosity as they age. Men also show comparable change across quadrants, except in the anterior radius, where porosity accelerates with age relative to other quadrants. Error bars = 1 SD from the mean. Reproduced from Bone, 52:623-31, Copyright (2013), with permission from Elsevier.

Micromechanical Properties and Ibandronate Independent of Tissue Mineral Density

Bala et al analysed 110 iliac biopsies from patients treated for 22 or 34 months with placebo (n=36), 2.5 mg daily oral ibandronate (n=40), or 20 mg intermittent oral ibandronate (n=34) (23). The annual cumulative exposures were about half the therapeutic doses licensed for postmenopausal osteoporosis women. Degree of mineralization of bone (DMB) and its distribution did not differ from placebo. Hardness (Hv) was higher in the cortical, cancellous, and total bone, but DMB and Hv, measured in 3760 bone structural units, correlated (r=0.59-0.65, p<0.0001). The authors infer that a low annual cumulative exposure of ibandronate altered the bone micromechanical properties irrespective of changes in secondary mineralization. The reasons for the increase in hardness remain unknown.

Burden of Hip Fractures in Osteoporosis

Oden et al assessed the number of hip fractures for 2010 and the proportion attributable to osteoporosis (24). The total number of new hip fractures for 58 countries was 2.32 million (741,005 in men, 1,578,809 in women). Of these, 1,159,727 (50%) would be saved if BMD in individuals with osteoporosis were set at a T-score of -2.5 SD. The majority (83%) of these 'prevented' hip fractures were found in men and women at the age of ≥70 years. The 58 countries assessed accounted for 83.5% of the world population aged ≥50 years. Extrapolation to the world population using age- and sex-specific rates gave an estimated number of hip fractures of about 2.7 million in 2010, of which 1,364,717 were preventable by avoiding osteoporosis (264,162 in men, 1,100,555 in women). Osteoporosis accounts for about half of all hip fractures.

The Second Hip Fracture

Omsland et al studied all hip fractures in Norwegian hospitals during 1999-2008 (25). Among the 81,867 persons who sustained a first hip fracture, 6161 women and 1782 men suffered a second. Risk was no different by sex; but after taking competing risk of death into account, the age-adjusted HR of a second hip fracture was 1.40 (95% CI 1.33-1.47) in women compared to men. The greater risk in women was due to a higher mortality in men. The authors estimate that 15% of women and 11% of men will have suffered a second hip fracture within 10 years of the first.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 4

Ego Seeman

Editor

By Ego Seeman Wed, 05/08/2013 - 09:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Volume 13, Issue 4

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Decline in Hip Fracture Incidence

Korhonen et al determined the current trend in the number and incidence (per 100,000 persons) of hip fracture among older adults in Finland (1). The authors accounted for all persons 50 years of age or older admitted to hospitals for primary treatment of hip fracture between 1970-2010. The number of hip fractures rose sharply till the end of 1990s (from 1857 in 1970 to 7122 in 1997), then levelled (7594 fractures in 2010). Similarly, the age-adjusted incidence of hip fracture increased until 1997 but declined thereafter. The decline was clear in women whose age-adjusted incidence was 515.7 (per 100,000 persons) in 1997 and 382.6 in 2010. In men, the corresponding incidence was 245.3 in 1997 and 210.7 in 2010. Reasons for this development are uncertain, but nevertheless, the number of hip fractures will increase 1.8-fold by 2030 even with the current 2010 incidence rates because the size of the 50-year-old or older population is likely to increase.

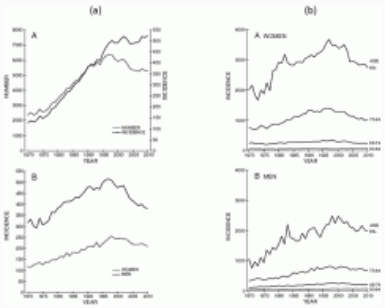


Figure 1. (a) Hip fractures in Finland in people ≥50 years of age between 1970-2010. A Number and crude incidence (per 100,000 persons). B Age-adjusted incidence (per 100,000 persons). (b) Age-specific incidence (per 100,000 persons) of hip fracture in Finland in people ≥50 years of age between 1970-2010: A women; B men. Reproduced from Osteoporos Int 2013;24:1599-1603 with permission from Springer.

Mortality Following Fracture

Melton et al determined long-term survival following fractures in 2901 Olmsted County residents ≥35 years old experiencing any fracture in 1989-1991 (2). These subjects were followed for up to 22 years for death from any cause. Standardized mortality ratios (SMRs) compared observed to expected deaths. During 38,818 person-years of follow-up, 1420 deaths were observed when 1191 were expected (SMR 1.2; 95% CI 1.1-1.3). The overall SMR was greatest soon after fracture, especially among the men, but remained elevated for over a decade thereafter. Adjusting for age and sex, relative death rates were greater for pathological fractures and less for severe trauma fractures compared to the fractures due to moderate trauma. In the latter, long-term mortality was increased following fractures at many skeletal sites. After further adjustment for cause, overall SMRs were elevated following fractures at the distal forearm, proximal humerus, thoracic/lumbar vertebrae, and proximal femur combined (SMR 1.2; 95% CI 1.1-1.3) and following all other fracture types combined (SMR 1.2; 95% CI 1.1-1.4), excluding the hand and foot fractures not associated with any increased mortality.

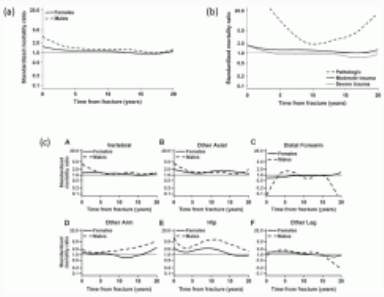


Figure 2. (a) Standardized mortality ratio among 2901 Olmsted County, MN, USA, women and men, adjusted for age, by time following any fracture in 1989-1991. (b) Standardized mortality ratio among 2901 Olmsted County, MN, USA, residents following a fracture in 1989-1991, adjusted for age and sex, for fractures due to different precipitating events. (c) Standardized mortality ratio among 2901 Olmsted County, MN, USA, residents following a fracture due to no more than moderate trauma in 1989–1991, adjusted for age, by fracture site, and sex. Reproduced from Osteoporos Int 2013;24:1689-96 with permission from Springer.

Cost Following Fracture

Leslie et al reported costs among 16,198 incident fracture cases and 48,594 matched nonfracture controls identified in the province of Manitoba, Canada (1997-2002) (3). The authors calculated the difference in median direct healthcare costs for the year pre-fracture and 5 years post-fracture in 2009 Canadian dollars adjusted for expected age-related healthcare cost increases. Incremental median costs for a hip fracture were highest in the first year ($25,306 in women, $21,396 in men), remaining above prefracture baseline to 5 years in women but fell below pre-fracture costs by 5 years in men. In those who survived 5 years following a hip fracture, incremental costs remained above pre-fracture costs at 5 years ($12,670 in women, $7933 in men). Incremental costs were consistently increased for 5 years after spine fracture in women. Total incremental healthcare costs for all incident fractures combined showed a large increase over pre-fracture costs in the first year ($137 million in women, $57 million in men) but fell below pre-fracture costs within 3-4 years. Elevated total healthcare costs were seen at year 5 in women after wrist, humerus and spine fractures, but these were offset by decreases in total healthcare costs for other fractures. High direct healthcare costs post-fracture are seen in the first year, but costs fall below pre-fracture levels, perhaps due to healthy survivor bias. Among those who survive 5 years following a fracture, healthcare costs remain above pre-fracture levels.

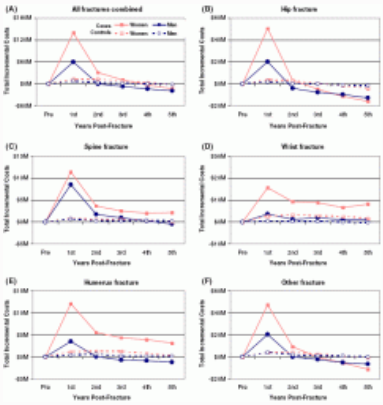


Figure 3. Total incremental healthcare costs over baseline costs from a third-party healthcare payer perspective for fracture cases (solid figures and lines) and controls (open figures and dotted lines, costs for controls divided by 3 due to 1 to 3 matching). Costs are in millions of 2009 Canadian constant dollars. Reproduced from Osteoporos Int 2013;24:1697-1705 with permission from Springer.

Burden of Disease in Men

Brenneman et al analyzed administrative claims from a national health plan were analysed in men ≥45 years with ≥1 medical claim for a new closed fracture between January 1, 2005 and December 31, 2008 (4). Commercially insured (COM) and Medicare Advantage Plan (MAP) members were analyzed separately. The authors identified 18,917 (COM 16,191; MAP 2726) men with new closed fractures. Nonhip, nonvertebral fractures (NHNV) were the most common fracture in both populations. Fracture costs ranged from $7121 to $15,830 for vertebral fractures, from $22,601 to $30,900 for hip fractures, and from $6078 to $8344 for NHNV fractures.

Cardiovascular Disease and Osteoporosis

Makovey et al studied 358 peri- and postmenopausal women, mean age 59.3 (range 45-74) years (5). Fracture risk was assessed using the WHO FRAX algorithm and cardiovascular

disease (CVD) risk using the Framingham Risk Tool. Women with higher 10-year risk of major osteoporotic fracture had higher cardiovascular risk (4.6% vs. 8.4%, p=0.001). In multiple regression analysis, 5-year CVD risk was associated with the 10-year risk of having major osteoporotic (β=0.095, p=0.001) and hip (β=0.055, p=0.001) fracture. Women with the highest CVD risk were 5.4 times more likely to have higher risk of major osteoporotic fracture. Awareness regarding these concurrent risk factors needs to be raised so that appropriate risk reduction can be implemented.

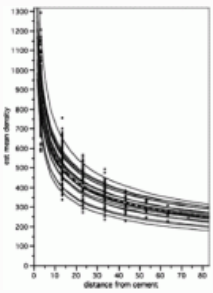
Chen et al identified patients with vertebral fracture (n=380) and 10 age- and sex-matched controls per case (n=3795) were chosen from a nationwide representative cohort of 999,997 people from 1998-2005 (6). Both groups were followed up for stroke during 3 years with adjustments for covariates. The incidence rate of stroke in the osteoporotic vertebral fracture group (37.5 per 1000 person-years; 95% CI 27.5-51.2) was higher than in controls (14.0 per 1000 person-years; 95% CI 12.0-16.4, p<0.001; adjusted HR 2.71, 95% CI 1.90-3.86, p<0.001). Patients with osteoporotic vertebral fracture have a higher risk of stroke (i.e., both ischemic and hemorrhagic) and require stroke prevention strategies.

Osteocytes and Osteonal Refilling

The negative bone balance between the volumes of bone resorbed and formed is the necessary and sufficient cause of bone loss and structural decay. This negative balance may be the result of a reduced volume of bone formed in the setting of normal, increased or lesser reduced volumes of bone resorbed. Whatever the case, the explanations for the reduction in the volume of bone deposited is are not apparent.

Following excavation of a tunnel in cortical bone by osteoclasts or trench upon trabecular and endocortical surfaces, bone formation by the osteoblasts of that BMU proceeds from the cement line centrifugally refilling the cavity. Refilling must be incomplete to leave the central Haversian canal. The amount and rate of bone deposited decreases progressively as the cone closes. **Power et al** reported that osteocytes within the osteon are 2-fold more common adjacent to the cement line than nearer the canal (7). Large and small osteons appear to have similar osteocyte densities near the cement line, but patients with femoral neck fractures have lower osteocyte densities close to the canal. The authors suggest that osteocyte formation declines more rapidly than matrix formation as osteonal infilling proceeds. A shrinking supply of precursor osteoblasts due to previous osteocyte recruitment, apoptosis, or both could produce this effect. Sclerostin negative osteocytes adjacent to the canal were associated with reduced canal size in controls, but not in hip fracture cases.

*Figure 4. Logarithms of the estimates of (est) mean osteocyte densities in the osteons of individual subjects (points), fitted linearly to the logarithms of distance from the cement line, and replotted on the linear scale. Thin continuous lines: fits to data for individual subjects. Thick dashed line: weighted mean fit for all subjects. Units: ordinate osteocytes·mm^{-2}; abscissa mm*10^{-3}. Reproduced from Bone, 50:1107-14, Copyright (2012), with permission from Elsevier.*



Material Composition and Drug Therapy

Antiresorptive agents reduce the risk of fracture by around 50% for vertebral fracture even though changes in BMD vary greatly. Explanations for this observation are not apparent. **Burket et al** report that in 25 mature adult ewes, raloxifene increased indentation modulus and hardness throughout trabeculae by 10% (8). Zoledronic acid increased these properties only at the surfaces of trabeculae (indentation modulus +12%, hardness +16%). Nanomechanical alterations correlated with changes in tissue mineralization, carbonate substitution, crystallinity, and aligned collagen. The nanomechanical improvements within trabeculae with both treatments improved the predicted theoretical bending stiffness of trabeculae when idealized as cylindrical struts. The authors suggest that small tissue level alterations in critical locations for resisting trabecular failure could account for some of the discrepancy between the reduction in fracture risk despite the modest changes in BMD with antiresorptive treatments.

Antiresorptive agents reduce remodelling rate so bone that would have been resorbed and replaced is not and so undergoes more complete secondary mineralization. **Misof et al** evaluated cancellous and cortical mineralization density distribution (BMDD) in biopsies from 82 patients receiving zoledronic acid 5mg yearly and 70 controls (9). Higher cancellous and cortical (Cn.CaMean 3.2%, Ct.CaMean 2.7%) and mode calcium (Cn.CaPeak 2.1%, Ct.CaPeak 1.5%), increased percentage highly mineralized bone areas (Cn.CaHigh 64%, Ct.CaHigh 31%), lower heterogeneity of mineralization (Cn.CaWidth -14%, Ct.CaWidth -13%), and decreased percentages of low mineralized bone areas (Cn.CaLow -22%, Ct.CaLow -26%) were observed vs. placebo (all p<0.001). Cn.BMDD also revealed a shift to higher Ca concentrations. Those with lower Cn.MS/BS had a higher degree of bone matrix mineralization.

Examining the effects of odanocatib (ODN) on tissue mineralization is particularly interesting because this treatment may reduce remodelling rate less than other antiresorptive agents, at least in the appendicular skeleton, and so, theoretically, should have a lesser effect on tissue mineralization density in the appendicular than axial skeleton. The basis for this statement is the histomorphometric studies in monkeys by **Cusick et al** who reported a reduction in the surface extent of remodelling upon trabecular surfaces but perhaps less so upon the endocortical surface

(10).

Frazzel-Zelman et al evaluated the effects of ODN on bone mineralization density distribution (BMDD) in vertebral trabecular bone, distal femoral metaphyseal and cortical shaft from monkeys (aged 16-23 years) treated with vehicle (n=5) or ODN (6 mg/kg, n=4 or 30 mg/kg, n=4, PO daily) for 21 months (11). In vertebrae, there was a shift to higher mineralization in samples from ODN-treated groups compared to vehicle: CaMean (+4%), CaPeak (+3%), CaWidth (-9%), CaLow (-28%) in the 6 mg/kg group and CaMean (+5.1%, p<0.023), CaPeak (+3.4%, p<0.046), CaWidth (-15.7%, p=0.06) and CaLow (-38.2%, p<0.034) in the 30 mg/kg group. In distal femoral metaphyseal cancellous bone, there was a trend to a dose-dependent increase in matrix mineralization. However, primary and osteonal bone of the distal cortical diaphyses showed no change in BMDD, whereas bone mineral density was increased after treatment.

ODN increased trabecular BMDD, but no changes in BMDD in cortical bone sites. The interpretation of the rise in BMD is tricky. This drug appears to reduce the depth or resorption rather than the number or remodelling sites and so, if the volume of bone deposited in each of the persisting large number of remodelling sites on the endocortical and cortical surface, this may slow bone loss but for an increase in BMD the BMU balance must become positive. The rise in BMD is therefore likely to be due to and increase in the tissue mineralization density in trabecular bone and perhaps due to a reduction in intracortical porosity given that remodelling seems to be reduced in cortical bone. As always, more research is needed!

Collagen Crosslinking and Pentosidine

Nonenzymatic glycation (NEG) and advanced glycation endproducts (AGEs) contribute to bone fragility by crosslinking bone collagen. In vitro studies using nonenzymatic ribation reported loss of ductility in the cortical bone. However, some studies report positive associations between collagen crosslinking and work-to-fracture/toughness. **Willett et al** reported that in 15 bone beam triplets cut from bovine metatarsi, ribation increased nonenzymatic collagen modification and pentosidine content and reduced post-yield strain and flexural toughness (12). Fracture surfaces were smoother with less collagen fibril deformation or tearing than observed in controls. However, pentosidine content and thermomechanical measures of crosslinking correlated positively with measures of strain and energy absorption before failure. Thus, as reported previously, nonenzymatic ribation reduces cortical bone post-yield strain accommodation. However, increased crosslinking may not provide a complete explanation for increased bone brittleness.

Reznikov et al report orientations and local collagen fibril dispersion in circumferential lamellae from rat tibiae (13). The authors identified three distinct sublamellar structural motifs: a plywood-like fanning sublamella, a unidirectional sublamella and a disordered sublamella. The disordered sublamella is less mineralized than the other sublamellae. The hubs and junctions of the canalicular network, which connect radially oriented canaliculi, are intimately associated with the disordered sublamella.

Antisclerostin Antibody Therapy and Fracture Healing

Hamann et al used ZDF fa/fa rats, a model for type 2 diabetes with low bone mass to study bone healing (14). A sclerostin-neutralizing antibody (Scl-AbVI) was tested in femoral defects of 3 mm created in 11-week-old diabetic ZDF fa/fa and nondiabetic ZDF +/+ rats. Saline or 25 mg/kg Scl-AbVI s.c. twice weekly for 12 weeks. Diabetic rats had lower spinal and femoral bone mass. Scl-AbVI increased bone mass and reversed the deficit in bone strength in the diabetic rats, with 65% and 89% increases in maximum load at the femoral shaft and neck, respectively (p<0.0001). The lower bone mass in diabetic rats was associated with a 65% decrease in vertebral bone formation rate, which Scl-AbVI increased 6-fold. Nondiabetic rats filled 57% of the femoral defect, whereas diabetic rats filled 21% (p<0.05). Scl-AbVI increased defect regeneration by 47% and 74%, respectively (p<0.05). Sclerostin antibody reverses the adverse effects of type 2 diabetes mellitus on bone mass and strength, and improves bone defect regeneration in rats.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 5

Ego Seeman

Editor

By Ego Seeman Thu, 06/20/2013 - 09:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Orgins of Bone Fragility in Growth

Nagy et al reported that daughters of women with fracture have thinner cortices, and impaired trabecular microarchitecture at the distal radius and tibia (1). The authors included 115 women mean age 43 years whose mothers had sustained a fragility fracture and 206 women mean age 39 years whose mothers had not sustained a fracture. Women, whose mothers had fracture, had lower aBMD and lower total vBMD at the distal radius (-5%) and distal tibia (-7%). They also had lower cortical thickness and area at the distal radius (-5% and -4%, respectively) and at the distal tibia (-6%, and -4%, respectively). Trabecular vBMD was lower at the distal radius (-5%) and tibia (-8%), with a more spaced and heterogeneous trabecular network (4 and 7 % at the radius and 5 and 9 %, at the tibia, for Tb.Sp and Tb.Sp.SD, respectively). Several questions arise from this work. For example, what is the pathogenetic basis of these abnormalities? Do these subjects reflect the lower part of the normal trait distribution established very early in life, if not during intrauterine life such that they enter adulthood and the post menopausal years with thinner cortices and fewer trabeculae that are more susceptibly to decay after menopause? What sort of discriminatory power do these morphological differences have? What proportion of the daughters of women with fractures did and did not have these abnormalities? If the deficits have a genetic basis, they should be about half the deficit observed in the mothers with fractures.

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Warden et al reported that in 314 participants (n=155 males; n=164 Blacks) in early puberty, Blacks had greater cortical vBMD (implying lower cortical porosity and/or higher tissue mineralization density), mass and size compared to Whites (2). Blacks had 17.0% greater tibial polar strength-strain index (SSIP), higher osteocalcin and bone-specific alkaline phosphatase and lower N-terminal telopeptide than Whites, lower 25-hydroxyvitamin D and higher 1,25-dihydroxyvitamin D and PTH. Variation in bone cross-sectional area and SSIP attributable to race was partially explained by tibial length, 25-hydroxyvitamin D/PTH, and osteocalcin. Racial differences are established by the early stages of puberty.

Laine et al identified a heterozygous missense mutation in WNT1, c.652T->G (p.Cys218Gly) in 10 family members with dominantly inherited, early onset osteoporosis (3). In a separate family with two siblings affected by recessive osteogenesis imperfecta, they also identified a

homozygous nonsense mutation, c.884C->A, p.Ser295. The aberrant forms of the WNT1 protein showed impaired capacity to induce canonical WNT signalling, target genes, and mineralization. In mice, Wnt1 was expressed in B-cell lineage and hematopoietic progenitors; lineage tracing identified the expression of the gene in a subset of osteocytes, suggesting the presence of altered crosstalk in WNT signalling between the hematopoietic and osteoblastic lineage cells in these diseases.

Henstock et al applied hydrostatic pressure regimens of 0-279 kPa at 0.005-2 Hz to cultured ex vivo chick foetal femurs (e11) for 1 h/day/14 days (4). The mineralized developing femur was larger and/or denser than unstimulated controls. Constant (noncycling) hydrostatic pressure had no effect on bone growth. The increase in bone formation was proportional to stimulation frequency (R^2=0.917). Expression of type II collagen in epiphyses and diaphysis upregulated 1.48-fold and 1.95-fold, respectively, together with osteogenic (osteonectin and osteopontin) and the osteocyte maturation marker CD44. Hydrostatic forces may play a role in regulating bone growth and remodelling in vivo.

Putman et al used HR-pQCT to assess cortical and trabecular bone microarchitecture and microfinite element analysis in African-American (n=100) and Caucasian (n=173) women (5). African-American women had greater total area, aBMD, and total vBMD at the radius and tibia metaphysis, greater trabecular vBMD at the radius, and higher cortical vBMD at the tibia, higher cortical area, thickness, and volumes and lower cortical porosity at the tibia, greater estimated bone stiffness and failure load after adjustment for DXA aBMD.

Walker et al reported premenopausal Chinese-American women have more platelike trabecular (Tb) bone (6). The investigators applied individual trabecula segmentation and finite element analysis to images in premenopausal and postmenopausal Chinese-American and White women. Adjusted analyses at the radius indicated that premenopausal Chinese-Americans had a higher plate bone volume fraction (pBV/TV), Tb plate-to-rod ratio (P-R ratio), and greater plate-plate junction densities (P-P Junc.D) than White women resulting in 27% higher Tb stiffness. Greater cortical thickness and density (Ct.Th and Dcort) and more Tb plates led to 19% greater whole bone stiffness. Postmenopausal Chinese-Americans had similar pBV/TV and P-P Junc.D, yet a higher P-R ratio than white women. Postmenopausal Chinese-American had greater Ct.Th, Dcort, and relatively intact Tb plates, resulting in similar Tb stiffness but 12% greater whole bone stiffness. In both races, Ct.Th and Dcort were lower in postmenopausal than premenopausal women and there were no differences between races. Tb plate parameters were also lower in post than premenopausal women, but age-related differences in pBV/TV, P-R ratio, and P-P Junc D were greater ($p<0.05$) in Chinese-American women. Within-race there is greater loss of platelike Tb bone with aging in Chinese-Americans, though thicker cortices and more platelike Tb bone persists.

Kim et al reported macro- and microstructure at the distal radius in Asian (n=91, 53 males, 38 females, mean afe age 17.3 yrs) and Caucasian (n=89, 46 males, 43 females, mean age 18.1 yrs) adolescents and young adults (7). In males, Asians had 11% greater Tt.BMD, 8% greater Ct.BMD and 25% lower Ct.Po than Caucasians. Asians had 9% smaller Tt.Ar and 27% greater Ct.Th. In females, Asians had smaller Tt.Ar (16%), but this difference was not significant after adjusting for covariates. Asian females had 5% greater Ct.BMD, 12% greater Ct.Th and 11% lower Tb.Sp than Caucasians. Estimated bone strength did not differ between Asian and Caucasian males or females. Smaller bones of Asian have more dense, less porous and thicker cortices.

Schnitzler et al reported a unique study of cortical porosity during growth (8). They examined osteons and their canals for age-related changes in numbers, size and shape in 87 iliac crest bone samples of subjects aged 0-25 years. Three types of secondary osteons were identified. 1) Drifting osteons predominated to the midteens, were large, asymmetrical and had giant canals (remodeling space) with the resorption front drifting towards the marrow. Onset of formation appeared delayed, and commenced on the periosteum-facing surface. From the midteens numerical density of drifting osteons decreased, and so did porosity. 2) Eccentric osteons were smaller, more circular and had a small excentric canal; their numerical density increased with age. 3) Concentric osteons (adult bone) were the smallest, most symmetrical osteons, had a small central canal, and higher numerical density from the midteens. Boys showed greater overall porosity and greater numerical density of drifting osteons, and later change to concentric osteons than girls. Whites had greater numerical density and greater areal density of resorption cavities than Blacks. Structure of osteons and canals varied during growth. Large asymmetrical drifting osteons with giant active canals (remodeling space) predominated until the midteens and accounted for >70% of childhood cortical porosity. Thereafter, smaller concentric (adult type) osteons increasingly predominated. Gender differences may relate to greater fracture rates in boys, and race differences to greater fracture rates in Whites. The role of osteocyte-mediated mechanotransduction in osteonal structure and cortical porosity during growth warrants further exploration.

Fractures: Morbidity and mortality

Frost et al estimated the excess mortality attributable to hip fracture in elderly men and women in the Dubbo Osteoporosis Epidemiology Study (9). Over 2000 men and women aged 60+ as of 1989 were followed for 21 years. 151 women and 55 men sustained a hip fracture. Death occurred in 86 (57%) women and 36 (66%) men. In women, the cumulative relative survival post hip fracture at 1, 5 and 10 years was 0.83 (95% CI 0.76-0.89), 0.59 (95% CI 0.48-0.68), and 0.31 (95% CI 0.20-0.43), respectively; in men, the corresponding estimates were: 0.63 (95% CI 0.48-0.75), 0.48 (95% CI 0.32-0.63), and 0.36 (95% CI 0.18-0.56). On average post hip fracture women died 4 years earlier (median: 4.1, interquartile range (IQR) 1.7-7.8) and men died 5 years earlier (median=4.8, IQR 2.4-7.0) than expected. For every six women and for every three men with hip fracture, one extra death occurred above that expected in the population.

Bluic et al examined the long-term cumulative incidence of subsequent fracture and total mortality with mortality according to initial and refracture from the Dubbo Osteoporosis Epidemiology Study (10). There were 952 women and 343 men with incident fracture. Within 5 years following initial fracture, 24% women and 20% men refractured; and 26% women and 37% men died without refracture. Of those who refractured, a further 50% of women and 75% of men died, so total five-year mortality was 39% in women and 51% in men. Excess mortality was 24% in women and 27% in men. While mortality following refracture occurred mainly in the first five years post initial fracture, total mortality (post initial and refracture) was elevated for 10 years. Most of the 5-10 year excess mortality was associated with refracture. The long-term (>10 yr) refracture rate was reduced, particularly in the elderly due to their high mortality rate. The 30% alive beyond 10 years post fracture were at low risk of further adverse outcomes. Refractures contribute substantially to overall mortality associated with fracture.

Ahmed et al reported all incident nonvertebral fractures between 1994-2009 were registered in 27,158 participants in Tromso (11). In 3108 subjects with an initial fracture, subsequent fracture (n=664) risk was expressed as rate ratios (RR). The rates of initial and subsequent fractures increased with age. Compared with initial incident fracture rate of 30.8 per 1000 in women and 12.9 per 1000 in men, the overall age-adjusted RR of subsequent fracture was 1.3 (95% CI 1.2-1.5) in women, and 2.0 (95% CI 1.6-2.4) in men. Although the RRs decreased with age, the absolute proportions of those with initial fracture who suffered a subsequent fracture increased from 9% to 30% in women and from 10% to 26% in men, between 50-59 to 80+ years, respectively. In women and men, respectively, 45% and 38% of the subsequent hip or other major fractures, were preceded by initial minor fractures.

van der Jagt-Willems et al reported a prospective cohort study of 395 geriatric outpatients in whom mortality after 3 years was associated with prevalent vertebral fractures at baseline (12). The mortality risk was independently associated with the presence of ≥3 vertebral fractures at baseline. In the surviving patients, the risk of incident fractures was 26% of these patients. After 3 years, mortality was 46% and associated with prevalent vertebral fractures at baseline (OR 1.83; 95 % CI 1.23-2.74). The presence of three or more vertebral fractures at baseline was an independent risk factor for mortality (OR 3.32; 95 % CI 1.56-7.07). Higher cognitive capacity protected against mortality after 3 years.

Melton et al reported the long-term survival following fractures due to any cause at each skeletal site in 2901 Olmsted County (MN, USA) residents ≥35 years old who experienced any fracture in 1989-1991, followed for 22 years for death from any cause. Standardized mortality ratios (SMRs) compared observed to expected deaths (13). During 38,818 person-years of follow-up, 1420 deaths were observed when 1191 were expected (SMR 1.2; 95 % CI 1.1-1.3). The SMR was greatest soon after fracture, especially among the men but remained elevated for over a decade. Adjusted relative death rates were greater for pathological fractures and less for severe trauma fractures compared to the fractures due to moderate trauma. In the latter, long-term mortality was increased following fractures at many sites. After further adjustment for precipitating cause, overall SMRs were elevated for distal forearm, proximal humerus, thoracic/lumbar vertebrae, and proximal femur combined (SMR 1.2; 95 % CI 1.1-1.3), but also following all other fracture types combined (SMR 1.2; 95 % CI 1.1-1.4), excluding the hand and foot fractures not associated with any increased mortality.

Regional Specificity of Bone Structure and Bone Loss at the Femoral Neck

Kersh et al used high-resolution CT data to evaluate 457 cross-sectional slices along the femoral neck of 12 postmortem specimens (14). The distribution of cortical thicknesses was evaluated. Finite-element models were used to calculate the stresses in each cross-section resulting from the peak hip joint forces created during a sideways fall. In all cross-sections, cortical thicknesses were not normally distributed and skewed toward smaller thicknesses. The central tendency of cortical thickness was best estimated by the median. Stress increased as the median cortical thickness decreased along the femoral neck. The median cortical thickness combined with anterior-posterior diameter best predicted peak bone stress generated during a sideways fall (R^2=0.66, p<0.001). Heterogeneity in the structure of the femoral neck determines the diversity of its strength. The median cortical thickness best predicted peak femoral neck stress and is likely to be a relevant predictor of femoral neck fragility.

Johannesdottir et al used segmental QCT analysis to assess the superolateral (superior) and inferomedial (inferior) regions of the femoral neck in 400 older individuals (100 men and 300 women, aged 66-90 years) during a median follow-up of 5.1 yr. (mean baseline age 74 years) (15). At baseline women had lower bone values in the superior region than men. At follow-up all bone values were lower in women, except cortical vBMD inferiorly. The relative losses in all bone values estimated in the superior region were about 3-fold and greater compared to those estimated in the inferior region in both sexes. Women lost cortical thickness and cortical vBMD more rapidly than men in both regions; and this was only weakly reflected in total femoral neck DXA-like results. The higher rate of bone loss in women at critical locations may contribute materially to the greater femoral neck fracture incidence among women than men.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 6

Ego Seeman

Editor

By Ego Seeman Fri, 07/05/2013 - 08:35

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Combined Therapy in Osteoporosis
Don't dismiss this option

Combining an anabolic agent like PTH with an antiresorptive makes sense, but initial studies combining PTH with alendronate reported blunting of the effect on bone density and remodeling markers (1). Not all studies reported blunting. Some as the combination of PTH and zoledronic acid reported a greater BMD response than either drug alone, while others reviewed below report comparable effects of combined and single therapy.

Despite the (i) inconsistent observations, (ii) lack of evidence that changes in BMD or remodeling markers are sensitive and specific markers of antifracture efficacy, and (iii) lack of data concerning morphology or antifracture efficacy, the perception in the scientific community is that combined therapy as not useful in fracture prevention. This is a regrettable situation given there are limited options available for patients who cannot tolerate bisphosphonates or patients who sustain fractures despite compliance with bisphosphonates.

The assumption that a lesser effect of combined therapy on BMD reflects a less antifracture efficacy is not evidence based. The main determinant of a rise in BMD following bisphosphonate therapy is baseline remodeling rate. The more rapid the baseline remodeling rate, the greater the BMD response to the *same* dose of bisphosphonate or other antiresorptive agent. The net increase in BMD is due to the following: (i) a reduction in porosity as cortical pores and trenches upon trabeculae excavated prior treatment refill – the higher the remodeling rate, the greater the number of excavated pores and resorption pits upon trabecular surfaces that will refill when an antiresorptive is administered. (ii) The appearance of fewer resorption cavities – denosumab virtually eliminates the birth of new cavities, alendronate reduces these by about 50-60%, zoledronic acid by 90% in the first month then similar to alendronate based on suppression of remodeling markers. (iii) Secondary mineralization of the bone matrix that is not resorbed (because remodeling rate is reduced) and more complete mineralization of osteons formed months earlier as secondary mineralization takes many months to complete. The net effect of reduced porosity is likely to reduce bone fragility. The secondary mineralization is the dominant

mechanism of the increase in BMD after about 12 months and this may be beneficial or deleterious depending on the pretreatment tissue density; if initially high, further increases may compromise the toughness of the material; its ductility may diminish.

What happens with PTH? The anabolic effect of PTH has two components, a remodeling dependent effect said to account for over 70% of the anabolic effect and a modelling based effect accounting for the remaining 30% of the anabolic effect. When administered alone, the rise in P1NP and increase in BMD may be a consequence of either or both. The rise in BMD may underestimate the increase in bone matrix volume in either situation because newly deposited bone by direct periosteal, intracortical, endocortical or trabecular bone formation may initially deposit bone of low tissue density resulting in a net under estimate in rise in net BMD or even misleadingly produce a fall in BMD. The same may occur when PTH stimulates bone formation within remodeling sites; the newly deposited bone may be undermineralized initially. If PTH replaces older more mineralized bone with a larger volume of new bone, BMD may fall again, misleadingly suggesting there this bone loss when in fact bone matrix volume increases; quite a misleading as deposition of new bone upon the periosteum or upon trabeculae is likely to be of benefit to bone strength.

There have been no studies examining the antifracture efficacy of combined or sequential therapy using antiresorptives and anabolic agents and no studies examining the effect on bone microarchitecture. The lack of data leaves only BMD and remodeling markers as the outcome variables and this is a serious problem because neither can be relied upon as valid surrogates of antifracture efficacy. There is a lot at stake. The below papers should be viewed in this light.

In a study by **Yang et al**, 3 month old female rats were divided into sham or ovariectomy (OVX, PTH, IBN and COM). Weekly low-dose PTH and/or ibandronate or vehicle were administered (2). PTH, ibandronate or its concurrent treatment reversed ovariectomy induced deterioration in trabecular and cortical bone. PTH plus ibandronate preserved BMD and increased periosteal formation and a decreased endocortical resorption.

Muschitz et al reported coadministration of raloxifene or alendronate following 9 months of teriparatide in 125 postmenopausal women (3). Open-label alendronate (70 mg/week), raloxifene (60 mg/d) or no medication were given in addition to continued teriparatide (18). P1NP did not change during teriparatide monotherapy and decreased with alendronate and raloxifene; CTX did not change with teriparatide monotherapy, decreased in the alendronate group and remained elevated in the raloxifene group. The increase in spine BMD was 5% in the alendronate and 6% in the raloxifene combination groups compared with 2.8% in the teriparatide monotherapy group. The increase of spine BMD for alendronate and raloxifene groups was superior to teriparatide monotherapy. Total hip BMD changes were 4% for the alendronate combination group and 1.4% for the teriparatide monotherapy, and 1.4% for the raloxifene combination group. With the exception of no differences in the trabecular compartment of femoral neck, volumetric BMD changes in the alendronate combination group for all other comparisons were superior to the two other groups. The authors infer alendronate added to teriparatide results in a more robust increase in BMD.

Tsai et al enrolled postmenopausal women with osteoporosis to receive 20 µg TPTD daily, 60 mg denosumab every 6 months, or both during 12 months (4). Spine BMD increased more in the combination group 9.1% than in the teriparatide (6.2%) or denosumab groups. Femoral neck BMD also increased more in the combination group (4.2%) than in the teriparatide (0.8%) and denosumab (2.1%) groups, as did total hip BMD (combination, 4.9%; teriparatide, 0.7%; denosumab, 2.5%). The authors infer combination treatment might be useful to treat patients at high risk of fracture. Note that a large proportion of the subjects has previous bisphosphonate therapy. While the authors say the results were no different excluding these subjects, the data was not shown and residual effects on increments in BMD and prolonged suppression of remodeling may influence percent changes in these traits.

Schafer et al reported that postmenopausal women with low bone mass (n=43) were treated with 6 months of PTH(1-84) (100 µg/day), either as one 6- or two 3-month courses, with ibandronate (150 mg/month) during 2 years (5). Changes in HR-pQCT parameters did not differ between treatments. The groups were pooled. Trabecular BMD increased at radius and tibia. Cortical thickness and BMD decreased at the radius but did not change at the tibia. Cortical porosity increased at the tibia, not radius. Stiffness and failure load decreased at the radius but did not change at the tibia. The authors infer cortical and trabecular changes in response to the PTH/ibandronate were different at the nonweight-bearing radius vs. the weight-bearing tibia, with more favorable overall changes at the tibia. They suggest that weight bearing may optimize the effects of osteoporosis therapy. If these measurements are correct then how is antifracture efficacy achieved?

Do We Need Randomized Comparator Trials?

Lindsay et al reported a comparison between the anti-hip fracture efficacy of alendronate and risedronate (6). While it is tradition to compare treatments in a randomized controlled comparator trial, the authors took a rather different approach in a post hoc analysis comparing the results with a ‘control’ group of patients filling a single bisphosphonate prescription only and thereby assuming this was a no treatment group. In previous trials there was a suggestion of an earlier reduction in fracture rates with risedronate than alendronate, perhaps because of the lower binding affinity or risedronate to mineral allowing this drug to penetrate more deeply into cortical bone than ALN and thereby accessing and inhibiting intracortical remodeling sooner or more effectively than alendronate. The authors observed three cohorts of women who initiated once-a-week dosing of bisphosphonate; (1) patients adherent to alendronate (n=21,615), (2) patients adherent to risedronate (n=12,215), or (3) patients filling only a single bisphosphonate prescription (n=5390) as a referent population. In this cohort, the authors reported that at 12 months a significant reduction of hip and nonvertebral fractures with risedronate but not with

alendronate. At the end of 2 years, the cumulative incidence of hip fractures in the referent cohort was 1.9%, and incidence of nonvertebral fractures was 6.3%. Relative to the referent, 6 months after initiating therapy and continuing through 2 years, both risedronate and alendronate cohorts had approximately a 45% lower incidence of hip fractures and a 30% lower incidence of nonvertebral fractures. The authors infer that both risedronate and alendronate reduce the risk of hip and nonvertebral fracture after two years of treatment with an earlier effect of risedronate. Ultimately, the test needed remains a randomized comparator trial as factors other than the therapy influencing fracture outcomes, whether known or unknown, can only be assumed to be equally distributed in the two groups when participants are randomly allocated to therapy and compliance is monitored. If this principle is ignored the veracity of the scientific method is in question.

Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)

Mozzati et al reported 700 consecutive patients treated with oral bisphosphonates who underwent 1480 extractions: 864 in the mandible and 616 in the maxilla (7). 334 were treated with delicate surgery and closure by primary intention and 366 were treated with nontraumatic avulsion and closure by secondary intention. No intraoperative complications were observed, and there was no evidence of postoperative bisphosphonate-associated osteonecrosis of the jaw.

Atypical Subtrochanteric Fractures

Atypical femur fractures (AFFs) located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking bisphosphonates, and in patients on denosumab, but also occur in patients with no exposure to these drugs. In this report, **Shane et al** reviewed studies on the epidemiology, pathogenesis and medical management of AFFs published since 2010 (8). AFFs are stress or insufficiency fractures. The original definition was revised to highlight radiographic features that distinguish AFFs from ordinary osteoporotic femoral diaphyseal fractures and to provide guidance on the importance of their transverse orientation. The requirement that fractures be noncomminuted was relaxed to include minimal comminution. The periosteal stress reaction at the fracture site was changed from a minor to a major feature. The association with specific diseases and drug exposures was removed from the minor features. Studies with radiographic review consistently report associations between AFFs and bisphosphonate use, although the strength of associations and magnitude of effect vary. Although the relative risk of patients with AFFs taking bisphosphonates is high, the absolute risk of AFFs is low, 3.2-50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (approximately 100 per 100,000 person-years). Bisphosphonates localize in areas that are developing stress fractures; suppression of targeted intracortical remodeling at the site of an AFF could impair healing. When bisphosphonates are stopped, risk of an AFF may decline. Lower limb geometry and Asian ethnicity may contribute to the risk of AFFs. There is inconsistent evidence that teriparatide may advance healing of AFFs.

Schilcher et al reported that in a previous nationwide study in Sweden, 59 atypical and 218 ordinary fractures were diagnosed (9). The fracture angle (0-180°) was measured. Presence of local lateral cortical thickening (a callus reaction), more than two fragments, or a medial spike was noted. Frequency distribution analysis of the fracture angle showed 57 (25%) of 277 fractures with a mean of 89° and SD of 10°. Forty-two of 57 patients used bisphosphonates, whereas 27 of 213 others did (specificity 0.93; 95% CI 0.88-0.96). Presence of a callus reaction had also a high specificity for bisphosphonate use (0.96; 95% CI 0.92-0.98). The ASBMR criteria had a lower specificity, increasing the number of atypical fractures without bisphosphonate use from 13 to 31. This led to a decrease in age-adjusted relative risk associated with bisphosphonate use from 47 (95% CI 26-87) to 19 (95% CI 12-29). Differences in diagnostic criteria may partially explain the large differences in relative risk between different population-based studies.

From August 2009 to March 2011, **Allison et al** reported 220 femoral radiographs in 110 asymptomatic patients (101 women, 9 men, age 47-94) were reviewed by two radiologists (10). All patients received bisphosphonate for at least 3 years and had no history of hip/thigh pain. MRI was performed when a fracture was suspected on radiographs. Two of 110 patients (1.82%, CI 0.6-6.3%) had 3 incomplete fractures. Both patients, age 50 and 57, were Caucasian, active and on bisphosphonate for 8 years. MRI confirmed radiographic findings in both patients. Both women had T-scores in the osteopenic range at two sites and osteoporotic range at one site. The 1.82% frequency of incomplete fractures in asymptomatic patients on long-term bisphosphonate therapy is higher than that suggested in the literature. Statistical differences between fracture and nonfracture groups were not presented as the patient population was too small to draw any significant conclusions.

Bisphosphonates and Protection against Myocardial Infarction

Bisphosphonates have been reported to be associated with reduce mortality in patients with osteoporotic fractures. **Wolfe et al** sought to determine if bisphosphonate use is associated with a reduced risk of myocardial infarction (MI) in 19,281 patients with rheumatoid arthritis (11). Among 5689 patients treated with bisphosphonates, the risk of MI while treated with bisphosphonate compared to when not treated was 0.56 (95% CI 0.37-0.86; $p<0.01$). In models including all 19,281 treated and untreated patients, the adjusted risk of first MI was 0.72 (95% CI 0.54-0.96; $p=0.02$) and of all MIs it was 0.72 (95% CI 0.53-0.97; $p=0.03$) in bisphosphonate users compared to nonusers.

Poor Compliance and Fractures

Olsen et al reported a national dataset was extracted with all treatment-naive patients who began oral bisphosphonate treatment for osteoporosis in Denmark between 1997-2006 (N=54,876, 87% women) (12). Patients who survived for at least two years (N=47,176) were divided into groups based on medication possession ratio (MPR). For alendronate, the adjusted risk of major osteoporotic fractures was reduced (OR 0.768; 0.686-0.859), including fractures of the hip (0.718; 0.609-0.846) and humerus (0.54; 0.431-0.677) with MPR ≥0.8. The risk reduction was lower with etidronate. Over two years, 171 hip fractures and 53 other major osteoporotic fractures were attributed to suboptimal or poor refill compliance, with an excess cost of 13.7 M DKK (2.5 M USD).

Undercarboxylated Osteocalcin and Testosterone

In animal studies, undercarboxylated osteocalcin (ucOC) is reported to be important for male fertility and testosterone production by testes. **Kanazawa et al** reported ucOC is positively associated with free testosterone in 69 men with type 2 diabetes (13). ucOC and ucOC/total OC (TOC) ratio were associated with free testosterone and negatively with LH (for ucOC, β=0.30, p=0.042 and β=-0.52, p=0.048; for ucOC/TOC ratio, β=0.31, p=0.031 and β=-0.54, p=0.036, respectively) independent of age, duration of diabetes, BMI, and hemoglobin A1c.

Bisphosphonates reduce osteocalcin levels. **Bolland et al** determined whether reductions in osteocalcin induced by zoledronic acid impact negatively on testosterone levels in 43 HIV-infected men treated for two years using annual 4 mg zoledronic acid (14). Serum testosterone was measured at baseline, 3 months, and 2 years; luteinizing hormone at 3 months and 2 years; and total osteocalcin at 2 years in 28 participants. At 2 years, total osteocalcin was 39% lower in the zoledronic acid group than the placebo (zoledronic acid mean 10.1 [SD 3.0] µg/L, placebo 16.5 [SD 4.9] µg/L, P=0.003). Testosterone levels did not change over time in either group and there were no between-group differences over time, P=0.4 (mean change at 2 years [adjusted for baseline levels] in zoledronic acid group -0.4 nmol/L, 95 % CI -2.5 to 1.6; placebo group 0.4 nmol/L, 95 % CI -1.6 to 2.5).

Lactation
A fascinating model of uncoupling

Collins et al reported that Ctcgrp (calcitonin/calcitonin gene related peptide α) null mice lose 50% of spine mineral content during lactation but restore it fully (15). Ctcgrp null mice have twice as many osteoclasts and 30-40% fewer osteoblasts compared with wild-type during lactation but no deficit in osteoblast numbers after weaning. Genomewide microarray analyses on tibial RNA showed differential expression of 729 genes in wildtype mice at day 7 after weaning vs. prepregnancy, whereas the same comparison in Ctcgrp null mice revealed only 283 genes. Downregulation of Sost and Dkk1, and inhibition of Mef2c, a sclerostin stimulator, was observed. Ctsk, a gene expressed during osteoclast differentiation, and Igfbp2, which stimulates bone resorption, were inhibited. Differential regulation of genes involved in energy use was compatible with a net increase in bone formation. The most marked changes occurred in genes not previously associated with bone metabolism. The postlactation skeleton shows dynamic activity with more than 700 genes expressed. Some promote bone formation during postweaning by stimulating the proliferation and activity of osteoblasts, inhibiting osteoclasts, and increasing energy use.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 7

Ego Seeman

Editor

By Ego Seeman Wed, 08/07/2013 - 14:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Volume 13, Issue 7

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Odanocatib
Is the new kid as good as the golden oldie?

Here are two studies comparing the effects of odanocatib (ODN) and alendronate (ALN) on bone morphology. One of the main observations of the study was that cortical thickness increased even though there was no detectable change in periosteal perimeter, i.e., no detectable evidence of periosteal apposition. Both studies suggested greater efficacy of odanocatib on cortical morphology than observed with alendronate. While encouraging, and perhaps correct, the work raises several interesting issues about the mechanism of action of these drugs and our ability to measure morphological changes accurately.

Cortical thicknesses vary around the perimeter of a bone cross section and vary at every cross section along the length of a bone. It is a misnomer to refer to cortical 'thickness' as a single phenotype (1). It is derived by dividing the cortical area by the perimeter. So if the area increases but there is no change in periosteal perimeter, then medullary area must decrease, presumably due to net deposition of bone upon the endocortical surface. There was no data provided concerning medullary area. Another possibility is trabecular 'corticalization'. This occurs during metaphyseal growth. If bone formation occurs upon adjacent trabeculae abutting against the endocortical surface, coalesce of trabeculae may produce what seems to be cortical thickening. Another menchanism producing cortical 'thickening' is a reduction in porosity of the inner cortex adjacent to the medullary canal. This is the opposite of what occurs during aging where intracortical remodeling produces porosity which thins the cortex from within. There is one other change that may lead to the mistaken notion that the cortex is thicker. If treatment increases tissue mineral density of the cortical matrix this may alter edge detection which produces what seems to be an increase in 'thickness'.

The question is how does an antiresoprtive agent that either reduces the number of remodeling sites upon a surface, reduces the depth of each site, or both, detectably *increase* cortical

thickness. One way is that the more shallow resorption cavites excavated during ODN therapy refill or overfill if the amount of bone deposited in each is either unchanged or increases. This is possible but compelling evidence for an increase in the volume of bone deposited by each BMU during odanocatib therapy is lacking.

Williams et al compared low and high dose ODN (2 or 8 / 4 mg/kg/d), ALN (15 µg/kg, twice weekly, s.c.), and vehicle (VEH) initiated 10 days following OVX and continued for 20 months. Effects were similar by dose (2). ODN and ALN reduced resorption markers (uNTx and sCTx) compared to VEH. ODN reduced formation markers less than ALN. At month 18, ODN increased spine aBMD (11.4%), spine trabecular vBMD (13.7%), femoral neck (FN) integral vBMD (9.0%) and subtrochanteric proximal femur (SubTrPF) integral vBMD, (6.4%), FN cortical thickness (Ct.Th 22.5%) and cortical bone mineral content (Ct.BMC 21.8%), SubTrPF Ct.Th (10.9%) and Ct.BMC (11.3%). Compared to ALN, ODN increased FN Ct.BMC by 8.7%, and SubTrPF Ct.Th by 7.6% and Ct.BMC by 6.2%. ODN had comparable efficacy to ALN in aBMD and vBMD. FN cortical mineral content demonstrated superior efficacy of ODN vs. ALN.

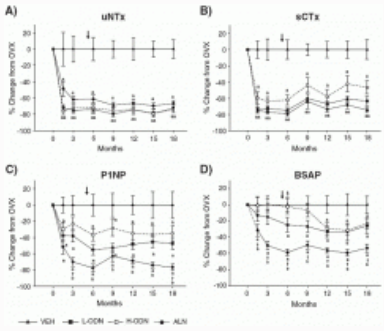

Figure 1. Effects of ODN and ALN on biochemical markers of bone turnover. Bone resorption markers urinary NTx (A) and serum CTx (B) and bone formation markers P1NP (C) and BSAP (D) were monitored at 1.5, 3, 6, 12, 18 and 20 months of dosing. Arrow indicates approximate time of dose change for H-ODN from 8 mg/kg to 4 mg/kg. Data represent mean ±SEM. [a]p<0.05 vs. VEH; [§]p<0.05 H-ODN vs. L-ODN; [†]p<0.05 L-ODN vs. ALN; [b]p<0.05 H-ODN vs. ALN. Reproduced from Bone, doi:10.1016/j.bone.2013.06.008, Copyright (2013), with permission from Elsevier.

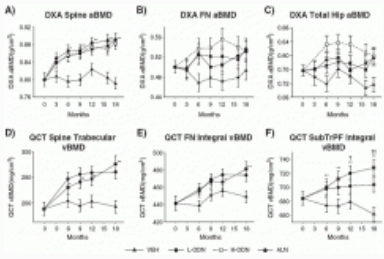

*Figure 2. Effects of ODN and ALN on selected DXA and QCT parameters at the spine and hip. DXA aBMD in spine (A); DXA aBMD in FN (B); DXA aBMD in total hip (C); QCT trabecular vBMD in spine (D); QCT integral vBMD in FN (E); and QCT integral vBMD in SubTrPF (F). Error bars represent standard errors. *p<0.05 L-ODN vs. baseline; **p<0.01 L-ODN vs. baseline; [†]p<0.05 L-ODN vs. ALN; [††]p<0.01 L-ODN vs. ALN. Reproduced from Bone, doi:10.1016/j.bone.2013.06.008, Copyright (2013), with permission from Elsevier.*

Cabal et al compared the effects of VEH, low (2 mg/kg/day, ODN), and ALN (30 µg/kg/week) given during 18 months on structure and estimated bone strength (3). ODN increased in integral UDR vBMD (13.5%), cortical thickness (24.4%), total bone volume fraction BV/TV (13.5%), FEA-estimated peak force (26.6%) and peak stress (17.1%), respectively. Increases were higher than that for ALN in DXA-based aBMD (7.6%), cortical thickness (22.9%), integral vBMD (12.2%), total BV/TV (10.1%), FEA peak force (17.7%) and FEA peak stress (11.5%), respectively.

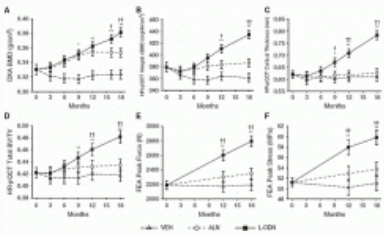

*Figure 3. Longitudinal changes from baseline through 18 months for the VEH, ALN, and L-ODN groups: A) DXA-BMD, B) HR-pQCT integral vBMD, C) HR-pQCT cortical thickness, D) HR-pQCT total BV/TV, E) FEA peak force and F) FEA peak stress. Statistically significant differences between L-ODN vs. baseline are depicted by *(p<0.05); **(p<0.01), and L-ODN vs. ALN are depicted by [†]p<0.05; [††]p<0.01. Error bars represent standard errors. Reproduced from Bone, doi:10.1016/j.bone.2013.06.011, Copyright (2013), with permission from Elsevier.*

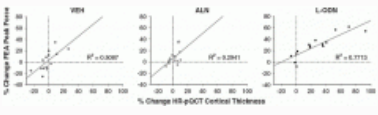

Figure 4. Percent changes between baseline and 18 months of the peak force (N) vs. cortical thickness for the VEH (left), ALN (middle), and L-ODN (right) groups. The correlation coefficients r^2 are indicated in the graphs. Reproduced from Bone, doi:10.1016/j.bone.2013.06.011, Copyright (2013), with permission from Elsevier.

Low Dose Zoledronic Acid

Zoledronic acid (ZOL) is a potent remodeling suppressant and as administered annually, it represents an excellent way of reducing fracture risk while minimizing the problem of frequent administration and issues with compliance. However, there is accumulating evidence that even annual infusion may not be needed. A single infusion has been shown to reduce remodeling markers for 3-5 years and now there is evidence that a single infusion may reduce fracture rates during three years similar to that observed by three annual infusions (4-6).

In this study, **Grey et al** report that 180 postmenopausal women with osteopenia were randomized to a single baseline intravenous ZOL in doses of 1, 2.5 or 5 mg, or placebo (7). Changes in spine BMD were greater than with placebo difference vs. placebo: ZOL 1 mg 4.4%;

2.5 mg 5.5%; 5 mg 5.3%, P<0.001 each dose. Changes total hip BMD were greater in each of the ZOL groups than placebo: ZOL 1 mg 2.6%; 2.5 mg 4.4%; 5 mg 4.7%, P<0.001 each dose, and β-CTX and P1NP were lower in each of the 2.5 mg and 5 mg groups than the placebo. Changes were similar in the 2.5 and 5 mg groups, while those in the 1 mg group were smaller. Single administrations of ZOL 1 mg or 2.5 mg produce antiresorptive effects that persist for at least 2 years.

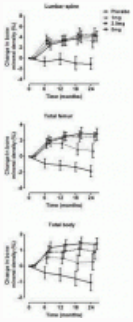

Figure 5. BMD at the lumbar spine (top), total hip (middle) and total body (bottom) over 2 years. Data are mean percent change from baseline (95% CI). At each site, BMD was higher in each of the ZOL groups than placebo (P<0.0001 each point). Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2009 with permission of the American Society of Bone and Mineral Research.

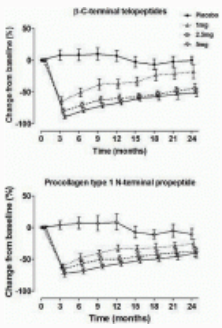

Figure 6. Effects on β-CTX (top), and P1NP. Data are mean percent change from baseline (95% CI). The level of each turnover marker was lower in each of the 2.5mg and 5mg ZOL groups than placebo (P<0.0001 each point); in the 1 mg ZOL group, β-CTX and P1NP were lower than the placebo group at each point (P<0.0001) until 18 months and 24 months, respectively. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2009 with permission of the American Society of Bone and Mineral Research.

Denosumab and Estimated Bone Strength

Keaveny et al studied FEA of hip and spine QCT scans in a subset (N=48 placebo; N=51 denosumab) at baseline, 12, 24, and 36 months (8). Hip strength increased from 12 months (5.3%; p<0.0001) and through 36 months (8.6%; p<0.0001) in the denosumab group. For the placebo group, hip strength decreased at 36 months (-5.6%; p<0.0001). Similar changes were observed at the spine: strength increased by 18.2% at 36 months for the denosumab group (p<0.0001) and decreased by -4.2% for the placebo (p=0.002). Strength associated with the trabecular bone was lost at the hip and spine in the placebo group, whereas strength associated with both the trabecular and cortical bone improved in the denosumab group.

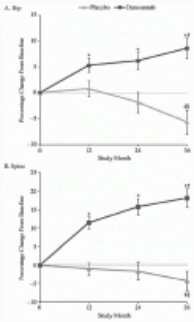

*Figure 7. Mean percentage change in strength for the hip (A) and spine (B) estimated using the FEA. *p<0.0001 vs. both baseline and placebo; †p<0.0001 vs. 12 months; ‡p<0.005 vs. baseline; §p<0.05 vs. 12 months. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2024 with permission of the American Society of Bone and Mineral Research.*

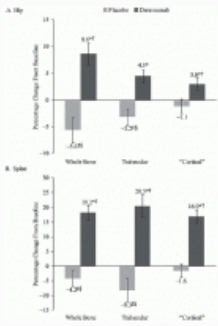

*Figure 8. Mean percentage change in whole bone, trabecular, and "cortical" compartment strength for the hip (A) and spine (B) estimated using FEA, at 36 months. *p<0.0001 vs. both baseline and placebo; †p<0.01 vs. 12 months; ‡p<0.005 vs. baseline; §p<0.05 vs. 12 months. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2024 with permission of the American Society of Bone and Mineral Research.*

Eight Years Denosumab

McClung et al report that denosumab treatment for 8 years was associated with continued gains in BMD and persistent reductions in bone turnover markers (9). In the 4-year study, postmenopausal women with low BMD were randomized to placebo, ALN, or denosumab. After 2 years, subjects were reallocated to continue, discontinue, or discontinue and reinitiate denosumab; discontinue alendronate; or maintain placebo or two more years. The parent study was then extended for 4 years where all subjects received denosumab. Of the 262 subjects who completed the parent study, 200 enrolled in the extension, and of these, 138 completed the extension. For the subjects who received 8 years of continued denosumab, BMD at the spine and

total hip increased by 16.5 and 6.8 %, respectively, compared with their parent study baseline, and by 5.7 and 1.8 %, respectively, compared with their extension study baseline. For the 12 subjects in the original placebo group, 4 years of denosumab resulted in BMD gains comparable with those observed during the 4 years of denosumab in the parent study. Reductions in bone turnover markers were sustained. The authors infer that continued denosumab for 8 years was associated with progressive gains in BMD, persistent reductions in bone turnover markers, and was well tolerated.

The question is what are these gains in BMD? The increase at the spine from year 4 to 8 is similar or slightly less that the increase in the first 4 years and this is very difficult to explain based on remodeling theory. The most likely explanation in my opinion is that there is confounding by arthritic changes captured in the BMD measurement. The increase of around 1-2% in the second 4 years at the hip is consistent with the notion that this is the result of secondary mineralization of bone remodeled months or even years earlier. Is there a possibility that this is newly deposited bone – perhaps but we need data to support this contention and a propose mechanism. One might be the secondary increase in endogenous PTH that results when PTH is administered. This might have an anabolic effect, either modeling based, or remodeling based and if it occurs in the face of suppressed osteoclastogenesis and prevention of resorption of existing osteoclasts, there may be a net anabolic effect without bone resorption. It's plausible but unproven.

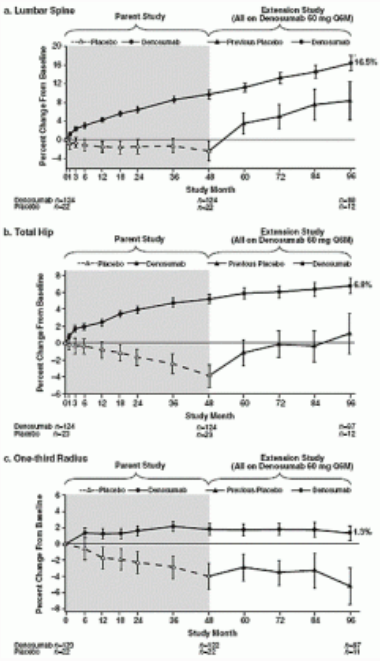

Figure 9. Effect of 8 years of continued denosumab treatment on BMD at the (a) lumbar spine, (b) total hip, and (c) one-third radius. BMD values are shown as percent change from parent study baseline (LSM+95% CI based on ANCOVA models adjusting for geographical location and parent study baseline BMD values). Gray boxes indicate the original 4-year parent study. Numbers shown at each time point reflect the number of subjects enrolled in the extension study with observed data at the selected time points of interest. Reproduced from Osteoporos Int 2013;24:227-35 with permission from Springer.

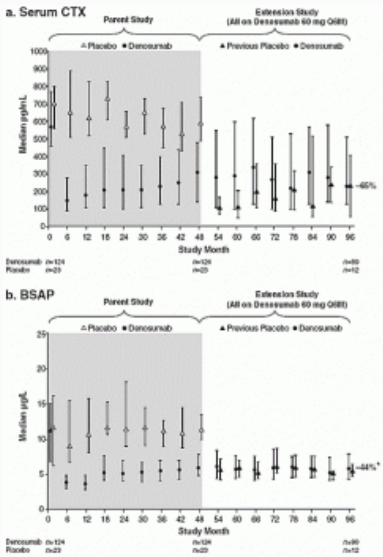

*Figure 10. Effect of 8 years denosumab on serum CTX and BSAP. Bone turnover markers are shown as actual values (medians with Q1 to Q3 interquartile ranges). Gray boxes indicate the original 4-year parent study. Numbers shown reflect the number of subjects enrolled in the extension study with observed data at the selected time points of interest. *A calibration discrepancy at the central laboratory may have led to BSAP results in some individual samples to be falsely elevated by up to 14% at months 90 and 96. Reproduced from Osteoporos Int 2013;24:227-35 with permission from Springer.*

Does Calcium Increase Mortality?

This is yet another paper suggesting a high calcium intake is associated with increased cardiovascular morbidity and mortality. The data are prospective but this is not a randomized controlled trial and whatever the outcome it does not prove causation. The authors acknowledge this. The signal it sends is clear however. We need a properly designed and executed trial with cardiovascular outcomes. For now, it remains advisable, as always to do no harm; avoid avoiding calcium nutrition but avoid intakes that are above 1200 mg daily too.

Michaëlsson et al investigated the association between dietary and supplemental calcium and death from all causes and cardiovascular disease.in a prospective longitudinal mammography cohort of 61,433 women followed for a median of 19 years (10). Primary outcome measures were time to death from all causes (n=11,944) and cause specific cardiovascular disease (n=3862), ischaemic heart disease (n=1932), and stroke (n=1100). Diet was assessed by food frequency questionnaires at baseline and in 1997 for 38,984 women, and intakes of calcium were estimated. Total calcium intake was the sum of dietary and supplemental calcium.

The risk patterns were nonlinear with higher rates around the highest intakes (≥1400 mg/day). Compared with 600 and 1000 mg/day, intakes above 1400 mg/day were associated with higher death rates from all causes (HR 1.40, 1.17 to 1.67), cardiovascular disease (1.49, 1.09 to 2.02), and ischaemic heart disease (2.14, 1.48 to 3.09), not stroke (0.73, 0.33 to 1.65). After sensitivity analysis, the higher death rate with low dietary calcium intake (<600 mg/day) or with low and high total calcium intake was no longer apparent. Use of calcium tablets (6% users; 500 mg calcium per tablet) was not associated with all cause or cause specific mortality; but among calcium tablet users with a dietary calcium intake above 1400 mg/day, the hazard ratio for all cause mortality was 2.57 (95% CI 1.19-5.55). The authors infer that high intakes of calcium in women are associated with higher death rates from all causes and cardiovascular disease but not from stroke.

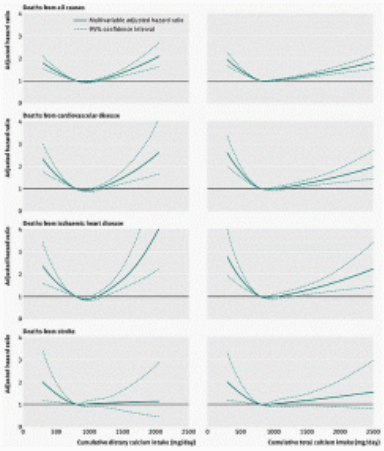

*Figure 11. Multivariable adjusted spline curves for relation between cumulative average of dietary and total calcium intake with time to death from all causes, cardiovascular disease, ischaemic heart disease, and stroke. *Adjusted for age, total energy and vitamin D intake, healthy dietary pattern, BMI, height, living alone, educational level, physical activity level, smoking status, use of calcium containing supplements, and score on Charlson comorbidity index. Reference value for estimation was set at 800 mg, which corresponds to the Swedish recommended level of calcium intake for women older than 50 years. The upper confidence limit for ischaemic heart disease is truncated at calcium intake levels higher than about 1800 mg/day. Reproduced from BMJ, 346:f228, Copyright (2013), with permission from Elsevier.*

Zoledronic Acid, Breast Cancer and Disease Free Survival

Aromatase inhibitor therapy is associated with increased bone loss and fracture risk. In the study by **Coleman et al**, postmenopausal women receiving adjuvant letrozole (2.5 mg/day for 5 years; N=1065) were randomly assigned to immediate ZOL 4 mg every 6 months for 5 years, or delayed ZOL (11). At 60 months, the mean change in spine BMD was +4.3% with immediate ZOL and -5.4% with delayed intervention (P<0.0001). Immediate ZOL reduced the risk of disease free survival events by 34% (HR=0.66; P=0.0375) with fewer local (0.9% vs. 2.3%) and distant (5.5% vs .7.7%) recurrences vs. delayed ZOL. In the delayed group, delayed initiation of zoledronate substantially improved disease free survival vs. no ZOL (HR=0.46; P=0.0334).

Subtrochanteric Fractures
The surprising role of corticosteroids

Atypical femoral fractures, which display characteristics of brittle material failure, are been associated with remodeling suppression drugs. Some evidence suggests concomitant use of corticosteroids may contribute. In the study by **Luo and Allen**, skeletally mature beagle dogs were either untreated controls, or treated with ZOL, dexamethasone (DEX), or both (12). ZOL (0.06 mg/kg) was given monthly for 9 months. DEX (5 mg) was administered daily for one week during each of the last three months of the 9 month experiment. DEX suppressed intracortical remodeling while ZOL and the combination nearly abolished intracortical remodeling. ZOL resulted in lower toughness, toughness in ZOL+DEX was identical to controls. Dexamethasone reverses the adverse effects ZOL.

Fracture Healing and Alendronate

Meganck et al studied the effect of ALN on fracture healing. Brtl/+ murine model of type IV OI had tibial fractures at 8-weeks and were untreated, treated with ALN before fracture, or treated before and after fracture (13). There were no differences in callus between untreated mice and

mice that received ALN before fracture. Both Brtl/+ and WT mice that received ALN before and after fracture had increases in the callus volume, bone volume fraction and torque at failure after 5 weeks of healing. Raman microspectroscopy results did not show any effects of ALN in wildtype mice, but calluses from Brtl/+ mice treated with ALN during healing had a decreased mineral-to-matrix ratio, decreased crystallinity and an increased carbonate-to-phosphate ratio. Treatment with ALN altered the dynamics of healing by preventing callus volume decreases later in the healing process. Fracture healing in Brtl/+ untreated animals was not significantly different from animals in which alendronate was halted at the time of fracture.

PTHrP 1-34 as an Anabolic Agent

The N-terminal fragment 1-34 of PTH is similar in structure and function to N-terminal PTHrP. PTH(1-34) and PTHrP also share a coreceptor, the PTH/PTHrP receptor. **Xu et al** used an OVX rat model to study the effects of PTHrP(1-34) (14). Subcutaneous PTHrP(1-34) (40 or 80 µg/kg body weight every day) increased lumbar and femoral BMD, improved bone biomechanical properties, enhanced bone strength, and promoted bone formation. 40 µg/kg of PTHrP(1-34) once per day or every other day improved the BMD and strength of OVX rats. Based on their results, intermittent low-dose PTHrP(1-34) injection promoted bone formation in OVX rats, suggesting a high potential for therapeutic use in osteoporosis patients.

Osteocytes
What fascinating cells

Intracortical porosity increases as age advances and is due to intracortical remodeling initiated upon Haversian or Volkmann canal surfaces. Porosity results when exavation initiated at a point upon the canal surface erodes matrix beneath and so enlarges the canal focally. With time, canals coalesce forming giant pores in cross section. The increase in porosity with age should then be partly a function of peak porosity achieved during growth (i.e., the number of osteons, each with their central Haversian canal). If so the number of pores does not increase, their size increases, and indeed, the number may decrease as pores coalesce (15,16). Most data suggest this is the mechanism of increased cortical porosity. Another possibility is that there is an increase in the number of canals. This may occur if the excavation first enlarges an existing canal but then excavation creates a new Howships lacunae and a new canal is dug parrellel to the previous canal. Another mechanism may be the creation of new pores which originate within osteocyte lacunae.

Jilka et al selectively deleted Bak and Bax, two genes essential for apoptosis in osteoblasts and in osteocytes (17). Attenuation of apoptosis in osteoblasts increased their lifespan and femur cancellous bone mass. In osteocytes, however, it caused intracortical femoral porosity associated with increased production of receptor activator of nuclear factor-κB ligand and vascular endothelial growth factor. Old and/or dysfunctional osteocytes may contribute to increased intracortical porosity in old age.

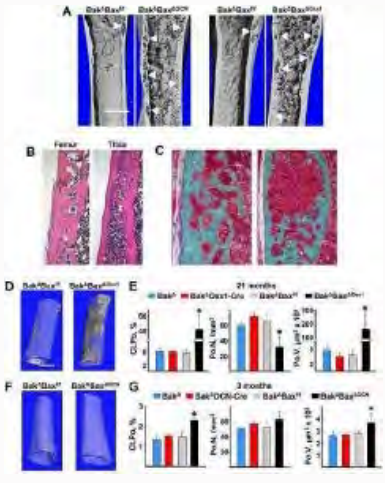

*Figure 12. Lack of Bax and Bak increases cortical porosity in aged mice. (A) Representative micro-CT images of femora from 22-month-old female Bak$^{\Delta}$Bax$^{\Delta OCN}$ and Bak$^{\Delta}$Bax$^{f/f}$ littermates (left panel), and 21-month-old female Bak$^{\Delta}$Bax$^{\Delta Osx1}$ and Bak$^{\Delta}$Bax$^{f/f}$ littermates (right panel), scale bar, 1 mm. White arrowheads mark location of pores in cortical bone. (B) Representative femoral and tibial H&E-stained decalcified sections from 21-month-old female Bak$^{\Delta}$Bax$^{\Delta Osx1}$ mice, with the periosteal surface on the left; scale bar, 1 mm. (C) Representative femoral Trichrome-stained nondecalcified sections of femoral cortex from 22-month-old female Bak$^{\Delta}$Bax$^{\Delta OCN}$ mice, with the periosteal surface on the left.; scale bar, 50 µm. (D) Inverse micro-CT images of the distal half of femora from 21-month-old female mice. Void areas are depicted in grey within a transparent bone matrix. (E) Cortical porosity (Ct.Po), pore number (Po.N) and pore volume (Po.V) in the cortex of the distal half of femora from 21-month-old female mice, n=3-4/group. (F) Inverse micro-CT images of the distal half of femora from 3-mo-old female mice. (G) Porosity, pore number and pore volume in 3-month-old female mice, n=3/group, *p<0.05 vs. littermate controls. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2007 with permission of the American Society of Bone and Mineral Research.*

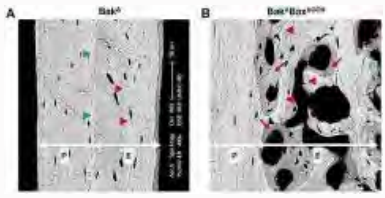

Figure 13. Increased cortical porosity of aged Bak$^{\Delta}$Bax$^{\Delta OCN}$ mice is restricted to the endosteal zone. Representative BSEM images of the femoral diaphyseal cortex from (A) a 22-month-old female Bak$^{\Delta}$ mouse, and (B) a 22-month-old female Bak$^{\Delta}$Bax$^{\Delta OCN}$ mouse. Endosteal ("E") and periosteal ("P") zones are separated by a highly mineralized boundary, indicated by green arrowheads. Red arrowheads mark highly mineralized cement lines that reflect previous remodeling activity. Red arrows denote areas of recently remodeled bone that have not yet achieved full mineralization. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2007

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The role of osteocytes during mineral homeostasis and their influence on bone material quality was assessed by **Kerschnitzki et al** (18). These investigators visualized and quantified the osteocyte network in mineralized bone sections with confocal laser scanning microscopy. Synchrotron small angle X ray scattering is used to determine nanoscopic bone mineral particle size and arrangement relative to the cell network. Most mineral particles reside within less than a micrometer from the nearest cell network channel and that mineral particle characteristics depend on the distance from the cell network. The network architecture optimizes transport costs between cells and to blood vessels. Osteocytes interact with their mineralized vicinity and participate in bone mineral homeostasis.

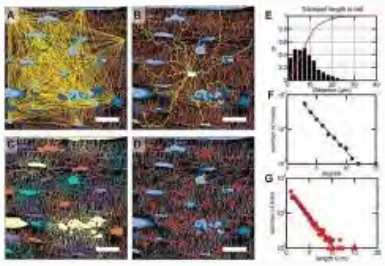

Figure 14. Cell-cell interconnectivity and canalicular network analysis. (A) Yellow lines depict direct connections between individual cells (blue) via the canaliculae. (B) The shortest direct connection through canaliculae to neighboring cells is depicted in yellow. (C) Color coding of canalicular network voxels depending on their nearest cell as a measure of the network area controlled by each cell. (D) Classification of canalicular junctions (nodes) according to the number of attached connections (degree). Red points depict interwoven nodes featuring a degree >5. (E) Histogram (black) and cumulative plot (red) of the travel distance from canalicular voxels to the nearest cell through the network showing that almost 70% of the canalicular network resides within a 10-mm travel distance. (F) The degree distribution of canalicular junctions is exponential (black line) revealing the single-scale character of the canalicular network. There is a high abundance of junctions with dendritic character (65% of nodes show d=3), but junctions with up to 10 connecting canaliculi are also present. The mean degree of nodes is 3.25. (G) The length distribution of individual canalicular structures is exponential (black line) with individual lengths up to 15 µm. The mean canalicular length between two nodes is 2.15 µm. Scale bars = 20 µm. Reproduced from J Bone Miner Res 2013; 28:1837-45 with permission of the American Society of Bone and Mineral Research.

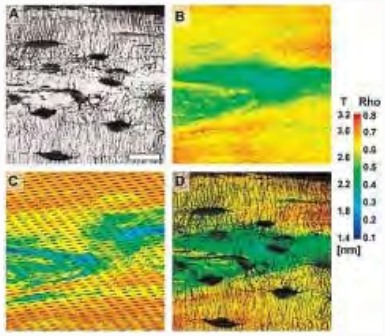

Figure 15. Osteocyte network and nanoscopic mineral particle properties. (A) Visualization of the osteocyte network showing highly organized (dense) osteocyte network structures at the top and the bottom and poorly organized (loose) network structures in the center. Synchrotron small angle X-ray scattering measurements of the mineral particle thickness (T-parameter) (B) and the mineral particle orientation (Rho parameter) (C) along the visualized network structures. Mineral particles in dense network regions are thicker and more oriented compared to the loose regions in the center. The direction of alignment of mineral particles is always perpendicular to that of the canalicular structures. (D) Colocalization of T-parameter maps with the osteocyte network reveals thinner mineral particles around individual osteocyte lacunae. Scale bar = 20 µm. Reproduced from J Bone Miner Res 2013; 28:1837-45 with permission of the American Society of Bone and Mineral Research.

Osteocytes produce RANKL suggesting these cells participate in osteoclastogenesis and bone resorption. Sclerostin increases RANKL-mediated osteoclast activity. There is evidence that osteocytes liberate mineral from bone in osteocytic osteolysis. **Kogawa et al** investigated sclerostin-stimulated mineral dissolution by human primary osteocyte-like cells (hOCy) and mouse MLO-Y4 cells (19). Sclerostin upregulated osteocyte expression of carbonic anhydrase 2 (CA2/Car2), cathepsin K (CTSK/Ctsk) and tartrate resistant acid phosphatase (ACP5/Acp5). Sclerostin stimulated CA2 mRNA and protein expression in hOCy and in MLO-Y4 cells and induced a decrease in intracellular pH (pHi) and in extracellular pH (pHo) with release of calcium ions from mineralised substrate. These effects were reversed by acetozolamide. Car2-siRNA knockdown in MLO-Y4 cells inhibited the ability of sclerostin to reduce the pHo and release calcium. Knockdown in MLO-Y4 cells of each of the putative sclerostin receptors, Lrp4, Lrp5 and Lrp6, using siRNA, inhibited the sclerostin induction of Car2, Catk and Acp5 mRNA, as well as pHo and calcium release. Human trabecular bone samples treated *ex vivo* with recombinant human sclerostin for 7 days exhibited an increased osteocyte lacunar area, an effect that was reversed by acetozolamide.

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OVERVIEW, VOL 13, ISSUE 8

Ego Seeman

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By Ego Seeman Fri, 08/09/2013 - 07:50

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Strontium Ranelate is Not a Dual Acting Agent

Chavassieux et al report data that challenges the notion that strontium ranelate (SR) has a 'dual action' – increasing bone formation and reducing resorption (1). In this 12 month multicenter, double-blind, controlled trial, the investigators performed transiliac bone biopsies at 0, 6 or 12 months in 387 postmenopausal women with osteoporosis given SR 2 g/day (n=256) or alendronate 70 mg/week (n=131).

In the intention-to-treat group (268 women with paired biopsies), static and dynamic parameters of remodeling decreased with alendronate (ALN) consistent with the known effect of this drug in reducing remodeling. The SR group also had a modest but less decrease in the surface extent of remodeling, reflected in reduced activation frequency and mineralizing surfaces. Static parameters of formation were unchanged from baseline except for a decrease in the proportion of the surface (Ob.S/BS) covered by osteoblasts at 6 months. However, as there was no calcium + vitamin D-alone group and no strontium-alone group to permit comparison, it is plausible that the modest decreases in activation frequency and some remodeling indices could be due to the concomitant administration of calcium + vitamin D supplementation. ALN also decreased resorption parameters. SR did not.

Moreover, in the SR group, compared to the baseline, mean wall thickness (MWT), the two dimensional measure of the volume of bone formed by a BMU, decreased at 6 not 12 months and cancellous bone volume per unit tissue volume (BV/TV), trabecular thickness and number decreased. No mineralization defect was reported with either drug.

ALN is a remodeling suppressant. SR does not substantially modify the surface extent of remodeling – neither the surface extent of bone formation nor the surface extent of bone resorption, each reflecting the birth rate of BMUs and their life span. Surfaces undergoing bone formation do not decrease because remodeling continues. This is not evidence of an anabolic

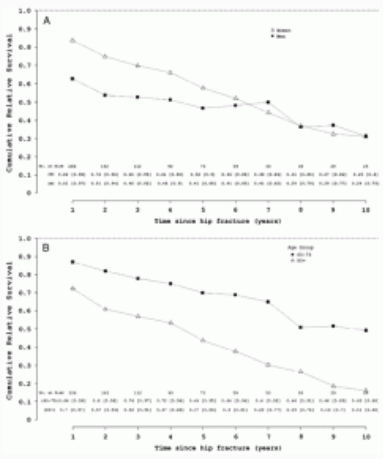
effect – there is no increase in MWT, indeed, there was a decrease. There is also no evidence of reduced surface extent of bone resorption.

The data, whilst based only on iliac crest bone, call to question the notion that SR is a dual acting drug. It seems reasonable to infer this drug reduces fracture risk but it is likely to be due to changes in morphology produced by the cellular machinery of bone remodeling. This drug does not appear to substantially affect bone remodeling. It is likely to mediate its benefits by influencing the matrix properties of bone – a worthwhile and important distinction from other therapies. The authors are to be congratulated in performing this important study.

Morbidity and Mortality

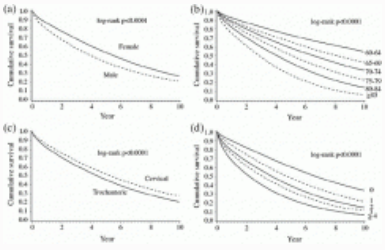
Frost et al report that in over 2000 elderly men and women followed for 21 years, 151 women and 55 men sustained a hip fracture. Death occurred in 86 (57%) women and 36 (66%) men (2). The cumulative relative survival post hip fracture at 1, 5 and 10 years was 0.83 (0.76-0.89), 0.59 (0.48-0.68), and 0.31 (0.20-0.43), respectively, in women and 0.63 (0.48-0.75), 0.48 (0.32-0.63), and 0.36 (0.18-0.56) in men. After hip fracture, women died 4.1 (IQR 1.7-7.8) years earlier, and men died 4.8 (IQR 2.4-7.0) years earlier than expected. For every 6 women and for every 3 men with hip fracture, one extra death occurred above that expected in the population.

Figure 1. Plots of relative survival following hip fracture comparing women and men (panel A) and age groups (panel B). Observed survival and [expected survival] added to the bottom of each plot. Reproduced from Bone, 56:23-9, Copyright (2013), with permission from Elsevier.



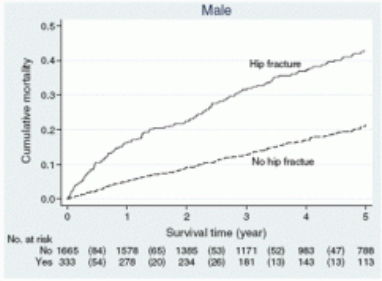
Few studies report mortality of hip fracture among Asian populations. **Wang et al** report that among 143,595 patients with hip fracture, from 1999-2005, hip fracture incidence increased and then fluctuated after 2006 (3). From 1999-2009, annual mortality decreased from 18.10% to 13.98%, and the male-to-female ratio of annual mortality increased from 1.38 to 1.64, while the annual SMR decreased from 13.80 to 2.98. Follow-up SMR at 1, 2, 5, and 10 years postfracture was 9.67, 5.28, 3.31, and 2.89, respectively. Females had higher follow-up SMR in the younger age groups (60-69 years of age) but lower follow-up SMR in the older age groups (over 80 years of age) relative to males. Hip fracture affects short-term but not long-term mortality.

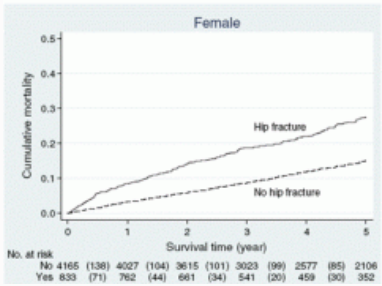
Figure 2. Ten-year overall survival curves by (a) gender, (b) age group, (c) fracture type, and (d) CCI number. Reproduced from Bone, 56:147-53, Copyright (2013), with permission from Elsevier.



To determine all-cause and cause-specific mortality risk in the first 5 years after hip fracture in an Asian Chinese population, **Koh et al** studied 63,257 middle-aged and elderly Chinese men and women in Singapore followed for hip fracture and death (4). 1,166 hip fracture cases were matched with 5 nonfracture subjects by age and sex. Increase in all-cause mortality risk persisted 5 years after hip fracture, aHR=1.58 [1.35-1.86] for females and aHR=1.64 [1.30-2.06] for males. Men had higher risk for mortality risk after hip fracture from stroke and cancer up to one year postfracture, but women with hip fracture had higher coronary artery mortality risk for 5 years postfracture. Men had higher risk of death associated with pneumonia while women had increased risk of death associated with urinary tract infections. All-cause mortality risk persisted for 5 years after hip fractures in men and women.

Figure 3. Cumulative incidence of all-cause mortality according to hip fracture for males and females. Reproduced from Osteoporos Int 2013;24:1981-9 with permission from Springer.





Roux et al report that 1822 fractures occurred (57% minor nonhip, nonvertebral [NHNV] – wrist/hand, ankle/foot, rib/clavicle; 26% major NHNV – pelvis/leg, shoulder/arm; 10% spine; 7% hip) in 50,461 postmenopausal women over one year (5). Health-related quality of life was analyzed using the EuroQol EQ-5D tool and the SF-36 health survey. Spine fractures had the greatest detrimental effect on EQ-5D, followed by major NHNV and hip fractures. Decreases in physical function and health status were greatest for spine or hip fractures.

Figure 4. Distribution of incident fracture types. Major NHNV pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow; minor NHNV wrist, hand, ankle, foot, rib, and clavicle. Reproduced from Osteoporos Int 2012;23:2863-71 with permission from Springer.

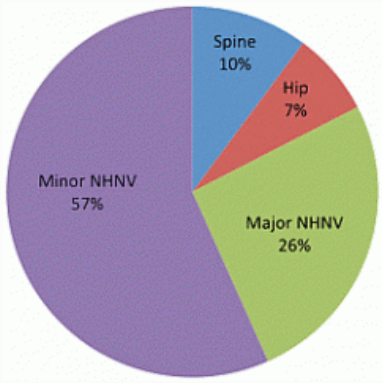


Figure 5. Distribution of incident fracture types. NHNV nonhip, nonvertebral. Reproduced from Osteoporos Int 2012;23:2863-71 with permission from Springer.

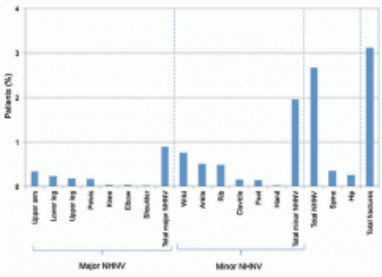
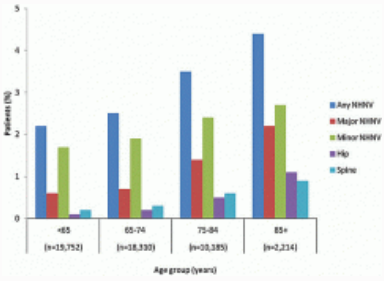
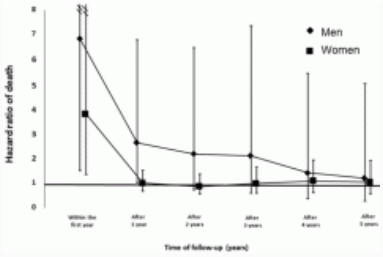


Figure 6. One-year incidence of fractures in GLOW by age group. Reproduced from Osteoporos Int 2012;23:2863-71 with permission from Springer.



Michaelsson et al reported that in 286 hip fracture discordant monozygotic twins, 143 twins with a hip fracture died (50%) compared to 101 twins (35%) without a hip fracture (6). Through the first year after hip fracture, the rate of death was 4-fold in women (HR 3.71; 95% CI 1.32-10.40) and 7-fold in men (HR 6.67; 1.47-30.13). The high rate in women only persisted during the first year after hip fracture, whereas the corresponding HR in men was 2.58 (95% CI 1.02-6.62). The higher risk in men after the hip fracture event attenuated during follow-up. After 5 years, the hazard ratio in men with a hip fracture was 1.19 (95% CI 0.29-4.90). On average, hip fracture contributed to 0.9 years of life lost in women (95% CI 0.06-1.7) and 2.7 years in men (95% CI 1.7-3.7). The potential years of life lost associated with the hip fracture was pronounced in older men (>75 years), with an average loss of 47% (95% CI 31-61) of the expected remaining lifetime.

Figure 7. Hazard ratios (HRs) of death after hip fracture analyzed by pairwise Cox regression analysis in identical twin pairs discordant for hip



fracture by sex and time of follow-up. The HRs were adjusted by a propensity score that included age, number of comorbidities, Charlson index, smoking status, physical activity level, visual impairment, hearing aid, marital status, use of estrogen replacement therapy, any prescribed medication, nonprescribed medication or supplement use, present use of corticosteroids, BMI, weight, height, abstainer, alcohol or drug abuse, any psychiatric disease, and an index for activity of daily living (ADL). Reproduced from J Bone Miner Res 2013;doi:10.1002/jbmr.2029 with permission of the American Society of Bone and Mineral Research.

Genetics of Bone Microstructure

To differentiate genetic determinants of cortical volumetric BMD (vBMD), trabecular vBMD, and bone microstructural traits, **Paternoster et al** reported cortical vBMD GWA meta-analysis (n=5878) followed by replication (n=1052) and identified genetic variants in 4 loci (RANKL, rs1021188; LOC285735, rs271170; OPG, rs7839059; and ESR1/C6orf97, rs6909279) (7). Trabecular vBMD GWA meta-analysis (n=2500) followed by replication (n=1022) identified one locus (FMN2/GREM2, rs9287237). In a subset of the GOOD cohort (n=729), rs1021188 was associated with cortical porosity while rs9287237 was associated with trabecular BV/TV. The genetic variant in the FMN2/GREM2 locus was associated with fracture in the MrOS Sweden (HR per extra T allele 0.75, 0.60-0.93) and GREM2 expression in human osteoblasts. Thus genetic variants associated with cortical and trabecular bone differed. The authors propose that a genetic variant in the RANKL locus influences cortical vBMD partly via effects on porosity, and a genetic variant in the FMN2/GREM2 locus influences GREM2 expression in osteoblasts and trabecular number and thickness and fracture risk.

Fragility Originates During Growth

Chevalley et al report that in 196 healthy premenopausal women aged 45.9±3.7 (±SD) years with (FX, n=96) and without (NO-FX, n=100) a history of fracture, differences in T-scores were: radial metaphysis: aBMD, -0.24; cortical vBMD, -0.38; cortical thickness, -0.37; cross-sectional area, +0.24; and endosteal perimeter, +0.28; stiffness, -0.15; failure load, -0.14; and apparent modulus, -0.28 trabecular vBMD, while thickness did not differ (8). The risk of fracture for 1 SD decrease in radius bone parameters was: radial metaphysis aBMD: 1.70 (1.18-2.44); cortical vBMD: 1.86 (1.28-2.71); cortical thickness: 2.36 (1.53-3.63), stiffness: 1.66 (1.06-2.61); failure load: 1.59 (1.02-2.47); and apparent modulus: 1.76 (1.17-2.64).

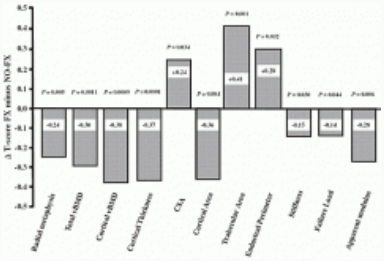


Figure 8. Difference in bone variable T-scores between healthy premenopausal women with (FX) and without (NO-FX) a history of fracture. The absolute differences and the probability (P) of statistical significance are indicated within each and above each column, respectively. These differences were adjusted for age, menarcheal age, height, weight, calcium and protein intakes, and physical activity. Reproduced from Bone, 55:377-83, Copyright (2013), with permission from Elsevier.

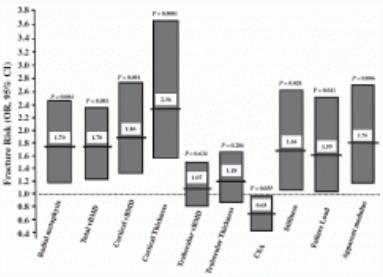
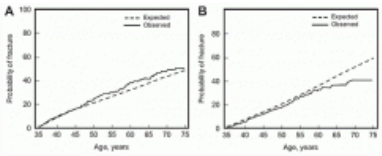


Figure 9. Risk of fracture in healthy premenopausal women for 1 SD decrease in radial aBMD or in microstructure and strength variables of the distal radius. Each column corresponds to odds ratios ±95% CI (horizontal line=mean) adjusted for age, menarcheal age, height, weight, calcium and protein intakes, and physical activity. The probability (P) of statistical significance is indicated above each column. Reproduced from Bone, 55:377-83, Copyright (2013), with permission from Elsevier.

Amin et al report that in 1776 children ≤18 years of age, from Olmsted County, MN who had a distal forearm fracture in 1935-1992, fractures occurring at age ≥35 years were identified and standardized incidence ratios [SIR] assessed (9). In 1086 boys (mean±SD age; 11±4 years) and 690 girls (10±4 years) followed for 27,292 person-years after age 35 years, fractures were observed in 144 (13%) men and 74 (11%) women, men (SIR, 1.9; 95% CI 1.6-2.3) but not women (SIR, 1.0; 95% CI 0.8-1.2). Fragility fractures at both major osteoporotic (hip, spine, wrist, and shoulder) sites (SIR, 2.6; 95% CI 2.1-3.3) and remaining sites (SIR, 1.7; 95% CI 1.3-2.0) were increased in men, irrespective of age at distal forearm fracture as boys. A distal forearm fracture in boys, not girls, is associated with an increased risk for fractures as adults.

Figure 10. Observed compared to expected cumulative incidence of fracture in age >35 years among Olmsted County, MN residents with a first distal forearm fracture in 1935–1992 at age ≤18 years and who had follow-up to at least



age 35 years, by age, and separately for men (A) and women (B). Reproduced from J Bone Miner Res 2013;28:1751-9 with permission of the American Society of Bone and Mineral Research.

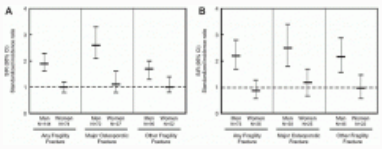


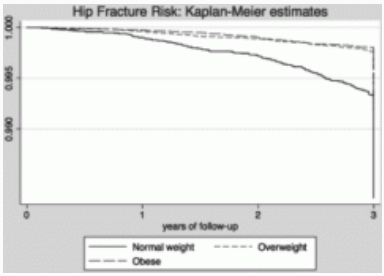
Figure 11. Standardized incidence ratio (SIR) for the risk of future fragility fracture occurring at age ≥35 years (A) or age ≥50 years (B) for Olmsted County, MN men and women following a distal forearm fracture in childhood at age ≤18 years in 1935–1992. Reproduced from J Bone Miner Res 2013;28:1751-9 with permission of the American Society of Bone and Mineral Research.

Kim et al used HR-pQCT to determine whether differences in macro- and microstructure, BMD, and bone strength at the distal radius were apparent in Asian (n=91, 53 males, 38 females, [mean ±SD] 17.3±1.5 years) and white (n=89, 46 males, 43 females, 18.1±1.8 years) adolescents and young adults (10). In males, Asians had 11% greater Tt.BMD, 8% greater Ct.BMD, and 25% lower Ct.Po than whites. Asians had 9% smaller Tt.Ar and 27% greater Ct.Th. In females, Asians had smaller Tt.Ar than whites (16%), but this difference was not significant after adjusting for covariates. Asian females had 5% greater Ct.BMD, 12% greater Ct.Th, and 11% lower Tb.Sp than whites. Estimated bone strength did not differ between Asian and white males or females. Smaller bones have, on average, more dense, less porous, and thicker cortices.

The Bigger They Are The Harder They Fall?

Premaor et al categorized 139,419 (74.9%) men as underweight/normal (BMI<25, n=26,298), overweight (25-30, n=70,851), and obese (BMI>30, n=42,270) (11). Spine and hip fractures were fewer in obese (RR 0.65; 0.53-0.80 and RR, 0.63; 0.54-0.74, respectively), and overweight (RR, 0.77, 0.64-0.92 and RR, 0.63; 0.55-0.72, respectively) relative to underweight/normal men. Obese men had fewer wrist/forearm (RR, 0.77; 0.61-0.97) and pelvic (RR, 0.44; 0.28-0.70) fractures. Multiple rib fractures were more frequent in overweight (RR, 3.42; 95% CI 1.03-11.37) and obese (RR, 3.96; 95% CI 1.16-13.52) men.

Figure 12. Kaplan-Meier estimates of hip fracture probability according to BMI WHO category. Reproduced from J Bone Miner Res 2013;28:1771-7 with permission of the American Society of Bone and Mineral Research.



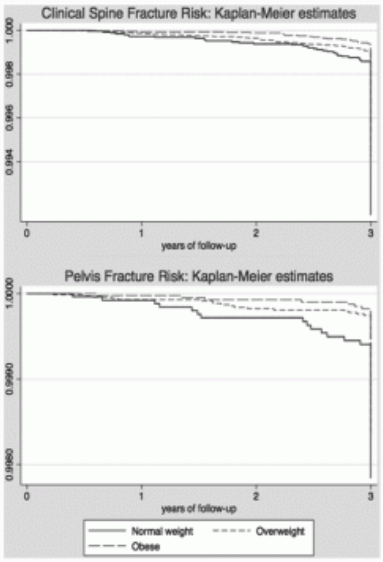


Figure 13. Kaplan-Meier estimates of clinical spine and pelvis fracture probability according to BMI WHO category. Reproduced from J Bone Miner Res 2013;28:1771-7 with permission of the American Society of Bone and Mineral Research.

Johansson et al reported that among 398,610 women, average age of 63 years, followed 2.2 million person-years, 30,280 fractures (6457 hip) were observed (12). Obesity (BMI>30) was present in 22%. 81% of all fractures and 87% of hip fractures arose in nonobese women. Relative to a BMI of 25, a BMI of 35 was protective HR 0.87 (0.85-0.90) and 1.16 (1.09-1.23) adjusted for BMD but was a risk factor for upper arm (humerus and elbow) fracture. When adjusted for BMD, high BMI remained a risk factor for upper arm fracture but was also a risk factor for all osteoporotic fractures. Low BMI was a risk factor for hip and all fracture, but protective for lower leg fracture. When adjusted for BMD, low BMI remained a risk factor for hip fracture but was protective for osteoporotic fracture, tibia and fibula fracture, distal forearm fracture and upper arm fracture. At a population level, high BMI remains a protective factor for most sites.

Figure 14. Relationship between BMI and risk of fracture (HR vs. BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age and time since baseline. Reproduced from J Bone Miner Res 2013;doi:10.1002/jbmr.2017 with permission of the American Society of Bone and Mineral Research.

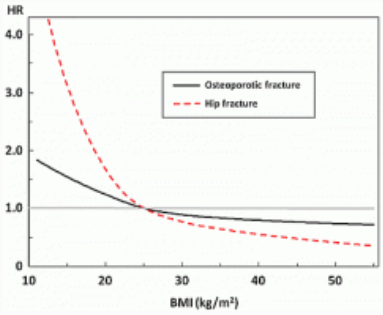
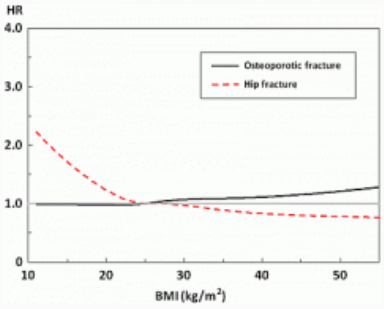


Figure 15. Relationship between BMI and risk of fracture (HR vs. BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age, time since baseline and BMD. Reproduced from J Bone Miner Res 2013;doi:10.1002/jbmr.2017 with permission of the American Society of Bone and Mineral Research.



Compston et al report that among 52,939 women, 3628 (6.9%) had an incident clinical fracture during 3 years (13). BMI showed an inverse association with hip, clinical spine, and wrist fractures: HRs per increase of 5 kg/m^2 were 0.80 (0.71-0.90), 0.83 (0.76-0.92), and 0.88 (0.83-0.94), respectively. For ankle fractures, HR per 5-kg increase 1.05 (1.02-1.07). For upper arm/shoulder and clavicle fractures, only linear height was associated: adjusted HRs per 10-cm increase were 0.85 (0.75-0.97) (p=0.02) and 0.73 (0.57-0.92), respectively. For pelvic and rib fractures, the best models were for nonlinear BMI or weight (p=0.05 and 0.03, respectively), with inverse associations at low BMI/body weight and positive associations at high values. The relationships between fracture and weight, BMI, and height are site-specific.

Taller women are at increased risk for fracture. As wider bones require less material to achieve a given bending strength, **Bjornerem et al** hypothesized that taller women assemble bones with relatively thinner and more porous cortices (14). In a twin study of 345 females aged 40-61 years, 93 with at least one fracture, each SD greater height was associated with a 0.69 SD larger tibia total cross-sectional area (CSA), 0.66 SD larger medullary CSA, 0.50 SD higher medullary CSA/total CSA and 0.42 SD higher porosity (all p<0.001). Cortical area was 0.45 SD larger in absolute terms but 0.50 SD smaller in relative terms. In multivariable analyses, distal tibia, medullary CSA/total CSA, and porosity predicted fracture independently; height was no longer significant. Each 1 SD greater porosity was associated with fracture; distal tibia, OR=1.55 (95% CI 1.11-2.15); distal fibula, OR=1.47 (95% CI 1.14-1.88); and distal radius, OR=1.22 (95% CI 0.96-1.55). Taller women assemble wider bones with relatively thinner and more porous cortices predisposing to fracture.

Figure 16. Distal tibia total CSA, medullary CSA, medullary CSA/total CSA and cortical CSA/total CSA as a function of height (upper panels). Cortical porosity as a function of height, total CSA, medullary CSA/total CSA, a measure of relatively cortical thickness and cortical CSA/total CSA (lower panel). Reproduced from J Bone Miner Res 2013;28:2017-26 with permission of the American Society of Bone and Mineral Research.

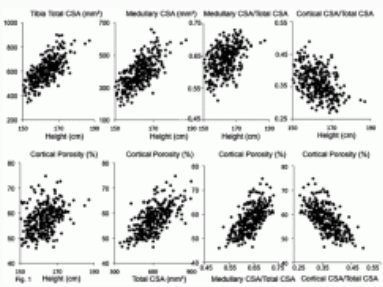
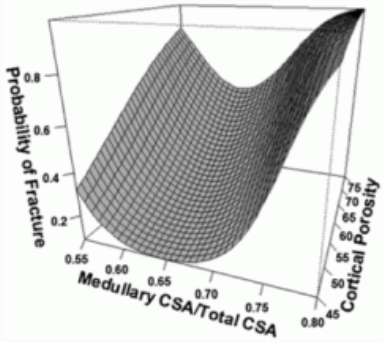


Figure 17. Higher probability of fracture is

associated with a higher cortical porosity and a larger ratio of medullary CSA to total CSA, a surrogate reflecting a relatively thinner cortex. Reproduced from J Bone Miner Res 2013;28:2017-26 with permission of the American Society of Bone and Mineral Research.



Bone Remodeling Markers as Independent Predictors of Fracture

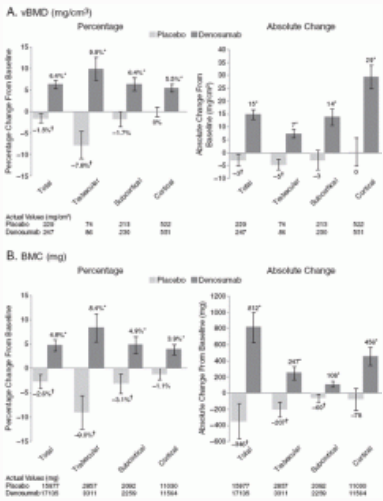
Tamaki et al evaluated how bone turnover predicts vertebral fracture risk in postmenopausal women during 10 years after adjusting for age and femoral neck bone mineral density in 522 postmenopausal women, with no diseases or medications affecting bone metabolism (15). Vertebral fractures were ascertained in three follow-up surveys (1999, 2002, and 2006). Initial fracture events were diagnosed morphometrically. 83 fracture events were diagnosed over a median follow-up period of 10.0 years. RR per SD for BAP was 4.38 (1.45, 13.21) among 65 subjects with years since menopause (YSM) <5 years. RRs per SD for BAP, tDPD, and fDPD were 1.39 (1.12, 1.74), 1.32 (1.05, 1.67), and 1.40 (1.12, 1.76), respectively, among 457 subjects with YSM ≥5 years. Of the 451 women followed at least once until 2002, RRs per SD for BAP, tDPD, and fDPD over 6 years were not significantly different from those over 10 years.

Denusumab and the Appendicular Skeleton

Simon et al examined the effects of denosumab on radius cortical and trabecular bone density, mass, and strength, and wrist fracture incidence in the FREEDOM. Radius BMD and polar moment of inertia were evaluated in two prespecified substudies (placebo, n=209; denosumab, n=232) or quantitative CT (placebo, n=48; denosumab, n=62). Prespecified analysis assessed wrist fracture incidence in all FREEDOM participants (placebo, N=3906; denosumab, N=3902), and post hoc subgroup analyses evaluated those with higher fracture risk (baseline femoral neck T-score<2.5; placebo, N=1406; denosumab, N=1384) (16). Denosumab increased aBMD and vBMD, BMC, and polar moment of inertia compared with placebo, in radius cortical and trabecular bone. Wrist fracture incidence was 2.9% for placebo and 2.5% for denosumab (RR reduction, 16%; P=0.21) on month 36. Participants with a femoral neck T-score<2.5 were at increased risk for wrist fracture, and denosumab reduced wrist fracture incidence (placebo, 4.0%; denosumab, 2.4%; RR reduction, 40%; absolute risk reduction, 1.6%; P=0.03).

Genant et al report that in the FREEDOM study, hip QCT was performed at baseline and months 12, 24, and 36 months in placebo (N=26) and denosumab (N=36) groups (17). Denosumab resulted in improvements in total hip integral vBMD and BMC. At month 36, the mean percentage increase from baseline in total hip integral vBMD and BMC was 6.4% and 4.8%, respectively. These gains were accounted for by increases in vBMD and BMC in the trabecular, subcortical, and cortical compartments. In the placebo, total hip integral vBMD and BMC decreased at month 36 by -1.5% and -2.6%, respectively. The differences between denosumab and placebo were also significant for integral, trabecular, subcortical, and cortical vBMD and BMC.

*Figure 18. QCT MIAF percentage and absolute changes in hip vBMD and BMC at month 36. A. vBMD (mg/cm^3). B. BMC (mg). Least-squares means, 95% CIs, and p-value from analysis of covariance model are presented. *p<0.0001 compared with both baseline and placebo; †p<0.05 compared with baseline. Month 12, n=60; month 24, n=59; month 36, n=62. BMC, bone mineral content; MIAF, Medical Image Analysis Framework; QCT, quantitative computed tomography; vBMD, volumetric bone mineral density. Reproduced from Bone, 56:482-8, Copyright (2013), with permission from Elsevier.*



Suppressed Lymphangiogenesis and ONJ

Kuroshima et al report that in mice receiving zoledronic acid (ZA) with cytotoxic drug melphalan, or dexamethasone, first molars were extracted 3 weeks after the initiation of treatment and

wound healing assessed at 4 weeks post-extractions. Mice receiving ZA and melphalan developed ONJ, while ONJ-like lesions were not found in mice on ZA or melphalan, or the combination of ZA and dexamethasone. Lymphatic vessel formation was suppressed with decrease in F4/80(+) macrophages VEGFC. Suppressed lymphatics were also found in the draining lymph nodes of mice on ZA and melphalan (18).

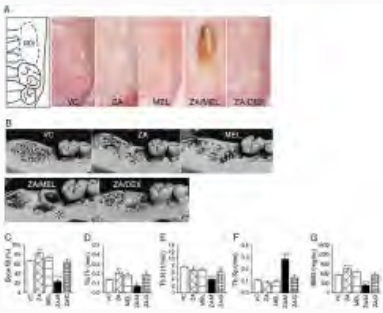


*Figure 19. µCT assessment of tooth extraction sockets. (A) Gross healing of tooth extraction wounds at 4 weeks. Gross healing in the ZA, MEL, and ZA/DEX groups was normal and similar to VC, while healing was impaired and exhibited ONJ-like lesions in the ZA/MEL group. ROI indicates tooth extraction wounds. (B) Representative reconstructed µCT images of extraction sockets. Scant bone fill (*) was noted in the ZA/MEL group while the extraction sockets were mostly filled with trabecular bone in all other groups. (C) Quantitatively, ZA/MEL treatment significantly suppressed bone fill in the sockets while ZA treatment enhanced bone fill. (D) Trabecular bone was significantly thinner in the ZA/MEL group and thicker in both the ZA and ZA/DEX groups compared to VC. (E) The numbers of trabeculae was significantly lower in the ZA, ZA/MEL, and ZA/DEX groups vs. VC. (F) Trabecular bone separation was similar between groups except the ZA/MEL group. (G) ZA treatment enhanced BMD while ZA administered with melphalan decreased BMD. n=7/group, *p<0.05, **p<0.01, ***p<0.001. Reproduced from Bone, 56:101-9, Copyright (2013), with permission from Elsevier.*

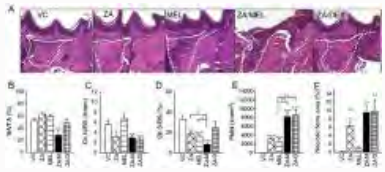


*Figure 20. Histomorphometric assessments of the tooth extraction wounds. (A) The dotted line outlines the original extraction sockets and the solid line indicates the newly formed bone level. Nearly no bone fill and a lack of the epithelium were observed in the ZA/MEL group, while the sockets were filled with new bone in the all other groups. (B) Bone fill (BA/TA) was significantly lower in the ZA/MEL group vs. VC. (C) The osteoclast perimeters (Oc.N/BS) were significantly lower in the ZA, ZA/MEL, and ZA/DEX groups, but not in the MEL group. (D) The osteoblast surface (Ob.S/BS) was significantly lower in the ZA, MEL, and ZA/MEL groups vs. VC, while ZA/DEX treatment had no effect on the osteoblast surface. (E) The connective tissue of the extraction wounds was assessed. Minimal PMN infiltration was noted in the VC group, while significant PMN infiltration was observed in the ZA, MEL, ZA/MEL, and ZA/DEX groups. Immense PMN infiltration was noted in the combination treatment groups (ZA/MEL and ZA/DEX). (F) Significantly larger necrotic bone area was noted in the ZA, ZA/MEL, and ZA/DEX groups vs. VC. n >8/group, *p<0.05, **p<0.01, ***p<0.001. Reproduced from Bone, 56:101-9, Copyright (2013), with permission from Elsevier.*

Noninferiority of Ibandronate versus Risedronate

Nakamura et al report that patients aged ≥60 years were randomized to 0.5 or 1 mg/month i.v. ibandronate (IBN) plus oral placebo or 2.5 mg/day risedronate plus i.v. placebo over 3 years (19). 1265 patients were randomized. A total of 1134 patients formed the per-protocol set. Both IBN doses were noninferior to risedronate: 0.5 mg, HR 1.09 (0.77-1.54); 1 mg, HR 0.88 (0.61-1.27). The rate of first new vertebral fracture over 3 years was 16.8 % (12.8-20.8) for 0.5 mg IBN, 11.6 % (8.2-15.0) for 1 mg IBN, and 13.2 % (9.6-16.9) for risedronate. Analyses in women only showed similar results to the overall population.

Ibandronate and Tissue Mineralization Density

Misof et al examined the effects of 24 months IBN (3 mg/3 ml intravenously every 3 months) on material quality in 19 men with OP within an open-label, single-center, prospective phase III study (20). At baseline, cancellous bone matrix mineralization from mOP was lower than reference data (Cn.CaMean -1.8%). IBN increased calcium concentrations (Cn.CaMean +2.4%, Ct.CaMean, +3.0% both p<0.01), and reduced heterogeneity of mineralization (Cn.CaWidth -14%, p=0.044; Ct.CaWidth, -16%, p=0.001) leading to cancellous BMDD within normal range. IBN was associated with a decrease in porosity (-25%, p=0.01), increases in BMD at the lumbar spine, the femoral neck and the total hip (+3.3%, +1.9%, and +5.6%, respectively) and reductions in CTX (-37.5%), P1NP (-44.4%), and OC (-36.3%).

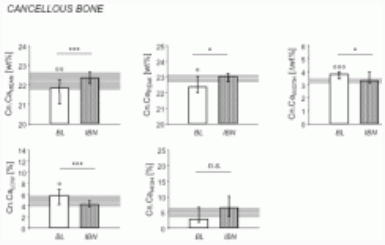


*Figure 21. Cancellous BMDD results (median (25th, 75th percentile)) for mOP (BL, white=baseline; IBA, dark grey=after 24 months with intravenous IBA). White dotted lines and grey areas in the background indicate mean ±1SD or median (25th, 75th percentile) of the normal reference range (from 19). ***p<0.001, *p<0.05 paired comparison vs. baseline (treatment effect), and °°°p<0.001, °°p<0.01, °p<0.05 vs. reference BMDD. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2035 with permission of the American Society of Bone and Mineral Research.*

Bisphosphonates and Bowel Cancer

Passarelli et al evaluated the association between oral bisphosphonate use and colonorectal cancer (CRC) incidence in 156,826 postmenopausal women, ages 50-79 years in the WHI trials (21). 1931 women were diagnosed with incident invasive CRC during a median follow-up of 12 years. Alendronate accounted for >90% of the total person-years of use. The association between oral bisphosphonate use and CRC risk (HR=0.88; 95%CI 0.72-1.07; p=0.19).

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OVERVIEW, VOL 13, ISSUE 9

Ego Seeman

Editor

By Ego Seeman Mon, 09/30/2013 - 08:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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Fracture Rates
Are they declining?

Amin et al report that during three years, 3549 residents ≥50 years of age experienced 5244 fractures (1). The age- and sex-adjusted incidence of any fracture was 2704 per 100,000 person-years (95% CI 2614-2793) and that for all fractures was 4017 per 100,000 (95% CI 3908-4127). Fracture incidence increased with age in both sexes, but was 49% greater in women. Overall, comparably adjusted fracture incidence rates increased by 11% (from 3627 to 4017 per 100,000 person-years; p=0.008) between 1989-1 and 2009-2011 mainly due to increases in vertebral fractures (+47% for both sexes combined), which was partially offset by a decline in hip fractures (-25%) among the women. There was also a 26% reduction in distal forearm fractures in the women; the increase in distal forearm fractures in men age 50+ years was not significant. The increase in vertebral fractures was attributable in part to incidentally diagnosed vertebral fractures.

BACK TO TOP

Of particular interest is the fall in hip fracture incidence which continues the steady decline observed in women in this community since 1950. More generally, the increases in the incidence of fractures at many skeletal sites observed decades ago have stabilized. The question is why. If there is a secular change in fracture incidence this may be the result of changes in peak bone strength in later bone generations, less bone loss or fewer falls. The challenge is how to explore these factors.

Figure 1. Age-specific incidence of all distal forearm fractures among Olmsted County, Minnesota, women (A) and men (B) ≥50 years of age, comparing 2009-11 with comparable data from 1989-91. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2072 with

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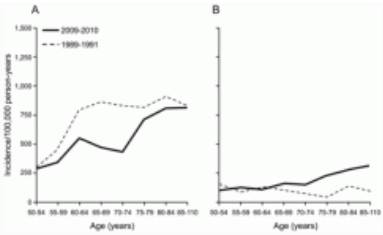
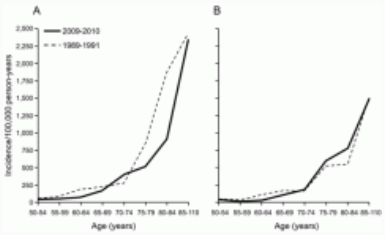


Figure 2. Age-specific incidence of all proximal femur fractures among Olmsted County, Minnesota, women (A) and men (B) ≥50 years of age, comparing 2009-11 with comparable data from 1989-91. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2072 with permission of the American Society of Bone and Mineral Research.



Testosterone for Lean Mass and Estrogen for Fat Mass in Men

Finkelstein et al treated 198 healthy men 20-50 years of age with goserelin (to suppress testosterone and estradiol) for 16 weeks and randomly assigned them to placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g/d of testosterone gel for 16 weeks (2). Another 202 healthy men received goserelin, placebo gel or testosterone gel, and anastrozole (to suppress the conversion of testosterone to estradiol). Percent body fat increased in groups receiving placebo or 1.25 or 2.5 g/d testosterone without anastrozole (mean testosterone level, 44±13, 191±78, and 337±173 ng/dl, respectively). Lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving 1.25 g of testosterone daily without anastrozole. Leg-press strength fell only with placebo. Sexual desire declined as the testosterone dose was reduced. The amount of testosterone required to maintain lean mass, fat mass, strength, and sexual function varied widely. Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency accounted for increases in body fat; and both contributed to the decline in sexual function.

Measurement of IGF-1, remodeling markers would have been of interest to determine whether changes in lean mass associated with testosterone deficiency were accounted for by lower levels of IGF-1 and if so, whether this may be attributable to the concomitant estrogen deficiency. Similarly, changes in remodeling markers might be insightful as acute estrogen deficiency appears to modify the life span of osteoclasts and osteoblasts in opposite directions, at least transiently. A shortening of the lifespan of osteoblasts and lengthening of the lifespan of osteoclasts might contribute to acute changes in bone loss, even in a short period of 16 weeks. The data suggest a more favorable approach to treatment of hypogonadism in men being aromatizable androgens over nonaromatizable androgens given the deleterious effects of estrogen deficiency in several endpoints. While of great interest, this will require trials designed to examine safety as well as efficacy.

Figure 3. Mean serum testosterone and estradiol levels from weeks 4-16, according to testosterone dose and cohort. T bars indicate standard errors. From N Engl J Med, Finkelstein JS et al, Gonadal steroids and body composition, strength, and sexual function in men, 369, 1011-22 Copyright © (2013) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

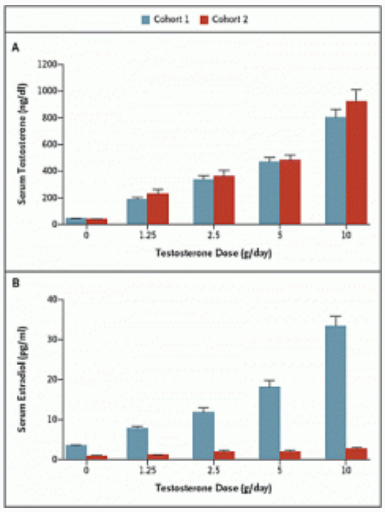
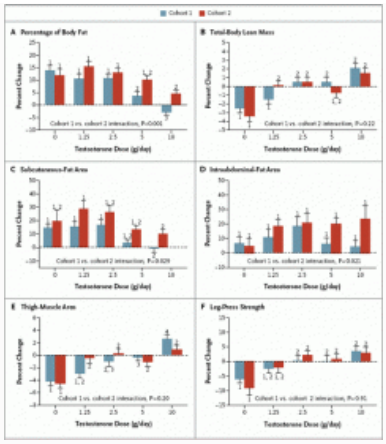


Figure 4. Mean percent change from baseline in percentage of body fat, lean body mass, subcutaneous- and intraabdominal-fat area, thigh-muscle area, and leg-press strength, according to testosterone dose and cohort. T bars indicate standard errors. Within each cohort, bars with the same number indicate no significant difference between dose groups. For example, the change in the percentage of body fat (Panel A) did not differ significantly among the groups that received 0 g, 1.25 g, or 2.5 g of



testosterone daily in cohort 1 (all labeled '1'). The change in each of those three groups differed significantly from the change in the group that received 5 g per day (labeled '2') and the change in the group that received 10 g per day (labeled '3'), and the change also differed significantly between these latter two groups. P values are for the cohort-testosterone dose interaction terms in analyses of variance comparing changes in each outcome measure between cohorts 1 and 2. From N Engl J Med, Finkelstein JS et al, Gonadal steroids and body composition, strength, and sexual function in men, 369, 1011-22 Copyright © (2013) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Genetic Factors Contribute to Variance in Microstructure

Variance in many traits is large; individuals vary several fold in bone size and mass, and in the rate of bone remodeling as reflected in measurements of bone remodeling markers. In many of these skeletal traits, a large proportion of the variance is accounted for by difference in genetic factors. That is, individuals differ from each other more due to differences in their genetic makeup than due to differences in life style factors. **Havell et al** examined right femurs from 101 baboons (74 females, 27 males; aged 7-33 years) from a single, extended pedigree to determine osteon number, osteon area (On.Ar), Haversian canal area, osteon population density, percent osteonal bone (%On.B), wall thickness (W.Th), and cortical porosity (Ct.Po) (3). Significant age and sex effects account for 9 (Ct.Po) to 21% (W.Th) of intracortical microstructural variation. After accounting for age and sex, genetic effects were evident for On.Ar (h^2=0.79, p=0.002), %On.B (h^2=0.82, p=0.003), and W.Th (h^2=0.61, p=0.013), indicating that 61-82% of the residual variation (after accounting for age and sex effects) is due to additive genetic effects. This corresponds to 48-75% of the total phenotypic variance. Thus, normal, population level variation in cortical microstructure in these subhuman primates is influenced by genes. This likely to be the same in human subjects. As a critical mediator of crack behavior in bone cortex, intracortical microstructural variation provides another mechanism through which genetic variation may affect fracture risk.

Racial Differences in Cortical Porosity and Tissue Mineral Density

Boutroy et al explored whether greater Ct.BMD in Chinese-American women is due to greater tissue mineral density (TMD) or reduced cortical porosity (Ct.Po) (4). 78 Chinese-American women (49 pre- and 29 postmenopausal) and 114 white women (46 pre- and 68 postmenopausal) were studied. Premenopausal Chinese-American vs. white women had greater Ct.Th, Ct.BMD and Ct.TMD at the radius and tibia; and decreased Ct.Po (p<0.05). A similar pattern was observed between postmenopausal Chinese-American and white women. Postmenopausal vs. premenopausal women had lower Ct.BMD at the radius and tibia in both races (p<0.001). Ct.Po increased between pre- and postmenopausal women, while Ct.TMD decreased by 3-8% (p<0.001) in both races. Age-related differences in Ct.Po and Ct.TMD did not differ by race.

The implications are of interest. First, differences in cortical porosity and tissue density may be achieved during growth. If so the implication is that Chinese-Americans assemble a smaller skeleton but the relatively thicker and less porous more mineralized cortex is achieved by excavation of a smaller medullary canal and fewer osteons (the main determinant of porosity being the Haversian and Volkmann canal density). Studies during growth to examine whether lower remodeling rate, an earlier menarche or both may achieve these morphological features. Second, if this is correct, then at menopause, Chinese-Americans might also experience lower rates of bone loss; this is a good thing because their more robust skeleton will undergo less bone loss and might be more resistant to the limited structural decay resulting.

Figure 5. Adjusted difference in SD, between Chinese-American and White women by menopausal status, at the radius and tibia. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2057 with permission of the American Society of Bone and Mineral Research.

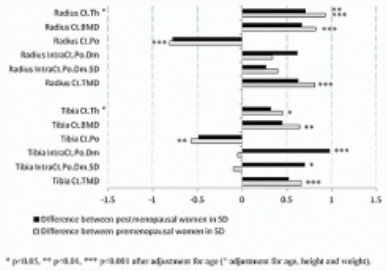
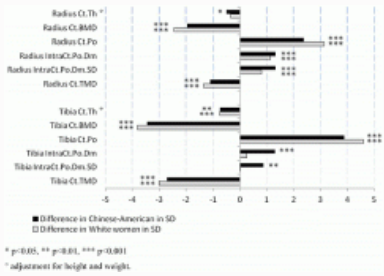


Figure 6. Difference in SD, between pre- and postmenopausal women by race, at the radius and tibia. Reproduced from J Bone Miner Res 2013; doi:10.1002/jbmr.2057 with permission of the American Society of Bone and Mineral Research.

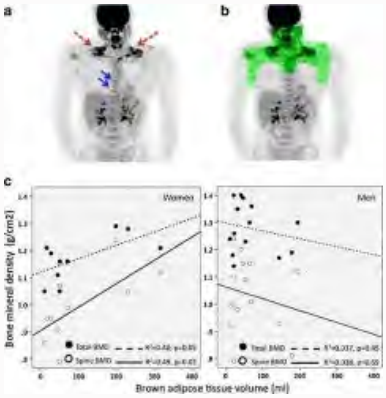


Marrow Fat
Confounder or independent variable?

Bone marrow fat (BMF) and BMD are negatively correlated. **Schwartz et al** assess relationships between vertebral BMF, BMD by QCT, and fracture in a cross-sectional study in 257 participants mean age 79 (SD 3.1) years from the Age Gene/Environment Susceptibility-Reykjavik cohort (5). Outcomes included vertebral BMF (L1-L4) measured using magnetic resonance spectroscopy, QCT and DXA scans of the hip and spine, and DXA vertebral fracture assessments. BMF was 53.5±8.1% in men and 55.0±8.4% in women. Those with prevalent vertebral fracture (21 men, 32 women) had higher BMF adjusted for BMD. The difference was significant only in men (57.3 vs. 52.8%, P=0.02). BMF was associated with lower trabecular spine vBMD (-10.5% difference for each 1 SD increase in BMF, P<0.01), total hip, and femoral neck, but not cortical vBMD, in women. In men, BMF was associated with trabecular spine vBMD (-6.1%, P=0.05). Total hip and spine aBMD were negatively correlated with BMF in women only. The authors infer that higher marrow fat correlated with lower trabecular not cortical BMD in older women, not men. Higher marrow fat was associated with prevalent vertebral fracture in men, even after adjustment for BMD.

In animals, defective brown adipogenesis leads to bone loss. Whether brown adipose tissue (BAT) mass relates to BMD in humans was explored by **Lee et al** who determined the relationship between BAT mass and BMD by cold-stimulated positron-emission tomography (PET) and DXA (6). In 24 healthy adults (age 28±1 years, F 10), BAT volumes were 82.4±99.5 ml in women and 49.7±54.5 ml in men. Women had higher BAT activity, by 9.4±8.1% than men. BAT volume correlated positively with total and spine BMD in women and remained a predictor after adjustment for age, fat, and lean body mass. Total and spine BMD were higher in women with detectable BAT on PET images than those without by 11±2% and 22±2%, respectively. No associations were observed between BAT parameters and BMD in men. The data suggest that brown adipogenesis may be physiologically related to modulation of bone density. Thus, adipose tissue is not just a confounder and opens a door to another world of regulators of bone remodeling.

Figure 7. (a) PET image of a 20-year-old woman demonstrating FDG uptake in cervical–supraclavicular BAT depots (red arrows). Uptake was also evident within the vertebra (blue arrows) that harbored the bone marrow with BAT characteristic. (b) A representative image of BAT uptake and the three-dimensional reconstruction of the torso-mantle (green) that was constructed to allow quantification of FDG uptake within BAT-specific region. (c) Positive correlations between BAT volume with total and spine BMD in women (left), but not in men (right). Reproduced from Osteoporos Int 2013;24:1513-8 with permission from Springer.



Collagen and Bone Strength

Wegrzyn et al studied the role of matrix composition on vertebra mechanics in 17 fresh frozen human lumbar spines (8 W, 9 M, aged 76±11years) (7). Collagen maturity correlated with whole vertebra failure load and stiffness (r=0.64 and r=0.54, respectively). The collagen maturity, mass and microarchitecture explained 71% of the variability in whole vertebra strength. There was no association between the matrix characteristics, mass or microarchitecture, mineral maturity, mineralization and crystallinity index to whole vertebra mechanics.

The Howship's Lacuna Dimensions

Osteoclast resorption route starts perpendicularly to the bone surface, and continues parallel to the bone surface, forming a trench. **Soe et al** report that relative rates of collagenolysis vs. demineralization play a role in resorption patterns (8). On bone slices, round pits containing demineralized collagen suggest pits are generated when demineralization is faster than collagen degradation while elongated trenches without demineralized collagen suggesting collagen degradation is as fast as demineralization. Osteoclasts given low dose carbonic anhydrase inhibitor to slow demineralization allow collagen degradation to proceed as fast resulting in a two-fold increase in trenches. When decreasing the rate of collagenolysis using a cathepsin K inhibitor, trenches=0%, and round pits become half as deep. Osteocytes and bone lining cells

surrounding the osteoclast may act on this balance to steer the osteoclast resorptive activity in order to give the excavations a specific shape.

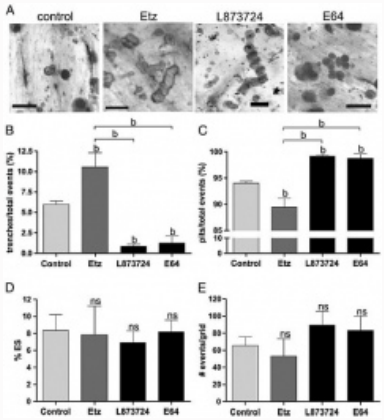


Figure 8. Effect of inhibitors of demineralization and collagenolysis on the relative numbers of resorption trenches and pits. Resorbing OCs were treated or not with (i) 0.74 µM ethoxyzolamide (Etz) to slightly slow down demineralization, (ii) 100 nM L1873724 to specifically inhibit CatK, or (iii) 48 µM E64 to inhibit CatK and other cysteine proteases. A) Representative images of toluidine blue-stained resorption cavities generated in these respective culture conditions. Scale bar=25 µm. B-E) Effect of the culture conditions on: B) the proportion of trenches expressed in percentage of the total number of resorption events, C) the proportion of pits expressed in percentage of the total number of resorption events, D) the percentage eroded surface (ES) per total bone surface, and E) the number of all resorption events per grid. The data are shown as mean±SD, n=5. Statistical analyses were done compared to control condition unless indicated otherwise: unpaired t-test, b: p<0.01, ns: not significant. Reproduced from Bone, 56:191-8, Copyright (2013), with permission from Elsevier.

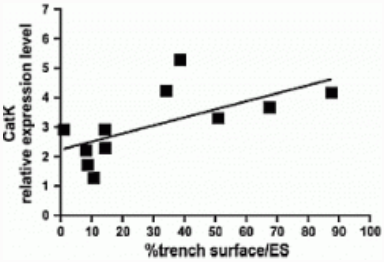


Figure 9. The levels of CatK expression correlate with the proportion of trenches and the degree of collagenolysis. The levels of CatK expression were evaluated byQ-RT-PCR in differentiated OCs from different blood donors. The analyses were normalized in two steps. In order to be able to compare the expression levels of different donors we prepared a reference standard curve from the same randomly selected donor for every gene tested. Thereafter, the CatK expression levels of the individual donor were normalized to the average expression levels of the housekeeping genes hGUS and hAbl. These adjusted CatK expression levels were plotted against the proportion of %trench surface/ES obtained from experiments with OCs of this particular donor. Statistics: Linear regression analysis, r^2=0.41, p=0.033. Reproduced from Bone, 56:191-8, Copyright (2013), with permission from Elsevier.

Antiresorptives Reduce BMU Depth

Antiresorptive agents reduce the rate of bone loss by reducing the number of remodeling sites initiating or progressing with resorption and replacement of bone upon the endosteal surface. The question is whether these agents also alter the balance between the volumes of bone resorbed and deposted by each BMU. There is not a great deal of information addressing this question.

Matheny et al explored whether antiresorptives reduce resorption depth by studying adult female rats (6 months) that were ovariectomized (n=17) or had sham surgery (SHAM, n=5) (9). One month later, the ovariectomized animals were separated into untreated (OVX, n=5), raloxifene (OVX+Ral, n=6) and risedronate (OVX+Ris, n=6). At 10 months of age, lumbar vertebrae were submitted to histomorphometry of individual resorption cavities and formation events. Maximum resorption depth did not differ in the SHAM (23.66±1.87 µm, mean±SD) and OVX (22.88±3.69 µm) groups but was smaller in the OVX+Ral (14.96±2.30 µm) and OVX+Ris (14.94±2.70 µm) groups (p<0.01). Antiresorptive treatment was associated with reductions in the surface area of resorption cavities and the volume occupied by each resorption cavity (p<0.01 each). The surface area and volume of individual formation events (double-labeled events) in the OVX+Ris group were reduced as compared to other groups (p<0.02).

This is a wonderful manuscript. Well worth reading. It is of interest that raloxifene treated animals showed similar amounts of bone remodeling (ES/BS and dLS/BS) compared to sham-operated controls but smaller cavity size (depth, breadth and volume). Thus, if remodeling rate is not reduced and the negative BMU balance is lessened but not abolished, bone loss will continue. In the case of raloxifene, this may account in part for the failure to demonstrate reduced hip and nonvertebral fractures.

Figure 10. Resorption cavities were identified as eroded surfaces in gray scale images (A) after examination at 2× magnification (B). Cavities were visualized in three-dimensions (C) and traced by a trained observer using gray scales images and the three-dimensional surface (D). Reproduced from Bone, 57:277-83, Copyright (2013), with permission from Elsevier.

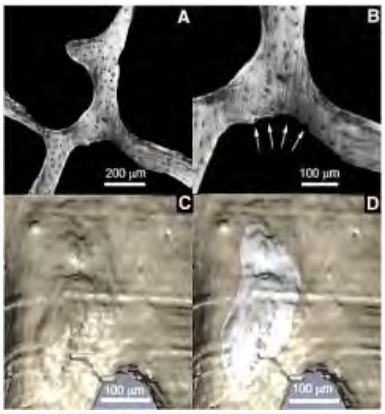
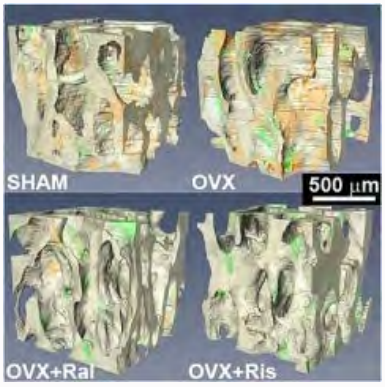


Figure 11. Three-dimensional images of cancellous bone fromthe rat lumbar vertebrae for the four groups are shownwith transparency to showregions of the first bone formation label (xylenol orange) and the second formation label (calcein green). Reproduced from Bone, 57:277-83, Copyright (2013), with permission from Elsevier.



Mineralization Kinetics in Murine Trabecular Bone

To measure how tissue mineral density (TMD) increases and how mineralization kinetics is influenced by mechanical stimulation **Lukas et al** assessed 15-week-old female mice (C57BL/6), where in one group the sixth caudal vertebra was mechanically loaded with 8N (10). Quiescent bone in the control group mineralize with a rate of 8±1 mgHA/cm^3 per week, about half that for newly formed bone. Mechanical loading increased the rate of mineral incorporation by 63% in quiescent bone. The week before resorption, demineralization could be observed with a drop of TMD by 36±4 mgHA/cm^3 in control and 34±3 mgHA/cm^3 in the loaded group.

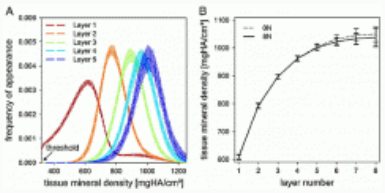
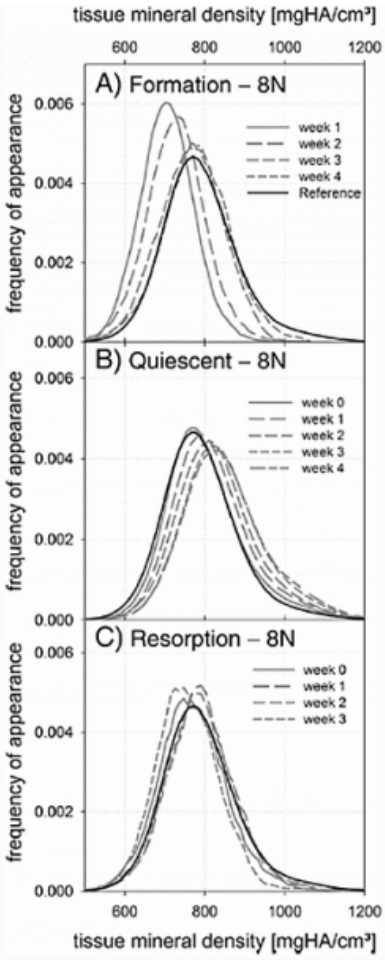


Figure 12. (A) Distributions of the tissue mineral density (TMD) for bone of the control group as a function of the layer number, i.e., the distance from the surface. The threshold value for the binarization of the µCT images (320 mgHA/cm^3) corresponds to the lowest value in the diagram. Error bars show the standard deviation. (B) Mean values and standard error of TMD as a function of the layer number. Reproduced from Bone, 56:55-60, Copyright (2013), with permission from Elsevier.

Figure 13. Time development of the distribution of the tissue mineral density (TMD) of bone formed within the first week (A), quiescent bone, which was present during all the 4 weeks of monitoring (B), and bone before being resorbed in the last week (C). Data shown corresponds to the loaded group and layer 2, the black line shows the reference distribution (Fig. 12A). Reproduced from Bone, 56:55-60, Copyright (2013), with permission from Elsevier.



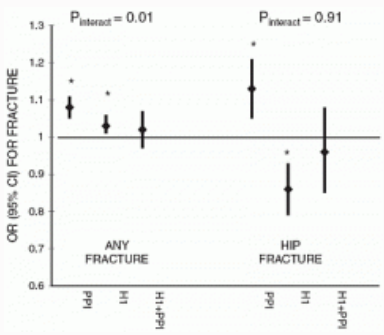
Gut Hormones and Osteoporosis

Gastrointestinal hormones such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP)-2 regulate bone turnover. **Ma et al** report that in OVX-induced osteoporosis in 12-month-old female Sprague Dawley rats, exendin-4, a GLP-1 receptor agonist, slowed body weight gain by decreasing fat mass, decreased urinary markers of resorption and increased serum ALP, OC and P1NP levels, prevented bone loss, and enhanced bone strength by preventing the deterioration of trabecular microarchitecture. Exendin-4 increased OPG/RANKL and promoted expression of OC, Col1, Runx2, and ALP (11).

Proton Pump Inhibition and H1 Receptor Blockade

Proton pump inhibitor (PPI) use may be associated with risk of fractures. Increased gastrin levels may cause histamine production through hypertrophy of gastric enterochromaffin like cells, which could lead to bone loss. H1 receptor antagonists (H1RA) use may reduce the effect of PPI on bone. **Abrahamsen & Vestergaard** studied 124,655 patients with fractures were matched 3:1 with nonfracture controls (12). PPI and H1RA use was associated wit adjusted OR 0.92, (95% CI 0.87-0.98) though not on hip fracture risk (adjusted OR 0.99, 95% CI 0.85-1.16). Fracture risk was higher in PPI users. H1RA users had lower risk of hip fractures than nonusers (adjusted OR 0.86, 95% CI 0.79-0.93). PPI effects on bone could be driven by in part by increased histamine release as the increased fracture risk can be modified by H1RA.

*Figure 14. Associations between fracture outcomes and the use of PPI, H1-antagonists or both. *p<0.05. Reproduced from Bone, 57:269-71, Copyright (2013), with permission from Elsevier.*



Strontium versus PTH

Bruel et al compared PTH, strontium ranelate (SrR), and PTH+SrR in preventing immobilization-induced bone loss in a rat model (13). Immobilization was induced by injecting 4 IU Botox (BTX) into the muscles of the right hind limb. Seventy-two female Wistar rats, 3-months-old, were

divided into Baseline, Controls, BTX, BTX+PTH, BTX+SrR, and BTX+PTH+SrR (n=12 in each group). PTH 60 µg/kg/d, and SrR as 900 mg/kg/d in the diet for 4 weeks. BTX resulted in lower trabecular bone formation rate (-68%) and periosteal bone formation rate (-91%), and a higher fraction of osteoclast-covered surfaces (+53%) compared with controls, reduced lower trabecular bone volume fraction (-24%), trabecular thickness (-16%), and bone strength (-14% to -32% depending on site). PTH counteracted losses in trabecular and periosteal bone formation rate, trabecular thickness (+25% vs. BTX) and femoral neck strength (+24% vs. BTX). SrR did not influence BTX-induced loss of bone formation rate, trabecular bone volume fraction, trabecular thickness, or bone strength. No additive effect was found when PTH and SrR treatments were combined.

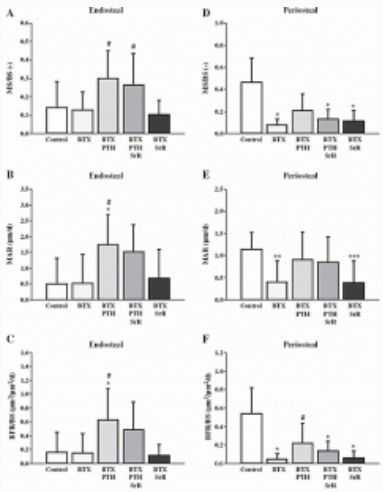


*Figure 15. Dynamic histomorphometry at the femoral diaphysis: endosteal mineralizing surface (A), endosteal mineral apposition rate (B), endosteal bone formation rate (C), periosteal mineralizing surface (D), periosteal mineral apposition rate (E), and periosteal bone formation rate (F) in rats with BTX induced hind limb immobilization treated with parathyroid hormone (PTH) and/or strontium ranelate (SrR). Mean±SD. *: P<0.05 vs. control, **: P<0.01 vs. control, ***: P<0.001 vs. control, #: P<0.05 vs. BTX. Reproduced from Bone, 53:51-8, Copyright (2013), with permission from Elsevier.*

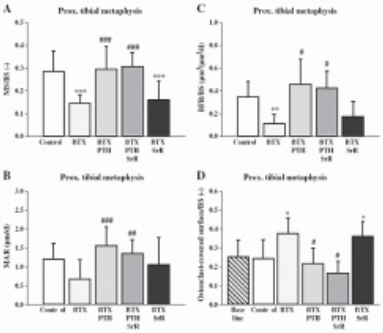


*Figure 16. Dynamic histomorphometry at the proximal tibial metaphysis: mineralizing surface (A), mineral apposition rate (B), bone formation rate (C), and osteoclast-covered surface (D) in rats with BTX induced hind limb immobilization treated with parathyroid hormone (PTH) and/or strontium ranelate (SrR). Mean±SD. *: P<0.05 vs. control, **: P<0.01 vs. control, ***: P<0.001 vs. control, #: P<0.05 vs. BTX, ##: P<0.01 vs. BTX, ###: P<0.001 vs. BTX. Reproduced from Bone, 53:51-8, Copyright (2013), with permission from Elsevier.*

Oral PTH

Henriksen et al aimed to establish the efficacy and safety of oral tablet of rhPTH(1-31)NH_2 and matching placebo tablets and open-label teriparatide positive control in postmenopausal women with osteoporosis during 24 weeks of once daily doses of 5 mg oral treatment or placebo, or open-label subcutaneous teriparatide (14). The oral tablet resulted in pharmacokinetic (PK) profiles with mean Cmax values similar to subcutaneous administration. In the rhPTH(1-31)NH_2 arm, a 2.2% increase in lumbar spine BMD (p<0.001), while no change was observed in the placebo. Open-label teriparatide resulted in a 5.1% increase in LS BMD. In the oral PTH study arm, the osteocalcin increased by 32%, 21% and 23% at weeks 4, 12 and 24, respectively. There was no increase in the level of the bone resorption marker CTx-1 in contrast to teriparatide.

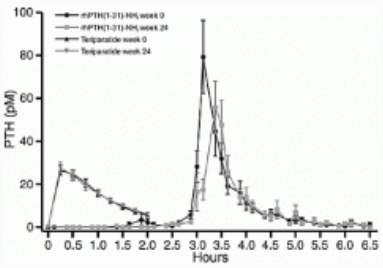


Figure 17. Mean PK profiles of the two PTH forms. rhPTH(1–31)NH_2 is shown as a time-shifted profilewhere the data are normalized to Tmax. The difference in Tmax between the subcutaneous teriparatide injection and the oral formulation is due to the time of gastric emptying and absorption required for the enteric coated oral tablet formulation. Reproduced from Bone, 53:160-6, Copyright (2013), with permission from Elsevier.

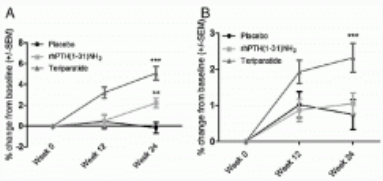


Figure 18. Percent change in BMD from baseline to Week 12 and to the end of treatment period in three study arms (means±SEM). A) Lumbar spine (L1-L4) BMD; B) Hip BMD. The asterisks indicate significant changes between group differences in BMD when comparing active treatments to placebo. Reproduced from Bone, 53:160-6, Copyright (2013), with permission from Elsevier.

Teriparatide and Vertebral Fracture Risk Reduction

Fujita et al conducted a randomized, double-blind trial to assess the effect of 28.2 µg teriparatide vs. placebo (1.4 µg teriparatide) on the incidence of vertebral fractures (15). Individuals enrolled included patients with primary osteoporosis with one to five vertebral fractures. 316 subjects participated during 131 weeks. Incident vertebral fractures occurred in 3.3% of treated subjects and 12.6% of placebo group during 78 weeks. Kaplan-Meier estimates of risk were 7.5 and 22.2% in the teriparatide and placebo groups, respectively, with a relative risk reduction of 66.4% (P=0.008). Lumbar BMD in the 28.2 µg teriparatide group increased by 4.4±4.7% at 78 weeks, which was higher than in the placebo (P=0.001).

PTH Administration and No Evidence of Osteosarcoma

Using Danish nationwide registers, **Bang et al** identified patients diagnosed with osteoporosis in the period 1995-2010. Each patient treated with rPTH ('case') was compared with 10 gender- and age-matched patients with osteoporosis but did not receive rPTH ('control') (16). A total of 4104 cases (80.3% females) were identified. The mean age at the beginning of rPTH was 70.9 (SD 9.7) years. During a follow-up time of 10,118 person-years for the cases and 88,005 person-years for the controls, a total of 255 cases (6.2%) compared with 2103 controls (5.1%) experienced a cancer (chi-square, p=0.003); adjusted cancer related HR of 1.1 (95% CI 0.9-1.4). Lung cancer was the only cancer type with increased rate among patients receiving rPTH (HR 1.7; 95% CI 1.3-2.3). No cases developed osteosarcomas and 9 controls developed osteosarcoma. During follow-up, 627 (15.3%) cases died and 4175 (10.2%) controls died, which yielded an excess mortality risk of 26% (95% CI 16-37%). Osteosarcoma has not been diagnosed in any Danish patient receiving rPTH since the year 2003 when it was introduced on the market.

Eldecalcitol versus Alfacalcidol

Eldecalcitol reduces the risk of vertebral fractures in comparison to alfacalcidol. To evaluate the effects of eldecalcitol on the location and severity of vertebral fractures, and the changes in health-related quality of life (HRQOL), **Hagino et al** compared results with those of alfacalcidol in a post hoc analysis involving 1054 patients randomized to 0.75 µg eldecalcitol or 1.0 µg alfacalcidol daily for 3 years (17). The incidence of fracture at the lower spine was less in the eldecalcitol group than in the alfacalcidol group (p=0.029). The incidence of severe vertebral fracture (Grade 3) was 3.8% in the eldecalcitol group and 6.7% in the alfacalcidol group (p=0.036). Both improved HRQOL.

Ergocalciferol and Cholecalciferol Reduce PTH Similarly

Glendenning et al randomized 95 hip fracture patients (aged 83±8 years) with vitamin D deficiency (25OHD <50 nmol/L) to cholecalciferol 1000 IU/day (n=47) or ergocalciferol 1000 IU/day (n=48) for three months (18). Seventy participants (74%) completed the study. Total serum $1,25(OH)_2D$ did not change. Both treatments were associated with comparable increases in D binding protein (DBP) (cholecalciferol: +18%, ergocalciferol: +16%, p=0.32 between groups), albumin (cholecalciferol: +31%, ergocalciferol: +21%, p=0.29 between groups) and calculated free 25OHD (cholecalciferol: +46%, ergocalciferol: +36%, p=0.08), with comparable decreases in free $1,25(OH)_2D$ (cholecalciferol: -17%, ergocalciferol: -19%). In the treatment-adherent subgroup, the increase in ionized calcium was greater with cholecalciferol than ergocalciferol (cholecalciferol: +8%, ergocalciferol: +5%, p=0.03 between groups). There were no differences between the treatments on bioavailable concentrations or indices of free vitamin D metabolites. These findings may explain why cholecalciferol and ergocalciferol result in similar reductions in PTH.

Fluoride
A blast or whimper from the past

Trials of high-dose fluoride have reported increased bone formation and BMD but impaired mineralization. Whether lower doses may offer some benefit remains a worthwhile question. **Grey et al** conducted a double-blind, placebo-controlled randomized trial over one year in 180 postmenopausal women with osteopenia given daily placebo, 2.5, 5, or 10 mg fluoride (19). Compared to placebo, none of the doses altered BMD. P1NP increased in the 5 and 10 mg fluoride groups compared to placebo (P=0.04 and 0 .005, respectively). No differences were observed between placebo and any of the fluoride groups in levels of CTX. The authors infer that low-dose fluoride does not induce substantial effects on surrogates of skeletal health and is unlikely to be an effective therapy for osteoporosis.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 10

Ego Seeman

Editor

By Ego Seeman Mon, 11/18/2013 - 14:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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ADVANCES IN THERAPEUTICS

Several advances have been made in therapeutics and the most interesting work presented at the 2013 ASBMR Meeting in Baltimore is summarized below. Further work of interest will be presented in the next issue of *Progress in Osteoporosis*. As always, the interpretation of the data is based on the contents of the abstracts and presentations and must remain tentative until the work has undergone peer review and can be scrutinized when it is in published so that having written "…all your piety nor wit shall lure it back to cancel half a line, nor all your tears blot out a word of it" (Rubaiyat of Omar Khayyam).

Denosumab
Modeling unopposed by resorptive remodeling

There is net loss of bone from the skeleton during aging because bone loss from the intracortical, endocortical, trabecular components of the inner (endosteal) envelope is greater than any periosteal bone formation taking place concurrently. However, if endosteal bone loss was prevented, any continued periosteal bone formation during advancing age will no longer be offset and the total mineralized bone matrix volume should increase.

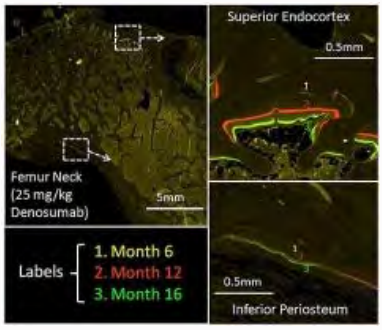
Ominsky et al (1) examined fluorochrome labeling at 6, 12 and 16 months in proximal femur sections from OVX adult cynomologus monkeys treated with vehicle (n=20) or 25 mg/kg QM denosumab (DMAb) (n=14). Despite suppressed remodeling, femoral neck BMD increased from 5.9% at month 6 to 11.3% above baseline at month 16. One explanation for the continued increase in BMD is more complete secondary mineralization of bone matrix no longer resorbed because remodeling is suppressed. While this is plausible given that secondary mineralization takes several years to reach completion, the increase in BMD should become asymptotic and this

does not seem to be the case in clinical studies in human subjects.

In this study of cynomologus monkeys, labeling upon trabeculae was low consistent with reduced remodeling upon trabecular surfaces but labels were detected upon the superior endocortical surface and the inferior periosteal surface. These labels occurred over smooth cement lines consistent with a modeling (not remodeling) dependent bone formation during denosumab treatment.

The authors do not suggest denosumab is an anabolic agent but rather speculate that that in the face of suppressed *remodeling*, existing slow bone *modeling* becomes detectable and might partly explain the continued increase in BMD at the hip in human subjects. Evidence for the occurrence of modeling dependent bone formation in humans is not strong and this may be because we have not explored this possibility sufficiently. It is also of interest to determine whether brief episodes of increased endogenous PTH associated with repeated v dosing may contribute to bone formation. In addition, a remaining question is what proportion of the increase in BMD is the result of more complete secondary mineralization.

Figure 1. Femoral neck from cynomologus monkeys treated with DMAb. Little trabecular labeling consistent with remodeling suppression. However, upon the superior endocortical surface and inferior periosteal surface labels are detected consistent with new bone deposition upon previously unremodeled bone. Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.

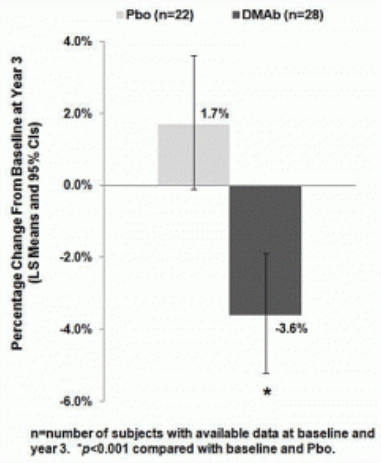


Denosumab Reduces Cortical Porosity of the Proximal Femur

Zebaze et al (2) measured cortical porosity of the femoral neck in women who received placebo (n=22) or 60 mg DMAb (n=28) every 6 months from hip images obtained at baseline and year 3. Cortical porosity correlated positively with serum CTX (p=0.017) and negatively with hip strength estimated using finite element analysis (p=0.027). DMAb reduced porosity across the entire cortex and in each compartment producing a net treatment effect (DMAb–placebo) of -1.8% (inner transitional zone), -5.6% (outer transitional zone), and -7.9% (compact-appearing cortex) (all p<0.001).

The reduction in cortical porosity is partly the result of perturbation of surface level remodeling. When an antiresorptive is administered, the many remodeling sites excavated prior to treatment refill while fewer new resorption sites appear simultaneously. The effect is a net reduction in porosity and a net increase in BMD. Secondary mineralization of osteons formed by remodeling months to several years earlier is likely to contribute because secondary mineralization takes months to years to complete. Another possibility is age-related modeling based bone formation upon the intracortical and endocortical surfaces may contribute unopposed by continued remodeling (as discussed above). Whether the reduction in porosity explains some or most of the reduced fracture rates reported using denosumab is yet to be established.

*Figure 2. Percent change from baseline after three years in the placebo and DMAb treated subjects. *Compared with baseline and placebo. Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.*

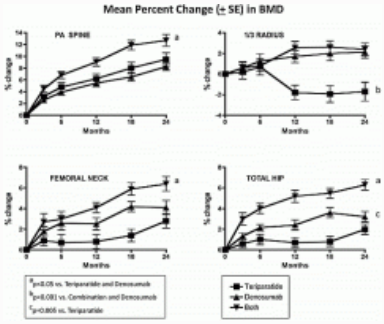


Combining Denosumab and Intermittent PTH

Leder et al (3) hypothesized that administration of PTH 1-34 may act primarily as a bone forming agent when given concurrently with DMAb. DMAb is a very powerful remodeling suppressant as it reduces the work and lifespan of existing osteoclasts and prevents the birth of new osteoclasts. If resorption is inhibited then remodeling sites that have completed their resorption phase and are in their formation phase may be stimulated by PTH. In addition, PTH may stimulate bone formation upon quiescent bone surfaces by promoting differentiation of lining cells while little, if any, of PTH action to increase remodeling would occur. Two studies in human subjects and a third in rats examined this interesting hypothesis.

In the study by **Leder et al** (3), 100 postmenopausal women were randomized to teriparatide (TPTD) (20 µg sc daily), DMAb (60 mg sc/6 months), or both. At 24 months, spine BMD (mean ±SD) increased by 12.7±5.1% with combined treatment, by 9.5±5.9% with TPTD, and by 8.3±3.4% with DMAb. Femoral neck BMD also increased more using combined treatment (6.4±3.8%) than TPTD (2.8±3.6%, P=0.002) or DMAb (4.1±3.8%, P=0.028) alone. BMD at the one-third distal radius increased similarly in the DMAb (2.0±3.7%) and combined groups (2.4±3.1%) but decreased by 1.7±4.6% in the TPTD group (P<0.001).

Figure 3. Regional changes in BMD following 2 years TPTD, DMAb or both (see text for details). Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.



From the same group of investigators, **Tsai et al** (4) report improvements in bone microarchitecture using combined therapy. At the tibia, DTot increased more using combined therapy (3.1±2.1%) than TPTD (0.0±2.3%) or DMAb (2.2±2.0%) alone. Ct.Th also increased more using combined therapy (5.4±3.8%) than using single therapy. The combination appeared to prevent the 5.6±10.3% increase in porosity with TPTD. Similar observations were reported at the distal radius. No between-group differences in trabecular microarchitecture were observed.

As reported in the studies in human subjects, **Tokuyama et al** (5) examined 3 month old OVX mice assigned to anti-RANKL monoclonal antibody (5 mg/kg injection), TPTD (80 mg/kg/d injection), or both. Combined therapy produced a greater increase in BMD at distal femur, shaft and spine than antibody alone. Cortical bone volume increased in combined and PTH groups compared with antibody use alone.

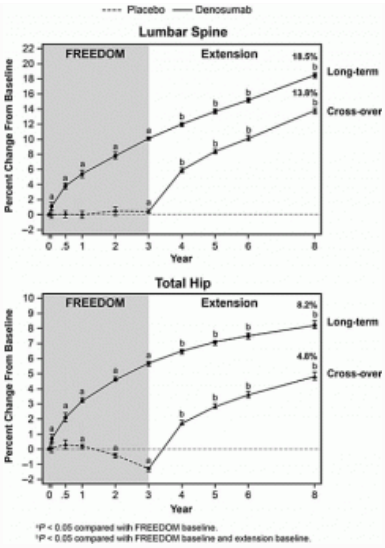
These studies support the notion that combining a powerful antiresorptive agent like a RANKL inhibitor may benefit bone structure. It remains feasible that the increase in porosity reported using PTH may be factitious. Newly deposited bone may be regarded as 'porosity' due to its lower tissue mineralization density. This new bone may be 'seen' as void or 'nonbone' during image analysis as voxels containing under mineralized attenuate photons less and the attenuation level may fall within the range nominated to be below the threshold for 'bone' and so may be designated as 'porosity'. If inhibition of osteoclast function results in a net improved anabolic effect of PTH then it is interesting to speculate that combining odanocatib with PTH may function in a similar fashion as this drug appears to reduce the resorptive activity of osteoclasts perhaps without influencing bone formation adversely.

Prolonged Treatment With Denosumab Are fracture rates reduced?

Papapoulos et al (6) report low fracture rates in subjects receiving 8 years 60 mg DMAb Q6M (3 years in FREEDOM and 5 years in extension n=1382) or the crossover group given 3 years placebo in FREEDOM then 5 years DMAb in the extension study (n=1296). Incidence of new vertebral and non-vertebral fracture remain low throughout the extension; hip fracture incidence during year 8 was 0.2% and 0.1% for the long-term and crossover groups, respectively. BMD increased by 18.5% (spine) and 8.2% (total hip) in the long-term group and by 13.8% (spine) and 4.8% (total hip) in the crossover group during 5 years.

The question is whether the low fracture rates are the result of treatment or sampling bias produced by inclusion of healthier compliers. As it is unethical to withhold therapy for 8 years, there was no control group, an understandable limitation but one that leaves this question unanswered. The continued increase in BMD at the spine may be the result of facet joint and intervertebral arthritic changes. The increase at the hip is unlikely to be confounded in this way (see above).

Figure 4. BMD continues to increase at the spine and total hip in the long term group and increased in parallel fashion in the cross-over group of the extension of the FREEDOM trial. Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.



Denosumab in Men and Histomorphometry

In the phase 3 ADAMO trial in men with low BMD, 1 year of DMAb (60 mg/6 months) increased BMD and reduced serum C-terminal telopeptide. **Dempster et al** (7) reported 29 subjects (n=17 DMAb; n=12 placebo) participated in a bone biopsy substudy. Qualitative bone histology showed normally mineralized lamellar bone. Structural indices, including cancellous bone volume and trabecular number and surface, were similar; 12/17 (71%) DMAb-treated and 12/12 (100%) placebo-treated subjects had double labels in trabecular and/or cortical compartments. In 6 DMAb-treated and 12 placebo-treated subjects, static and dynamic remodeling indices were lower in DMAb-treated than placebo-treated subjects. The authors infer that treatment of men with low BMD with DMAb for one year resulted in qualitatively normal bone with reduced bone turnover.

Odanocatib

Cathespin K inhibitors are potentially important additions to therapeutic options for osteoporosis. The results of the pivotal antifracture efficacy study are not yet available but independent review suggests the relevant antifracture endpoints have been met. The remaining question is whether this class of drug is safe. Time will tell. These agents prevent collagen degradation and so prevent bone resorption. They also may have beneficial effects on bone formation as osteoclast mediated bone resorption is inhibited but osteoclast numbers are normal or increased and the cells may participate in resorption-formation coupling at the level of the basic multicellular unit by producing local factors permissive for bone formation (8).

Chen et al (9) either sham-operated (n=20) or orchidectomized (ORX) (n=24/group) mature male rabbits. After 7.5 months, ORX-animals had reduced lumbar vertebral areal BMD (LV aBMD) by 5% vs. sham. ORX rabbits were randomized to vehicle (Veh), alendronate (ALN) (300 mg/kg/wk, sc) or odanacatib (ODN) (1.5 and 6 mg/kg) for 14 months. LV.BMD increased in ORX-rabbits treated with ODN 1.5 mg/kg by 9-19% and 6 mg/kg by 6-27% vs. Veh, and compared to an increase by 9% in the ALN group. Persistent reductions of the bone resorption marker helical peptide of collagen type I (HP) were observed in animals treated with each ODN dose (43-71% and 47-62%), compared to ALN (24-50%) vs. Veh. Bone specific alkaline phosphatase was reduced (16-34%) in the ALN group, maintained with ODN 1.5 mg/kg and trended up (16-30%) with ODN 6 mg/kg compared to Veh. Veh-treated ORX rabbits had decreased BV/TV by 19% vs. sham. ALN tended to increase BV/TV by 13% (p=0.124) vs. Veh. ODN at both doses increased BV/TV by 55-57% (p<0.001) vs. Veh, and 37-39% above ALN. ODN reduced lumbar spine MS/BS by 41-44%, BFR/BS by 51-52% and MAR by10 15%. Compared to ALN and Veh, trabecular osteoclast surface and number were higher in both ODN groups. Interpretation is difficult without comparisons versus baseline or a sham-operated group because the Veh-treated OVX group lose bone.

In the same study, **Pennypacker et al** (10) evaluated the effects of ODN on bone quality of the lumbar vertebrae (LV) and femur of male rabbits (age 11 months) that were sham-operated (N=20) or ORX (N=24/group) 7.5 months prior to treatment. ORX rabbits were randomized to Veh, ODN (1.5 or 6 mg/kg/d), or ALN (300 mg/kg/wk, sc) for 14 months. ORX resulted in ~9% bone loss in LV3-4 aBMD vs. sham (p<0.01). Relative to Veh, ODN increased LV aBMD by 21% and 26% for each respective dose (p<0.001), and 9.9% compared to ALN (p<0.01). pQCT-based LV5-6 trabecular (Tb) vBMC and vBMD increased in ODN groups (up to 88%, p<0.001) relative to vehicle. Similarly, ALN increased Tb.vBMC and BMD by 11% and 8%, respectively (both p< 0.05). ODN at both doses increased Tb thickness (32-51%, p<0.001). Significant increases in peak load, apparent strength, yield load, and yield stress, stiffness of LV5-6 were noted between ALN to Veh and ODN to Veh or sham. From compression testing of LV, peak load from all groups correlated with pQCT-vBMC (R=0.9383, p<0.001). ODN also dose-dependently increased aBMD of the total hip and distal femur, but did not change central femur (CF) aBMD compared to Veh. ODN 6 mg/kg increased cortical thickness and area by ~7% (p<0.01), and reduced endocortical perimeter by 4% (p<0.05) vs. Veh. ODN-treated CF tended to have higher peak load and increases in work-to-failure (25%, p< 0.05) and toughness (29%, p<0.01) vs. Veh. No changes in biomechanical parameters of CF were noted in the ALN group. CF peak load vs. pQCT-vBMC correlated (R=0.7555, p<0.001). ODN increased bone mass and strength in the

lumbar spine to levels above Veh and sham, as well as maintaining biomechanical properties at femoral sites of ORX male rabbits.

Cusick et al (11) studied the effects of ODN on fracture repair in a radial osteotomy model during reparative (6 weeks) and remodeling (25weeks) phases. Rabbits were randomized and pretreated for 12 weeks then osteotomy was performed. Treatment was Veh, ODN (1.5 or 6 mg/kg/d) or ALN (0.3 mg/kg/wk, sc). Postsurgery, ODN was continued (ODN/ODN) or discontinued (ODN/Veh). Fracture callus in ODN/ODN, ODN/Veh, ALN groups were no different to Veh. ODN/ODN and ALN increased pQCT-based total vBMD at 6 weeks (9-10%) and 25weeks (26-33%) without altering callus area vs. Veh. ODN/ODN enhanced callus vBMC by 15-18% at 6 weeks and 49-69% at 25 weeks vs. Veh. Mature callus vBMC with ALN was unaltered at 6 weeks and increased 9-18 at 25 weeks vs. Veh. Biomechanical tests of fractured and intact radii in all groups at 6 weeks were not different to Veh. At 25 weeks, peak load across the healing sites in ODN/Veh and ALN groups were the same as that in Veh, peak load in ODN/ODN groups increased by 18% and 25% for each dose, reaching intact contralateral levels. The authors infer that ODN does not delay fracture union and callus remodeling.

Fujii and Tanaka (12) synthesized peptidomimetic compounds which inhibit cathepsin K. SI-591 inhibited human cathepsin K with an IC50 of 1.4 nM, 8- to 320-fold more selective for cathepsin K than other human cathepsins. In vitro, osteoclast-like cells resorption pits formed on the slices. SI-591 (0.01-10 mM) dose dependently inhibited the release of CTX-I and decreased excavation of pits. In OVX adult female F344 rats, SI-591 dose-dependently inhibited urinary CTX-I release and prevented BMD loss at the vertebrae and femur. OVX rats were treated with vehicle or SI-591 (4-25 mg/kg p.o., b.i.d.) for 12 weeks from 12 weeks following surgery. SI-591 dose dependently inhibited urinary deoxypyridinoline release and prevented BMD loss in the vertebrae and femur. In OVX cynomolgus monkeys (aged 9-16 years) treated with a vehicle or SI-591 (4-36 mg/kg p.o. b.i.d.) for 6 months following surgery, SI-591 inhibited the NTX release and prevented BMD loss.

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PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 13, ISSUE 11

Ego Seeman

Editor

By Ego Seeman Mon, 12/02/2013 - 09:00

Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tPTH and Osteosarcoma
No evidence in human subjects ap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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ANABOLIC THERAPY

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PTH and Osteosarcoma
No evidence in human subjects

In rat toxicology studies, teriparatide given for their entire life caused a dose dependent increase in the incidence of osteosarcoma. In adults, the incidence of osteosarcoma is 2.7 cases per million person-years. The third annual linkage included 38 state cancer registries covering 86% of the US population linking 26,810 patients from the Forteo Patient Registry with 1641 adult osteosarcoma cases diagnosed since January 1, 2009. No matches were identified as of December 2012 of the 30,758 registrants. Evaluation of the first 3 years of data detected no signals of a possible association between teriparatide and osteosarcoma (1).

Once Weekly Teriparatide

Sugimoto et al (2) report the antifracture efficacy of weekly teriparatide injection (56.5 mg) in a randomized, double-blind, placebo-controlled trial of 542 Japanese patients with osteoporosis (65-95 years). Incident vertebral fracture occurred in 2.7% (7/261) treated subjects and 13.2% controls (37/281), RR 0.20. Fracture risk reductions were observed in subjects under 75 years (RR 0.06; p=0.007) and over 75 years (RR 0.32; p=0.015), in those with one prevalent vertebral fracture (RR 0.08; p=0.015), in those with >2 vertebral fractures (RR 0.29; p=0.009), in those with grade 3 deformity (RR 0.26; p=0.003), and those with spine lumbar <-2.5SD (RR 0.25; p=0.035).

Volume 13, Issue 11

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Human PTHrP Analog

Doyle et al (3) report that BA058, an analog of hPTHrP (1-34), was given 9 months post-OVX for 16 months to aged osteopenic, OVX cynomolgus monkeys >9 years of age at 0.2, 1 or 5 mg/kg. 1 and 5 mg/kg/day reversed OVX-induced osteopenia at the spine with increased yield load of ~50% for the vertebral core and ~20% for the vertebral body compared to OVX controls. These changes were consistent with the increases in BMD of up to ~25%. At 1 and 5 mg/kg/day, BA058 completely restored bone mass and bone strength (yield load) to values comparable to sham control. At 0.2 mg/kg/day, there were partial gains in BMD and strength.

Of interest is a manuscript just published by **Horwitz et al** (4). The investigators compared 400 or 600 mg/d PTHrP(1-36) and 20 mg/d PTH(1-34) in a 3-month randomized, prospective study of 105 postmenopausal women. The increase in CTX by PTHrP(1-36) (30%) was less than with PTH(1-34) (92%) ($p<0.05$). The increase in P1NP with PTHrP(1-36) (46% and 87%) was also less than with PTH(1-34) (171%) ($p<0.0005$). The increase in PINP was earlier (day 15) and greater than the increase in CTX for all groups. Lumbar spine, total hip and femoral neck BMD increased equivalently in each group, but proximal femur values were only significant for the two doses of PTHrP(1-36). PTHrP(1-36) 600 required a dose reduction for hypercalcemia in three subjects. Results of morphology will be of interest when available.

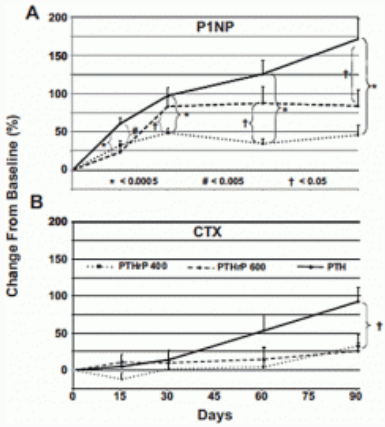

*Figure 1. Bone turnover markers. Bars indicate SEM. *,#,† Significance comparing groups. (A) PINP increased in all groups ($p<0.0005$) and was sustained to 90 days. The increase in PTHrP(1-36) was less than that with PTH(1-34). (B) CTX increased later than PINP, at day 90 in the PTHrP(1-36) groups and day 60 in the PTH(1-34) group. The change at day 90 was less in the PTHrP(1-36) groups than in the PTH(1-34) group ($p<0.05$). Reproduced from J Bone Miner Res 2013; 28:2266-76 with permission of the American Society of Bone and Mineral Research.*

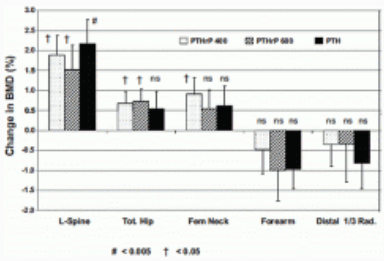

Figure 2. There was no difference in BMD change between groups at any site. Bars indicate SEM. #,† Significance compared baseline values. Lumbar spine BMD increased equivalently and significantly in all groups. Total hip and femoral neck BMD increased equivalently but was significant only for the two PTHrP(1-36) groups ($p<0.05$ vs. baseline) at the total hip and for the PTHrP(1-36) 400 group at the femoral neck ($p<0.05$ vs. baseline). There was no change in the forearm BMD in any group. Reproduced from J Bone Miner Res 2013; 28:2266-76 with permission of the American Society of Bone and Mineral Research.

Combining Anabolic Plus Antiresorptive Therapy

This approach to treatment took off with a bad start several years ago with two studies published in the *New Engl J Med* suggesting that administering an antiresorptive like alendronate (ALN) with PTH produced blunting relative to the effect of PTH alone on BMD and remodeling markers (5,6). The rationale examining this apparent blunting was that the anabolic effect of PTH is in large part remodeling based rather than modeling based. Suppression of remodeling using a bisphosphonate blunted that component of the effect of PTH. The inference made was that the combination is likely to be ineffective in lowering fracture rates or will be less effective than either treatment alone. No studies have been done examining the antifracture efficacy of combined versus either PTH alone or antiresorptive alone and in most studies, changes in BMD or remodeling markers are at best only weakly associated with reduction in fracture risk reported with any drug.

It is unfortunate that the use of combined therapy by stimulating bone formation using PTH and reducing resorption with remodeling suppressants has fallen out of favor because the notion of blunting may be incorrect and it is certainly not observed in most studies. For example, the study by Leder et al combining PTH with a most efficacious resorption inhibitor denosumab (7) challenges this notion, and an earlier study by Cosman et al using zoledronic acid and PTH also suggests this combination produces a better BMD response initially than either treatment alone (8). Several more recent studies support the use of combined therapy.

Whitmarsh et al (9) report changes in cortical mass and thickness from QCT scans 18 months after switching to teriparatide after 12 months prior raloxifene (n=25) or ALN (n=40) vs. 18 months after combining previous raloxifene (n=28) and ALN (n=41) with teriparatide. There was a global mass increase for the add group (2.8% raloxifene, 1.6% ALN) that was greater than switching (0.7% raloxifene, -0.8% ALN) and mainly located at the posterior trochanter. Cortical thickness increased in the combined therapy group (3.7% raloxifene, 1.9% ALN) but no greater or worse than the switch group (1.7% raloxifene, 3.0% ALN).

Figure 3. The mean thickness and mass changes. Reproduced from J Bone Miner Res 28 (Suppl 1)

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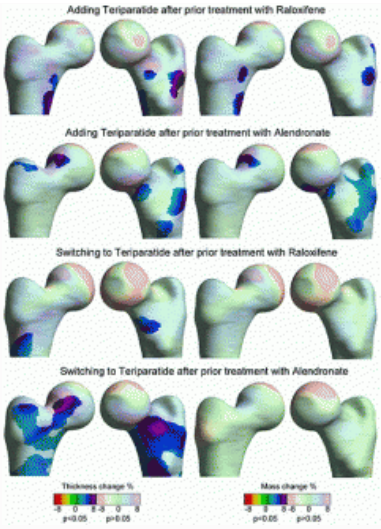


De Bakker et al (10) developed an in vivo dynamic imaging technique to test the hypothesis that combined PTH (60 mg/kg) and ALN (50 mg/kg) increase bone formation and inhibit bone resorption in 3-month-old rats during 12-days. Proximal tibia scans (Scanco vivaCT40) at days 4 and 12 were subtracted to identify formation and resorption sites. Compared to baseline, PTH+ALN caused a greater increase in BV/TV than PTH (45% vs. 33%), 300% greater BFR/BS and 110% greater MAR than vehicle or ALN, while PTH had 300% greater BFR/BS than vehicle. Combined therapy increases bone formation while inhibiting resorption which partially explains the additive effect over monotherapy.

Altman et al (11) hypothesized that combined PTH+ALN (n=9) would result in a greater improvement in trabecular bone structure and strength of the proximal tibia than PTH alone by enhancing bone formation upon trabecular surfaces. Saline (Veh, n=6), PTH (60 mg/kg, n=9), ALN (50 mg/kg, n=6), or both were given daily to 3-month-old rats for 12 days. Scanco vivaCT 40 scans showed PTH caused 7%, 19%, and 33% increase in BV/TV at day 4, 8, and 12. PTH+ALN resulted in 9%, 25%, and 45% increases, respectively. Similar increases in Tb.Th were observed for PTH (7-35%) and PTH+ALN (8-35%). Little or no change in Tb.Th or BV/TV was detected in the Veh and ALN groups. Tb.N showed no difference between groups. SMI suggests a 15% and 27% increase in platelike structures with PTH and PTH+ALN groups, respectively, compared with a 6% increase in the ALN group and no change in the Veh group. At day 12, the PTH+ALN group had 9% and 13% greater BV/TV and platelike structure than the PTH group. Overall, ALN, PTH, and PTH+ALN achieved 25%, 68%, and 103% increases in stiffness, respectively. PTH and PTH+ALN had reduced tissue mineralization (4.5% and 3.0%), possibly due to the new bone formation. The authors report an additive effect of combined PTH and ALN therapy over monotherapy on trabecular microstructure and strength in rats and improvement in SMI. Combined treatment is additive, blunting is not observed in this study.

Antisclerostin Antibody Treatment

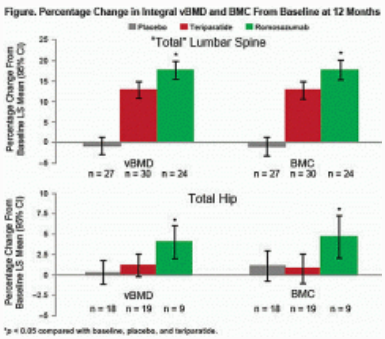
PTH molecules are currently the only anabolic therapy we have available for clinical use. There are several concerns. First, there are no studies showing that this drug reduces hip fractures. The pivotal study by Neer et al (12) was stopped due to concerns about the long term safety following the initial report of osteosarcoma in rats. PTH molecules may have anti-hip fracture efficacy, but there is just no data supporting this notion. Second, nonvertebral fracture risk reduction was reported in the pivotal study but this has not been confirmed in the later study using PTH(1-84) and nor in the study of weekly PTH. However, the study by Neer et al was a little less than rigorous regarding the classification of nonvertebral fracture as traumatic or ‘osteoporotic’, a decision left to the investigator. A close look at the types of fractures included as ‘osteoporotic’ makes the veracity of the conclusion tenuous. Third, there is only modest evidence that PTH molecules stimulate periosteal apposition and the biological significance of any periosteal apposition reported using histomorphometry is problematic. Fourth, the anabolic effect is largely remodeling based not modeling based. New bone deposited is mainly found upon crenated surfaces reflecting that most of the anabolic effect occurs upon existing remodeling sites; much less bone formation occurs upon quiescent bone surfaces. This is a limitation because about 80% of the bone surface is quiescent, so the surface available for building bone is vacant land, nothing is happening! Fifth, there is evidence that PTH administration is associated with an increase in intracortical porosity. This may be transitory and, in part, it may be factitious because deposition of new under mineralized bone may be registered by imaging techniques as void rather than ‘bone’ due to attenuation being below the threshold level nominated to represent mineralized bone tissue. Whatever the case, there is a real need for the development of bone forming treatments. The most promising on the horizon are the sclerostin inhibiting molecules.

Increased bone formation may be the result of increased numbers of osteoblasts by activation and differentiation of existing lining cells or the birth of new cells. **Ominsky et al** (13) investigated if the acute increase in bone formation in response to sclerostin antibody (Scl-Ab) is associated with an increase in RUNX2-positive (RUNX2+) cells adjacent to the cancellous bone surface and in the peritrabecular stroma (osteoprogenitors) in vertebrae from OVX rats following a single dose of Scl-Ab 100 mg/kg (Scl-Ab VI). Despite a 280% and 65% increase in OS/BS and MS/BS, respectively, RUNX2+ cells adjacent to the surface were not increased (Scl-Ab = 269,200±65,293; Veh = 251,600±29,711). The total number of peritrabecular RUNX2+ osteoprogenitor cells was also similar (Scl-Ab = 57,600±9,633; Veh = 60,000±18,547). The acute increase in bone formation following Scl-Ab treatment is not associated with an increase in surface-associated RUNX2+ cells or osteoprogenitor cells but may be mediated by activation of lining cells into matrix-producing osteoblasts.

Genant et al (14) report romosozumab (210 mg QM) stimulated bone formation, decreased bone resorption and increased BMD in 55–85 year old postmenopausal women. In this 12-month phase 2 study vBMD increased at the lumbar spine and total hip compared with placebo and teriparatide (20 mg QD). Trabecular vBMD increased similarly with romosozumab and teriparatide at the lumbar spine? (18.3 vs. 20.1%, respectively), more so with romosozumab at the total hip (10.8 vs. 4.2%). Romosozumab resulted in greater increases in cortical vBMD at the lumbar spine compared with teriparatide (13.7 vs. 5.7%) and greater increases in cortical BMC (23.3 vs. 10.9%). At the total hip, increases in cortical vBMD

(1.1%) and BMC (3.4%) were observed with romosozumab but not with teriparatide (perhaps due to issues in segmenting bone at this location). Nevertheless, the data look promising.

Figure 4. Increases at the averaged L1 +2 and total hip following treatment with placebo, PTH and romosozumab. Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.



Bone Strength

Keaveny et al (15) studied in 42 postmenopausal women mean age 62 years with low aBMD comparing placebo, blosozumab 180 mg every 2 or 4 weeks, or 270 mg every 2 weeks. In the treated groups, there were increases in spine and hip strength at 24 and 52 weeks. At the spine, blosozumab increased strength compared to baseline by up to 29.6 % at week 24 and 37.0% at week 52, and at the hip, blosozumab increased strength by up to 9.6% at week 24, and 12.6% at week 52. At the spine and hip, these strength changes were associated with increases in volumetric BMD of the trabecular and cortical compartments.

Ominsky et al (16) assessed 6-month-old OVX rats at 8 months of age treated with weekly vehicle, or 3, 10, or 50 mg/kg romosozumab for 12 months. Bone mass was dose dependently increased throughout the skeleton. BMD increased by 40% over baseline at the spine and whole femur at the 50 mg/kg/wk dose. At the tibia diaphysis, cortical thickness increased by pQCT at all doses compared to OVX controls, due to changes on periosteal and endocortical surfaces. Romosozumab increased ex vivo bone area and strength at the femur midshaft, neck, and lumbar vertebra at all doses. Peak load was dose dependently increased at the femur midshaft (41-121%), femur neck (33-46%), and vertebra (150-268%). These improvements correlated with bone mass with r2 values of 0.92, 0.41, and 0.94 at the femur shaft, femur neck, and lumbar vertebra, respectively. Material properties at the femur shaft suggested improved ultimate strength and toughness while elastic modulus remained unaffected.

Maintenance

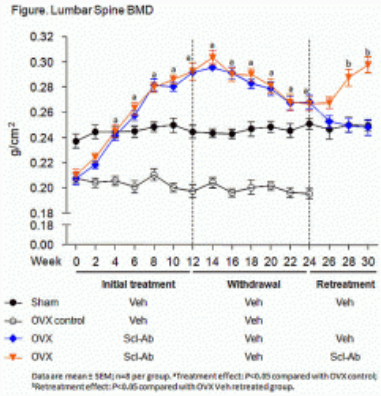
For reasons that are not understood, the effects of anabolic treatment attenuate when treatment is stopped. **Ma et al** (17) examined maintenance of benefits achieved using Scl-Ab by treating with raloxifene, ALN or a reduced frequency of Scl-Ab administration. Eight month old rats were OVX and allowed to lose bone for 2 months then treatment was started using Scl-Ab, 10mg/kg/week sc for 6 weeks, followed by a) vehicle, b) raloxifene 3 mg/kg/d sc, c) ALN 28 mg/kg/twice a week sc, d) Scl-Ab one injection at week 10. Scl-Ab weekly for 6 weeks restored OVX induced loss in vertebrae and femoral neck and improved strength compared to OVX control. Switching to vehicle or a single Scl-Ab injection resulted in a decline in BMD and strength at all sites. BMD and bone strength gains were largely maintained or slightly increased with raloxifene or ALN at all sites. By the end of the 8-week maintenance period, BMD and bone strength in all groups previously treated with Scl-Ab were still higher than those in the OVX controls, with the exception of the Scl-Ab single injection group, where femoral neck strength declined to a level not different from OVX control.

Rechallenge

Robinson et al (18) retreated 8-10 week old BALB/c mice with Scl-Ab and report increases in P1NP that peaks 4 days after dosing and returns to baseline after 7 days. After five doses of Scl-Ab (weekly, 10 mg/kg sc) the peak serum PINP (64 ng/ml) was lower than in age-matched animals dosed with Scl-Ab for the first time (101 ng/ml). An increase in P1NP was observed after each administration of Scl-Ab, but the fifth dose resulted in only 24% increase in P1NP from predose to peak levels measure 4 days later whilst age-matched animals dosed for the first time showed a 130% increase. Mice that had received five doses of Scl-Ab (showing an attenuated P1NP response) were allowed an 8 week interval after which these animals were redosed and produced a P1NP response similar to that in age-matched animals dosed for the first time. Rechallenge can be timed to overcome the attenuated response to Scl-Ab seen after multiple doses. A further 6 doses with Scl-Ab (weekly) again resulted in an attenuated response to Scl-Ab, which was again reversed after a second 8-week period without dosing. Each dosing interval was associated with increases in whole body areal BMD and each dosing interruption resulted in a decline in areal BMD. Thus, continued dosing attenuates the P1NP response but a first-dose level increase in bone formation can be achieved after a period of Scl-Ab discontinuation.

Li et al (19) explored the effects of Scl-Ab retreatment in 7-month-old OVX rats (11 wks post-OVX) treated with vehicle or Scl-Ab (Scl-Ab VI, 5 mg/kg, sc, twice a week) for 12 weeks, followed by vehicle for 12 weeks then one group of Scl-Ab-treated OVX rats received Scl-Ab and the other group received vehicle for 6 weeks. During initial treatment, P1NP increased in the Scl-Ab group at weeks 2 and 4 and returned to OVX control levels at week 10; it then remained at OVX control levels during the withdrawal phase (through week 24). During retreatment, Scl-Ab increases P1NP comparable to that observed after the initial treatment. Lumbar spine BMD increased throughout Scl-Ab treatment and peaked at week 14, two weeks after withdrawal, gradually returning to sham levels at week 24. After 6 weeks of retreatment, BMD increased again to the peak level at week 14. Trabecular (Tb), endocortical (Ec), and periosteal (Ps) bone formation rate (BFR/BS) peaked at week 6 in the Scl-Ab group and then returned to OVX controls at week 24, but Tb and Ec BFR/BS were greater in the Scl-Ab group than OVX controls at week 12. During the retreatment, the increases in Tb and Ec BFR/BS with Scl- Ab were similar to those following initial treatment; there were increases in Ps BFR/BS. For Tb and Ec eroded surface (ES/BS), similar decreases were observed in the Scl-Ab group compared with vehicle during initial and retreatment phases. After treatment withdrawal, Tb ES/BS increased to levels above OVX controls and Ec ES/BS returned to OVX control levels. Retreatment increased bone formation and BMD, and decreased bone resorption, as during initial treatment. Retreatment with Scl-Ab could be a viable way to increase bone mass.

Figure 5. Treatment increases BMD following OVX. There is a decline in BMD and then a decline which is followed by an increase with retreatment (orange triangle). Reproduced from J Bone Miner Res 28 (Suppl 1) with permission of the American Society of Bone and Mineral Research.



Disuse

Qin et al (20) studied the effects of Scl-Ab treatment following spinal cord injury (SCI). The authors performed complete spinal cord transection in sclerostin knockout (SOST-/-) mice. Eight weeks after SCI, bone loss was observed at the distal femur and proximal tibia in WT mice, no bone loss was observed in SOST-/- mice. Male Wistar rats underwent complete spinal cord transection; 7 days after SCI, the rats were treated with Scl-Ab at 25 mg/kg/week or vehicle for 7 weeks. SCI resulted in decreases in BMD (-25%) and trabecular bone volume (-66%) at the distal femur. Scl-Ab completely prevented the loss of BMD and trabecular bone volume. Tb.Th increased to levels above values for non-SCI controls, and Tb.N tended to be higher than SCI controls. Scl-Ab increased trabecular bone formation. In cultures of bone marrow cells, SCI increased the number of TRAP+ multinucleated cells as well as mRNA levels of osteoclast differentiation markers, and reduced the number of osteoblasts and mRNA levels of the osteoblast differentiation markers. None of these deleterious changes were observed in the Scl-Ab-treated group. Scl-Ab may represent a promising novel approach to mitigate bone loss after SCI.

Zhang et al (21) evaluated the effect of Scl-Ab in a bone loss model from both estrogen deficiency and immobilization (OVX rats with concurrent hindlimb suspension (HLS)). Four-month-old female rats were divided into 7 groups. HLS was introduced 2 weeks after sham and OVX. Scl-Ab (25 mg/kg) or vehicle was injected sc twice weekly for 5 weeks starting at the time of HLS. HLS or OVX alone resulted in loss of trabecular BV/TV, -29% and -71%, respectively, compared to sham control, whereas the OVX+HLS resulted in 87% bone loss. Scl-Ab preserved BV/TV in rats with HLS or OVX and partially prevented trabecular bone loss in rats with OVX plus HLS. Tb.Th increased to similar extent in HLS, OVX and OVX plus HLS rats treated with Scl-Ab. HLS or OVX+HLS was associated with lower stiffness compared with Sham. Scl-Ab prevented the decrease in stiffness due to HLS, OVX or OVX+HLS. Ultimate load was not lower in HLS, OVX or OVX plus HLS as compared with Sham, but it was greater in Scl-Ab-treated HLS or OVX rats as compared with vehicle controls and sham group. Scl-Ab-treated HLS plus OVX showed increased ultimate load, but not significant compared with OVX control.

Osteogenesis Imperfecta

Sinder et al (22) studied the effects of Scl-Ab in osteogenesis imperfecta (OI) in 3 week-old male Brtl/+ mice with dominant OI. Mineralizing surface (MS/BS) and mineral apposition rate (MAR) were quantified. MS/BS increased by about 100% on the posterior periosteal surface and anterior endosteal surface. On the opposing surfaces (posterior endosteal and anterior periosteal) where resorption would be expected to occur, MS/BS was lower (0-38%). Scl-Ab increased MS/BS on these low bone-forming surfaces in both WT and Brtl/+ mice. On high bone-forming surfaces, MAR was marginally elevated (posterior periosteal) or slightly reduced (anterior endosteal). Scl-Ab increased cortical thickness in both the anterior and posterior compartment of Brtl/+. Scl-Ab increased cortical thickness in Brtl/+ and WT mice by activating bone formation on regions of the cortex that typically undergo resorption as part of a modeling drift. These results highlight the ability of Scl-Ab to activate bone formation on quiescent or resorptive surfaces, while maintaining the modeling based bone formation that occurs in rapidly growing animals.

Grafe et al (23) assessed the efficacy of Scl-Ab in growth Crtap-/- mice, a model of recessive OI. One-week-old female Crtap-/- mice were treated for 6 weeks (Scl-Ab VI, 25 mg/kg, sc, twice a week), PBS treated Crtap-/- and WT mice served as controls (n=6/group). After treatment, spines and femurs were analyzed by µCT. At vertebral body L4, treatment improved BV/TV (+141%), Tb.N (+61%) and Tb.Sp (-45%) compared to PBS-treated Crtap-/- mice. Tb.Th was increased by 49% and not different from WT mice. Cortical thickness at the femur midshaft increased by 14%, and at the femur metaphysis, Scl-Ab increased Tb.N (+53%) and BV/TV (+63%), while Tb.Th remained unchanged.

Matrix Composition

Ross et al (24) determined whether Scl-Ab affects mineralization or the rate of matrix maturation in lumbar vertebrae (L2) in a study of 4-5 year old male cynomolgus monkeys treated with vehicle or 30 mg/kg romosozumab once every 2 weeks for 10 weeks. Treatment led to a 2-fold increase in BFR/BS (p=0.009), and a 46% reduction in the eroded surface (p=0.014) and 42% higher trabecular bone volume (p=0.001). The mean global mineralization was 0.8% lower in the treated group (p=0.097). The number of highly mineralized bone pixels was reduced (p=0.035) with only a marginal increase in low density pixels (p=0.092). Bone tissue between 0.5 and 2 weeks old was ~80% mineralized, and the tissue between 2 and 8 weeks old was 90% mineralized compared to the oldest tissue (8 weeks). Even though a larger fraction of the tissue in the treated group was young there was only a small non-significant lowering of mean global mineralization. Treatment did not affect mineralization kinetics despite the elevated bone formation rate.

Glucocorticosteroid-induced Osteoporosis

Achiou et al (25) investigated the effects of the Scl-Ab on the osteocyte in this animal model of glucocorticoid-induced osteoporosis. Thirty male Wistar rats, 4 months old, were randomly assigned to

control group subcutaneously injected 5 days a week with vehicle, (M) group subcutaneously injected 5 days a week with 5 mg/kg methylprednisolone and (M+S) group injected with both methylprednisolone and Scl-Ab (Scl-Ab VI, 25 mg/kg/day, twice a week) for 9 weeks. Between the groups, there were no significant differences in mean lacunar area (ranged from 28.5±2.4 to 34.6±3.6 mm2) or mean lacunar density (ranged from 634±37 to 660±63/mm2). Methylprednisolone caused a decrease in osteocyte lacunar occupancy (42 ± 3.8 vs 53 ± 4.1% for C group), that was prevented by Scl-Ab (60±3.2% M+S vs. 42±3.8% for M group). These changes in lacunar occupancy were inversely correlated with the fractional number of apoptotic osteocytes previously reported (r=-0.74; p=0.001). Scl-Ab prevents the decrease in osteocyte lacunar occupancy and the increase in osteocyte apoptosis caused by methylprednisolone treatment in rats.

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Summaries and Critical Analyses of the current literature

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Ego Seeman

Editor

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Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation"

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Calcium and Vitamin D from the ASBMR 2013

Several meta-analyses and some studies suggest that calcium supplements *increase* the risk of hip fracture and cardiovascular events, while vitamin D supplementation *increases* fracture risk. These studies and studies that claim a benefit of calcium and vitamin D supplementation have flaws in design and execution such as treatment of individuals that were not deficient in either nutrient, large numbers of dropouts, poor compliance, and post hoc analyses. However, the lesson is clear; inferences regarding the efficacy of calcium and vitamin D supplementation must await trials that are well designed and executed. The trials need to evaluate safety as well as efficacy. Even a small increase in risk for adverse events may produce net harm, particularly when large segments of the population at low risk for fracture are supplemented.

Several meta-analyses and re-analyses of several studies were presented at the ASBMR addressing the potentially deleterious effects of calcium on cardiovascular outcomes and overall, no increase in risk was observed. Fracture risk reduction was observed but the benefit was small. There are more meta-analyses and remeta-analyses than trials. We will not know whether supplementation does net good, net harm or does nothing until the definition of 'deficiency' is rigorously established. Will this ever happen? Well, given the prevailing view that conducting a trial with a calcium group taking under 200-300 mg daily with a 25(OH)D level of less than 30 nmol/L is unethical, it is hard to envisage a change in the prevailing uncertainty.

Frost et al (1) identified 9 primary RCTs examining the efficacy of Ca+D on fracture risk and 3 post hoc analyses of RCT concerning the association between Ca+D and cardiovascular disease (CVD) outcomes. The investigators used the Bayesian approach to estimate the probability that supplements increased or decreased the risk of an outcome by more than 10%. Ca+D supplementation was associated with an 11% lower fracture risk (RR 0.89; 95% CI 0.80-0.97), a 10% lower nonvertebral fracture risk (RR 0.90; 0.79-0.99), a 14% reduction in clinical vertebral fracture (RR 0.86; 0.75-0.99), but no significant reduction in hip fracture risk (RR 0.88; 0.71-1.06). There was 48% chance that supplements reduced fracture risk by at least 10%. Supplements were not significantly associated with myocardial infarction (RR 1.18; 0.73-1.74), stroke (RR 1.17; 0.75-1.70), myocardial infarction or stroke (RR 1.14; 0.74-1.64), or death (RR 1.01; 0.67-1.58). The number needed to treat to reduce a fracture was 85, and the number needed to incur a CVD event was 170; a benefit/risk ratio of 2.

Ebeling et al (2) assessed calcium intake using a food frequency questionnaire in 407 men and women followed for 17.7 (1.1) years with a mean (SD) baseline age of 53 (5.4) years or who 103 (29.8%) had 172 prevalent vertebral deformities while 229 (66.2%) did not. The OR for vertebral fracture was 0.46 (95% CI 0.27-0.78) in those with a median energy-adjusted calcium intake of 1076 mg/d compared with those with an intake of 641 mg/d. The OR was 0.31 (95% CI 0.12-0.78) for severe vertebral fractures with a high intake. Associations with nonvertebral and hip fractures were not reported, presumably because no association was detected. These odds ratios are similar, or greater, than seen with potent remodeling suppressants or anabolic agents – a surprising observation given calcium supplements have only modest effects in reducing remodeling rate. Observational studies such as this never test causation, only association and to infer that a risk reduction of 54-69% reported in this study is actually due to the higher calcium intake is courageous.

Bauer et al (3) report that among 5967 men (74±6 yr), calcium intake was 1142±590 mg/d; 65% used calcium supplements. During 10 years 2022 men died; 687 due to CVD. Compared to the highest quartile (1565 mg/d), those in the lowest quartile for calcium intake (621 mg/d) had higher total mortality (RH=1.19, CI 1.02-1.39) before, but not after adjustment - total (RH=1.06, CI 0.96-1.18), cardiovascular mortality (RH=1.00, CI 0.83-1.20).

Lewis et al (4) undertook a meta-analysis of trials of calcium supplementation ± vitamin D and identified 19 studies fitting predefined criteria. The 4646 deaths in 59,844 participants yielded a RR of 0.96 (0.91-1.02), P=0.18 for those randomized to supplements. RR for the 3334 ischemic heart disease events in 46,843 participants was 1.02 (0.96-1.09), P=0.53 (I^2=0%) while the RR for the 1097 myocardial infarction events in 49,048 participants was 1.09 (0.89-1.33), P=0.21. The data do not support that calcium supplementation ± vitamin D increase the risk of ischemic heart disease or total mortality in elderly women.

Prachi et al (5) suggest that the threshold for decreased calcium absorption occurs at a very low serum 25(OH)D level, 5 ng/ml. This inference was based on a study of 198 Caucasian and African American women (ages 25-45 years) randomized double blind to 400, 800, 1600, 2400 IU vitamin D3 or placebo for 12 months. Calcium intake was 1200-1400 mg/d. 128 women completed the study. Mean baseline serum 25(OH)D was 14.6 ng/ml (39 nmol/L) in Caucasians and 11.6 ng/ml in African Americans. Mean serum 25(OH)D increased to 40 ng/ml. There was no increase in calcium absorption with any dose of vitamin D. Baseline serum 25(OH)D of 20 ng/ml was divided into 5 ng/ml increments. There was no difference in absorption or in serum $1,25(OH)_2D$ amongst the groups. Vitamin D did not increase calcium absorption up to a dose of 2400 IU daily or mean serum 25OHD of 41 ng/ml. No threshold level of serum 25(OH)D for calcium absorption was found at baseline or in the longitudinal study.

Radford et al (6) report followup of the Auckland calcium study, a 5-year randomised controlled trial of 1 g/d calcium citrate in 1471 postmenopausal women. Approximately 5 years post-trial, the authors collected information on 1408 participants alive at trial completion, they contacted 1174 women by phone and measured BMD at 10 years in 194 women who took medication for 5 years in the original trial. There was no effect on total fracture (HR 0.90, 95 % CI 0.75-1.07) or hip fracture incidence (1.40, 0.89-2.21), but reductions in forearm (0.62, 0.43-0.89) and vertebral fractures (0.52, 0.32-0.85) in those assigned to calcium. There were no between-group differences in BMD at 10 years. The adverse cardiovascular outcomes observed in the 5-year trial did not persist post-trial. Calcium supplementation for 5 years had no effect on total fracture incidence at 10 years. The positive benefits on BMD and the adverse cardiovascular effects did not persist once supplements were stopped.

Vitamin D and BMD
Much ado about not much

Despite uncertainties regarding the benefits and risks of vitamin D supplementation, there is widespread use of vitamin D in the community. This study is well worth reading, especially the erudite iconoclastic discussion. **Reid et al** (7) investigated whether vitamin D supplementation affects bone mineral density by including all randomized trials comparing interventions that differed only in vitamin D content. Of 3930 citations identified by the search strategy, 23 studies (mean duration 23.5 months, comprising 4082 participants, 92% women, average age 59 years) met the inclusion criteria. Mean baseline serum 25(OH)D was less than 50 nmol/L in 8 studies (n=1791). In 10 studies (n=2294), individuals were given vitamin D doses <800 IU/d. BMD was measured at one to five sites in each study, so 70 tests of significance were done. There were six findings of benefit, two of detriment, and the rest were nonsignificant. One study showed benefit at more than one site. A small benefit at the femoral neck was seen (weighted mean difference 0.8%, 95% CI 0.2-1.4). No effect at any other site was reported, including the total hip. There was a bias toward positive results at the femoral neck and total hip. Continuing widespread use of vitamin D for osteoporosis prevention is difficult to justify.

Insights into Bisphosphonate Action
from the ASBMR 2013

Ebetino et al (8) report that the influence on bone remodeling of nitrogen-containing bisphosphonates (N-BPs) depends on the affinity of the drug to mineral and its potency in inhibiting farnesyl diphosphate synthase (FPPS) of osteoclasts and their precursors. Prolonged residence in bone is likely to be related to the high bone affinity. For a given potency in inhibiting FPPS, lower affinity for mineral may result in wider distribution in bone matrix enabling access to remodeling sites but shorter matrix residence time may reduce efficacy but produce less concern about potential long-term skeletal side effects.

The effects may be region specific. Trabecular bone has a high surface area and a low matrix volume formed by its thin platelike architectural configuration – this design may allow adequate access and distribution of highly bound drug to remodeling sites and so efficacious suppression of remodeling of trabecular bone but the same drug may be less efficacious in cortical bone because it is bound tightly to subendosteal matrix and fail to access peri-Haversian remodeling effectively.

The authors improved the profile of N-BPs by optimizing their inhibition of the FPPS enzyme while reducing matrix affinity. Among the many analogs made, OX-14 (1-fluoro-2-(imidazo-[1,2-a]pyridin-3-yl)-ethyl-bisphosphonic acid) had of high inhibitory potency on FPPS with low affinity for mineralized matrix. OX-14 (IC_{50}=2.5 nM), was a more potent inhibitor of FPPS than zoledronate (IC_{50}=4.1 nM). Urinary excretion after parenteral administration was greater than other N-BPs in rats, indicating lower retention.

With ibandronate as a control=1.0, the relative 24-h urinary excretion of alendronate, zoledronic acid, risedronate, OX-14 was 0.53, 0.61, 1.0, and 1.24 respectively. In assays of inhibition of bone resorption in vivo, OX-14 (D_{20}=0.0003 mg P/kg) was more potent than alendronate D_{20}=0.0016 mg P/kg; ibandronate D_{20}=0.0006 mg P/kg and comparable to zoledronic acid D_{20}=0.0001 mg P/kg (D_{20}= the dose producing a 20% increase in BMD above vehicle). In a model of collagen-induced arthritis in rats, OX-14 demonstrated efficacy similar to other potent N-BPs. In the knee, a 0.5 mg P/kg dose of OX-14 decreased resorption by 100%, as did zoledronic acid, while no dose tested of alendronate was completely antiresorptive. Since these lower bone affinity BPs, at maximally effective doses, may reduce turnover more globally, these potent new FPPS inhibitors may also offer enhanced therapeutic utility in other bone related diseases.

An example of the differing effects of bisphosohonates (BPs) at cortical and trabecular sites was published by **Smith et al** (9) a decade ago. This paper is well worth reading, the authors discuss this aspect of accessibility in some detail. The relevant information in this paper is summarized in Figure 1.

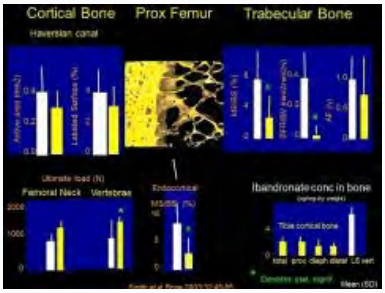


Figure 1. Suppression of remodeling upon the trabecular and endocortical surface relative to controls was observed using ibandronate, but Haversian canal remodeling was not suppressed significantly, presumably due to failure to access the remodeling occurring within the cortical compartment. The concentration of ibandronate was higher in extracts of trabecular bone than cortical bone. Adapted from Bone, 31:45-55, Copyright (2003), with permission from Elsevier.

Greater Suppression of Intracortical Remodeling by Denosumab than by Alendronate

Another illustration of the importance of access to intracortical remodeling can be seen in the study by **Zebaze et al** (10), who report greater reduction in cortical porosity by denosumab than alendronate. The investigators randomized postmenopausal women, mean age 61 years, to placebo (n=82), alendronate 70 mg weekly (n=82), or denosumab 60 mg every 6 months (n=83) for 12 months. Denosumab reduced remodeling more rapidly and completely than alendronate, reduced porosity of the compact-appearing cortex (CC), outer and inner cortical transitional zones (OTZ, ITZ), at 6 months, more so by 12 months relative to baseline and controls, and 1.5- to 2-fold more so than alendronate. The respective changes at 12 months were [mean (95% CI)]; CC: -1.26% (-1.61, -0.91) vs. -0.48% (-0.96, 0.00), p=0.012; OTZ: -1.97% (-2.37, -1.56) vs. -0.81% (-1.45, -0.17), p=0.003; and ITZ: -1.17% (-1.38, -0.97) vs. -0.78% (-1.04, -0.52), p=0.021. Alendronate reduced porosity of the three cortical regions at 6 months relative to baseline and controls but further decreased porosity of the ITZ only at 12 months (Figure 2). By 12 months, CC porosity was no different than baseline or controls, OTZ porosity was reduced only relative to baseline, not controls, while ITZ porosity was reduced relative to baseline and 6 months, but not controls. Each treatment increased trabecular BV/TV volume similarly: 0.25% (0.19, 0.30) vs. 0.19% (0.13, 0.30), p=0.208.

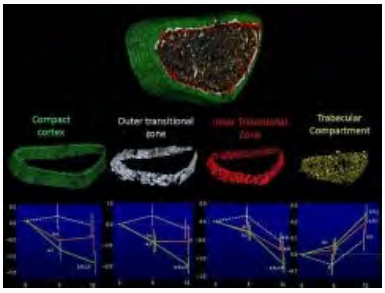


Figure 2. The top image shows three-dimensional reconstruction of the distal radius with the compact-appearing cortex (green), outer (white) and inner (red) transitional zone, and trabecular compartment (yellow). Middle images show each of the regions segmented and reconstructed and the graphs show the corresponding changes in porosity and trabecular bone volume fraction at 0, 6, and 12 months in controls, alendronate, and denosumab-treated subjects. p<0.05 compared with abaseline, bmonth 6, ccontrol, and dalendronate. White dashed line: control; red line: alendronate; green line: denosumab. Reproduced from Bone, 59:173-9, Copyright (2014), with permission from Elsevier.

Atypical Fractures Studies presented at the ASBMR 2013

Wang et al (11) followed 522,287 new BP users from their index prescription to diagnosis of subtrochanteric/femur shaft (n=948) or typical hip (n=9382) fracture. There were dose-dependent increases in incidences of subtrochanteric/femur shaft fractures with greater adherence. The age-adjusted rate (per 100,000 person years) of subtrochanteric/femur shaft fractures increased from 56.7 in the first year to 175.1 in the fifth year, compared with less compliant (from 44.3 to 66.6); a hazard ratio for compliant vs. less compliant of 1.23 (1.06-1.43) overall, 1.09 (0.89-1.34) before and 2.09 (1.48-2.95) after 3 years. Age-adjusted incidence of typical hip fractures was lower among compliant than less compliant (e.g., 873.8 vs. 1168.7 after 4 years, p<0.03).

Morin et al (12) hypothesized that patients with atypical femoral fracture (AFF) have geometrical variations of their lower limb so that tensile forces laterally are high. The authors compared the geometrical parameters in 25 subjects with AFF with duration of BP use of 10.6 SD [4.6] yrs. There were 40 AFF. Compared to women with diaphyseal fractures (n=11), those with subtrochanteric fractures (n=5) had a lesser femur neck-shaft angle (123.0° SD [3.3] vs. 129.2° SD [7.1]; p<0.05), longer femoral offset (4.2 SD [0.2] cm vs. 3.7 SD [0.6] cm; p<0.05), and less bowing in frontal plane (- 2.7° SD [5.6] cm vs. -4.2° SD [3.3]; NS).

Adams et al (13) compared 115 patients with an AFF and 107 patients with other subtrochanteric/diaphyseal fractures (subtroch group), and 115 patients with 'classic' femoral neck or intertrochanteric hip fractures (hip group). Compared to the subtroch group, AFF cases were younger, more likely to be Asian, to have osteoporosis and to use BPs (OR 6.4; 95% CI 3.0-13.4). AFF cases also used BPs for longer (median 6.6 vs. 2.0 years, p<0.01), with risk increasing from OR 5.8 (95% CI 1.9-17.2) for 4 years use to OR 13.3 (95% CI 4.2-42.2) for use >8 years. Compared to the hip group, younger

age, Asian race, osteoporosis, active use of BPs at index (OR 6.8; 95% CI 3.2-14.2), and longer duration of use of BPs were independent predictors of AFF status. AFF risk increased from OR 3.3 (95% CI 1.3-8.8) for 4 years BP use to 10.5 (95% CI 3.6-30.8) for >8 years use (p for trend<0.01).

Martelli et al (14) tested the hypothesis that AFF is associated with high cyclic tensile strains. The authors computed femur tensile strain distribution during walking in 10 postmenopausal women. A musculoskeletal model was scaled using anthropometry. The joint net moments were calculated using body motion and ground reaction forces during gait. Finite element analyses were performed applying muscle and hip reaction forces and using a full constraint condition distally. Five phases of walking including heel-strike (A), the first (B) and the second (D) peak of the hip reaction force, midstance (C) and toe-off (E) were studied. Peak tensile strains corresponded with the two peaks. For each peak, high tensile strains were found on the lateral femur diaphysis. The maximum tensile strain was 0.4%, corresponding with the second peak of the hip reaction force (4.5 bodyweight). AFFs may be initiated in subregions subjected to high cyclic tensile strains where microcracks may progress.

ONJ and Altered Material Composition

Olejnik et al (15) report bone sequesters from 24 patients with ONJ following a BP treatment have altered material composition. BP-exposed bone sequesters have increased mineral to organic ratio (+12%) and a decrease of relative proteoglycan content (-35%), and a decrease of crystallinity (-2%) and mineral maturation (-41%) compared to healthy bones. These modifications were observed in benign-BP and malignant-BP groups. In addition, a shift of the phosphate v_1 band was highlighted by PLS-DA between bones control and BP-exposed bone sequesters, revealing a disruption of the apatitic phosphate environment in the jaw bone sequesters. Jaw bone quality is altered with an overmineralization and ultrastructural modifications of apatitic mineral in bone sequesters of BP-related ONJ.

Coffee is OK

Hallstrom et al (16) report that in a cohort of 61,433 women born in 1914-1948, follow-up from 1987-2008 identified 14,738 women having any fracture and 3871 had a hip fracture. In 5022, bone density was measured and osteoporosis observed in 1012. After multivariable adjustment, there was no evidence of a higher rate of any fracture (hazard ratio per 200 mL coffee = 0.99; 0.98, 1.00) or hip fracture (HR 0.97, 0.95, 1.00) with increasing coffee consumption. A high coffee intake (≥4 cups daily) vs. a low intake (<1 cup daily) was associated with a 2-4% lower bone density (P<0.001), but the odds ratio for osteoporosis was 1.28 (0.88, 1.87). Thus, high coffee consumption was associated with a small reduction in bone density that did not translate into an increased risk of fracture.

Declining Initiation of Therapy

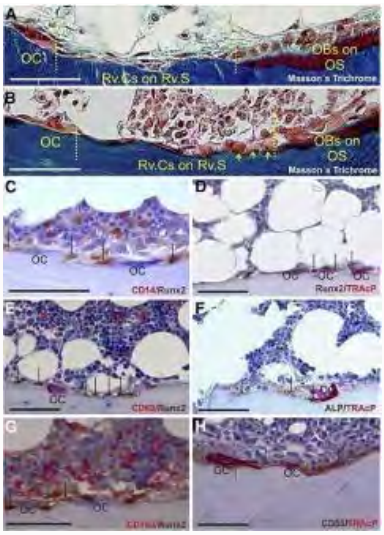
Wysowski et al (17) report ~21.3 million prescriptions for oral BPs were dispensed in U.S. retail pharmacies in 2002. This increased 46% to a peak of 31.0 million in 2007 and 2008, and declined by 53% in a 4-year period to 14.7 million in 2012. Sales data showed 66% increase from 2002-2007 and 51% decrease from 2007-2012. Intravenous BP sales grew 3.8-fold from 149.5 thousand packages in 2007 to 561.6 thousand in 2010, followed by a 22% decrease in 2012. Reasons for the decline need to be identified.

Coupling and the Reversal Phase of Bone Remodeling Cycle

Anderson et al (18) have written a timely and instructive review of the much neglected reversal phase of the bone remodeling cycle. Bone remodeling does not only have a resorptive followed by a formation phase. Coupling between the resorption and formation phases of the remodeling cycle is believed to occur during a reversal phase that was widely written about during the last century (yes, time flies) but since the 1970s, the reversal phase has been neglected. This is likely to be an important error of omission, much like failing to recognise the importance of the osteocyte and the importance of cortical bone.

As discussed by Anderson et al, the cells of the reversal phase prepare resorptive lacunae for bone formation. These 'reversal' cells cover >80% of the eroded surfaces, but their nature is not identified, and it is not known whether malfunction of these cells contributes to bone loss. In this review the authors report that reversal cells are immunoreactive for factors typically expressed by osteoblasts, but not for monocytic markers. A subpopulation of reversal cells showed several distinctive characteristics suggestive of an arrested physiological status. Their prevalence correlated with decreased trabecular bone volume and osteoid and osteoblast surfaces in postmenopausal osteoporosis. They were virtually absent in primary hyperparathyroidism in which the transition between resorption and formation occurs promptly. The authors suggest that arrested reversal cells reflect aborted remodeling cycles that did not progress to the bone formation. They propose that bone loss in postmenopausal osteoporosis does not only result from a failure of the volume of bone formed being less that the volume resorbed bone formed; bone loss may also be the result of failure of the reversal phase to initiate bone formation. This is not just a matter of semantics; if coupling is normal the imbalance in remodeling and bone loss may still occur due to mechanisms responsible for the birth, work and death of osteoclasts and osteoblasts. Abnormalities in coupling itself and the mechanisms responsible open an entirely new world of regulation, disregulation and therapeutic targets when this process is better defined and understand – the authors lead in this endeavor.

Figure 3. Histological appearance of reversal cells (Rv.Cs) in a biopsy from the iliac crest of patients with primary hyperparathyroidism. A and B: Masson's trichrome stained cross sections of bone remodeling surfaces with osteoclasts (OCs), Rv.Cs on the reversal surface (Rv.Ss), and bone-forming osteoblasts (OBs) on OSs. The Rv.Ss were identified as eroded surfaces (ES) with broken lamella without OCs, but with mononucleated Rv.Cs. Rv.Cs appear elongated, but sometimes are more cuboidal when



close to osteoid surface (OS, yellow arrows). Immunostaining (red) with the monocytic markers CD14 (C), CD68 (E), or CD163 (G) showed no immunoreactivity in the Runx2fl Rv.Cs (arrows, brown nuclei), whereas neighboring OCs were positive for CD68. Immunostaining with the osteoblastic markers, Runx2 (D), alkaline phosphatase (ALP; F), and CD56 (H), reveals immunoreactivity (brown staining) in Rv.Cs next to (black arrows) or below (red arrow) TRAcPfl OCs (red staining). Scale bars: 50 mm (AeH). Reprinted from Am J Pathol, Vol 183, Andersen TL et al., Understanding coupling between bone resorption and formation: are reversal cells the missing link?, Pages 235-45, Copyright (2013), with permission from Elsevier.

Does Odanacatib Produce Earlier Coupling and of Bone Formation by the BMU than Alendronate?

Jensen et al (19) make an attempt to examine the effects of drug therapy on the reversal phase of bone remodeling. The authors hypothesized that odanacatib modifies the nature of remodeling following the resorption phase. They suggest that odanacatib shortens the reversal phase during trabecular remodeling in vertebrae of estrogen-deficient rabbits. Odanacatib was suggested to shorten the reversal phase compared to alendronate and produced a faster initiation of osteoid deposition on the eroded surfaces, and higher osteoblast recruitment reflected by higher densities of mature bone forming osteoblasts and an increased subpopulation of cuboidal osteoblasts. An increase in the interface between osteoclasts and surrounding osteoblast lineage cells may favor the osteoclast-osteoblast interactions required for bone formation. Odanacatib, but not aledronate, resulted in shallower resorption lacunae, a geometry favoring bone stiffness.

Genetic Variance in Microstructure

Havill et al (20) examined right femurs from 101 baboons (74 females, 27 males; aged 7-33 years) from a single pedigree. Age and sex effects account for 9% (Ct.Po) to 21% (W.Th) of intracortical microstructural variation. After accounting for age and sex, 61-82% of trait variance was due to genetic effects for osteonal area (On.Ar) h^2=0.79, p=0.002), %On.B (h^2=0.82, p=0.003), and W.Th (h^2=0.61, p=0.013). This corresponds to 48-75% of the total phenotypic variance. Population-level variation in cortical microstructure is influenced by genes. As a critical mediator of crack behavior in bone cortex, intracortical microstructural variation provides another mechanism through which genetic variation may affect fracture risk.

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