PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 14, ISSUE 1

Ego Seeman

Editor

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By Ego Seeman Thu, 04/24/2014 - 08:13

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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I dedicate this issue of *Progress in Osteoporosis* to my mother whose journey through life ascended through the last glass darkly. She was magnificent in her silent and defiant stare into eternity without a good bye. But we never say goodbye. Those we love are with us always, even before we meet.

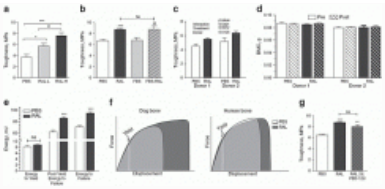
Antiresorptives

Water, raloxifene and bone strength

Two fascinating papers were published recently. **Samuel et al** report that water affects mechanical behavior of bone by interacting with the mineral and organic phases through hydrogen bonding and polar interactions (1). The authors soaked dehydrated bone in water, heavy water (D_2O), ethylene glycol (EG), dimethylformamide (DMF), and carbon tetrachloride (CCl4), compounds of different polarity, hydrogen bonding capability and molecular size. Of the matrix water in bone, 22.3% was replaced by CCl4, 71.8% by DMF, 85.5% by EG and ~100% by D_2O and H_2O. CCl4 soaked specimens showed similar mechanical properties as dehydrated ones. Despite great differences in replacing water, only slight differences were observed in the mechanical behavior of EG and DMF compared with dehydrated bone samples. D_2O preserved the mechanical properties. About 15% water in matrix spaces (into which molecules larger than 4.0 Å cannot enter) contributes to mechanical behavior.

Gallant et al machined bone beams from canine and human donors (2). Specimens were depleted of living cells and exposed to raloxifene ex vivo which improved intrinsic toughness by increasing matrix bound water due to its hydroxyl groups. Raloxifene alters the distribution of load between the collagen and mineral crystals, placing lower strains on the mineral allowing greater deformation prior failure. This drug has not been shown to reduce nonvertebral fractures, an important limitation given that 80% of all fractures in the community are nonvertebral. Studies examining raloxifene plus bisphosphonates (which may reduce toughness) have not been done.

Figure 1. Raloxifene (a) increases canine cortical toughness dose-dependently without or (b) with fetal calf serum and does so (c) in human bone (d) without change in BMC (e) and increases energy absorption in post yield portion of curve (f) shows



force displacement curves in dog and human bone, (g) toughness increases with raloxifene, or raloxifene followed by PBS compared to PBS. Reproduced from Bone, 61:191-200, Copyright (2014), with permission from Elsevier.

Denosumab

Zebaze et al report that postmenopausal women mean age 61 years (range 50-70) were randomized double blind to placebo (n=82), alendronate (ALN) 70 mg/week (n=82), or denosumab 60 mg/6 monthly (n=83) during 12 months (3). Denosumab reduced remodeling more rapidly and completely than ALN, reduced porosity at 6 months and more so by 12 months and 1.5- to 2-fold more so than ALN. By contrast, ALN reduced porosity at 6 months but no further at 12 months apart from porosity of the inner transitional zone (ITZ). So, by 12 months, compact cortex (CC) porosity was not different to baseline or controls, outer transitional zone (OTZ) and ITZ porosity was reduced relative to baseline. Each treatment increased trabecular BV/TV similarly.

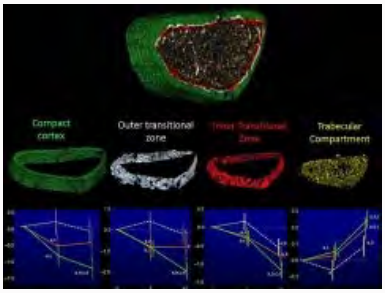


Figure 2. Both ALN and denosumab reduce cortical porosity at 6 months, but denosumab further reduces porosity by 12 months. No further reduction in porosity occurs in the second 6 months in the ALN treated group and porosity is no longer significantly reduced relative to controls. The increase in trabecular density is similar with both drugs, perhaps because the accessibility to trabecular remodeling is similar. Reproduced from Bone, 59:173-9, Copyright (2014), with permission from Elsevier.

The greater reduction in porosity of the cortex by denosumab may be due to greater inhibition of intracortical remodeling. ALN is tightly bound to matrix and may not access deeper intracortical remodeling. While this remains theoretical there is evidence based on histomorphometry in primates that ibandronate does not reduce Haversian canal remodeling more than controls while suppression of endocortical and trabecular remodeling is suppressed more than controls (4).

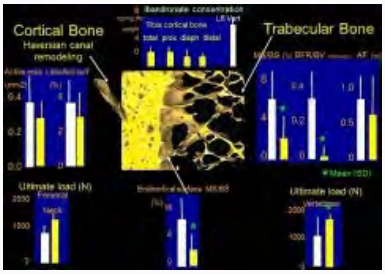


Figure 3. In cortical bone, Haversian canal remodeling is not suppressed relative to controls and there is no change in ultimate load. By contrast, remodeling upon the endocortical surface lining the medullary canal and the trabecular surfaces is suppressed and ultimate load is increased in trabecular bone reflecting the greater accessibility of this bisphosphonate to these surfaces and the higher concentration of the drug in trabecular rich spine than cortical bone of the tibia. Adapted from Bone, 31:45-55, Copyright (2003), with permission from Elsevier.

If denosumab has better access to intracortical remodeling than bisphosphonates, then the real test is whether it reduces nonvertebral fractures more greatly than denosumab. This requires a comparator trial. None have been done using fractures as an outcome. **Nakamura et al** report a phase 3 randomized, double-blind, placebo-controlled trial with an open-label active-comparator fracture study of 1262 Japanese women and men with osteoporosis aged 50 years or older, who had 1-4 prevalent vertebral fractures (5). Subjects were randomly assigned to denosumab 60 mg sc 6 monthly (n=500), placebo (n=511), or oral ALN 35 mg weekly (n=251). Denosumab reduced the risk of vertebral fracture by 65.7% with incidences of 3.6% in denosumab and 10.3% in placebo at 24 months (HR=0.343; 0.194-0.606, p<0.0001). No difference in adverse events was found between denosumab and placebo. Regrettably, the antifracture efficacy of denosumab vs. open label ALN was not reported.

Keaveny et al report that in 48 placebo and 51 denosumab treated women, compared with baseline, hip strength increased by 12 months (5.3%; p<0.0001) and through 36 months (8.6%; p<0.0001) in the denosumab group (6). In the placebo group, hip strength did not change at 12 months and decreased at 36 months (5.6%; p<0.0001). At the spine, strength increased by 18.2% at 36 months with denosumab (p<0.0001) and decreased by 4.2% with placebo (p=0.002). At 36 months, hip and spine strength increased for the denosumab group compared with the placebo group by 14.3% and 22.4%, respectively (both p<0.0001).

Cathepsin K inhibitors

The resorptive phase of remodeling by osteoclasts of a basic multicellular unit (BMU) is about 3 weeks in duration. The formation phase that follows lasts about 3 months during which osteoblasts of that BMU lay down new osteoid which then undergoes rapid primary primary mineralization. Secondary mineralization, the enlargement of calcium hydroxyapatite crystals proceeds to completion during the next two to three years. Between these two phases is the reversal phase, a phase where there are no osteoclasts or osteoblasts (7).

There is not much understood about this phase because it has not been thought about or studied comprehensively, but **Jensen et al** have taken the initiative and report that, compared with ALN, odanacatib (ODN) resulted in a shorter reversal phase with more rapid initiation of osteoid deposition on the eroded surfaces and higher osteoblast recruitment as a higher density of mature bone forming osteoblasts and an increased subpopulation of cuboidal osteoblasts (8). These authors suggest that an increase in the interface between osteoclasts and osteoblast lineage cells may favor the osteoclast-osteoblast interactions for bone formation.

I suspect that this initiative arises from the finding that after initiation of ODN, resorption markers decrease reflecting suppression of bone remodeling upon the trabecular and intracortical surfaces but not

on the endocortical surface, at least as assessed in subhuman primates (9). Socalled bone 'formation' markers appear to be suppressed less and tend, with time, to return to baseline while resorption markers continue to be suppressed.

The interpretation of these two observations is difficult. The continued suppression of resorption markers may reflect both continued remodeling – similar numbers of BMUs formed upon the endocortical surface and fewer upon the intracortical and trabecular surfaces excavate smaller resorption pits than were excavated before ODN treatment account for the persisting lower resorption markers (by about 50% of baseline). How about the return to baseline of formation markers? The inference is made that signals from the resorbed matrix or from osteoclasts (that don't resorb but still have other viable functions) continue and allow bone formation to continue. There is no evidence, that I am aware of, that the volume of bone deposited in the smaller pits increases – mean wall thickness has not been convincingly demonstrated except perhaps upon the periosteal surface but not upon the endosteal surfaces. So, from this, the formation markers should also remain suppressed, but they don't seem to be. I don't understand this.

It remains possible, that if the volume of bone deposited upon the more shallow pits is either the same as before treatment, then the net bone balance produced during each remodeling transaction should be lessened, or ideally made positive. In the latter situation, it becomes an advantage to keep remodeling rate high as each remodeling event will produce a net positive bone balance and so restore bone structure. A positive BMU balance could still result if the same volume of bone was deposited in a smaller resorption pit.

There is another mechanism that may account for continued bone formation. **Pennypacker et al** characterized the effects of ODN on the dynamics of cortical modeling of the central femur in adult OVX rhesus monkeys (10). Animals were treated with vehicle or ODN (6 or 30 mg/kg, qd, po) for 21 months. ODN increased periosteal and endocortical bone formation (BFR/BS), increased in endocortical mineralizing surface (102%, $p<0.01$) with the 6m g/kg dose. Both doses reduced remodeling hemiosteon numbers by 51% and 66% ($p<0.05$), respectively, and ODN 30 mg/kg numerically reduced activation frequency without affecting wall thickness. On the same endocortical surface, ODN increased modeling-based parameters, while reducing intracortical remodeling. ODN 30 mg/kg increased cortical thickness (CtTh, $p<0.001$), reduced marrow area ($p<0.01$) and increased femoral structural strength ($p<0.001$). Peak load correlated with the increases in BMC ($r^2=0.91$) and CtTh ($r^2=0.69$, both $p<0.0001$). The authors infer that reduced cortical remodeling and stimulating modeling-based bone formation, ODN improved cortical dimension and strength in OVX monkeys.

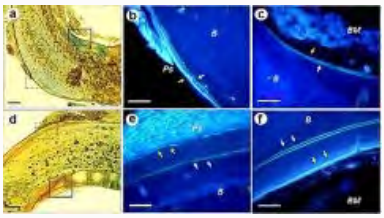


Figure 4. ODN increased periosteal and endocortical bone formation in the central femur of OVX monkeys. Central femurs treated with: (a-c) Vehicle and (d-f) ODN 30 mg/kg. (a&d) Light microscopic images of central femoral cross sections at low magnification; Bar=500 µm. (b&e) Fluorescent images of periosteal surfaces (insets with broken lines in a&d) at higher magnification to show calcein (15-d, white arrows) labeling at month 12, and tetracycline (15-d, yellow arrows) labeling at month 21. (c&f) Images of endocortical surfaces (insets with solid lines in a&d), showing bone formation by CAL and TCY labels; Bar=200 µm. B, bone; BM, bone marrow. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2211 with permission of the American Society of Bone and Mineral Research.

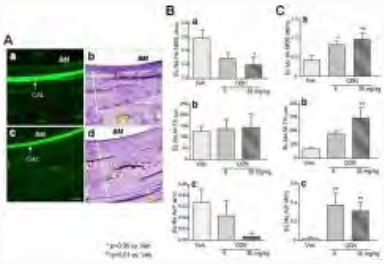
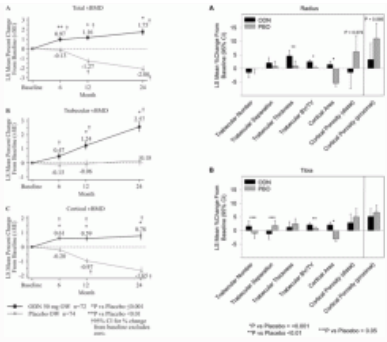


*Figure 5. Effects of ODN on remodeling- and modeling-based hemiosteons in the endocortical surfaces of the central femur. (A) The endocortical sections were stained with toluidine B and viewed under fluorescent (a&c) or light microscopy (b&d): (a&b) remodeling hemiosteon and (c&d) modeling hemiosteon were detected by calcein (CAL) labeling (white arrows) between two cement lines (Cm, yellow arrows), and wall thickness (WTh, double white arrowheads). B, bone; BM, bone marrow; Bar=50 µm. (B) Endocortical remodeling-hemiosteons, (scalloped cement lines), were measured including (a) the number of remodeling hemiosteons, (b) wall thickness and (c) activation frequency. (C) The same parameters from endocortical modeling-based hemiosteons, evident by the smooth cement line, were measured from central femur treated with ODN 6 mg/kg and 30 mg/kg vs. Veh. *p<0.05 and **p<0.01 vs. OVX-Veh. Mean±SEM. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2211 with permission of the American Society of Bone and Mineral Research.*

Cheung et al conducted a randomized, double-blind, placebo-controlled trial in 214 postmenopausal women (mean age 64.0±6.8 years, and baseline lumbar spine T-score -1.81±0.83) and that oral ODN 50 mg given for two years increases total vBMD at the distal radius and tibia assessed using HR-pQCT (11). Treatment differences from placebo were also significant (3.84% and 2.63% for radius and tibia, respectively). At both sites, significant differences from placebo were also seen in trabecular vBMD, cortical vBMD, cortical thickness, cortical area and strength (failure load) estimated using finite element analysis of HR-pQCT scans (treatment differences at radius and tibia = 2.64% and 2.66%). At the distal radius, ODN improved trabecular thickness and BV/TV vs. placebo. At a more proximal radial site, treatment attenuated the increase in cortical porosity seen with placebo (treatment difference=-7.7%, $p=0.066$). At the distal tibia, ODN improved trabecular number, separation, and BV/TV vs. placebo.

Figure 6. Left panel: Total trabecular and cortical volumetric BMD at the distal radius. Right panel: Two-year percent changes in other HR-pQCT parameters at (A) radius, (B) tibia. The distal radius and tibia (to the left of the vertical line) were scanned for trabecular number, separation, thickness, bone volume/total volume (BV/TV) cortical area and porosity. The more proximal regions (to the right of the vertical line) were scanned for assessment of cortical porosity. LS, least squares. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2194 with permission of the American Society of Bone and Mineral Research.



Nakamura et al report the efficacy and safety of ODN 10, 25, or 50 mg once weekly for 52 weeks in a double-blind, randomized, multicenter study in 286 Japanese patients with osteoporosis [94% female, mean age(SD) 68.2(7.1) years] (12). The least squares mean percent changes from baseline to week 52 in the groups receiving placebo, 10, 25 and 50 mg of ODN for spine BMD were 0.5, 4.1, 5.7, and 5.9% and for total hip BMD were -0.4, 1.3, 1.8, and 2.7 %, respectively. The changes in femoral neck and trochanter BMD were similar to those at the total hip. The effects of ODN on bone formation markers were less compared with the effects on bone resorption markers.

Figure 7. Percent change in BMD at the spine, total hip, femoral neck and trochanter. Reproduced from Osteoporos Int 2014;25:367-76 with permission from Springer.

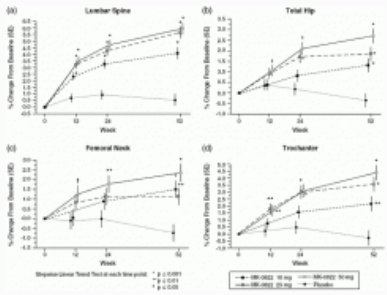
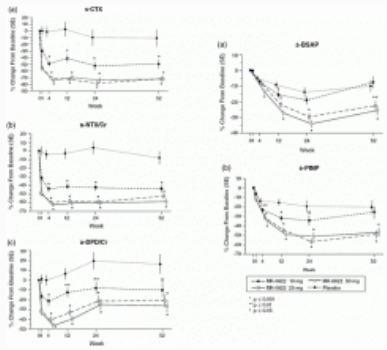


Figure 8. Percent change in serum CTX, urine NTX/Cr, urine DPD/Cr, serum BSAP and serum P1NP. Reproduced from Osteoporos Int 2014;25:367-76 with permission from Springer.



Eastell et al randomized 197 postmenopausal women with osteoporosis or osteopenia with one fragility fracture to ONO-5334 50 mg twice daily, 100 mg or 300 mg once daily, ALN 70 mg once weekly or placebo (13). After 24 months, all ONO-5334 doses increased BMD at the spine, total hip, and femoral neck ($p<0.001$). ONO-5334 300 mg suppressed urinary (u) NTX and serum and uCTX-I throughout 24 months and to a similar extent as ALN; other resorption marker levels remained similar to placebo (fDPD for ONO-5334 300 mg qd) or increased (ICTP, TRAP5b, all ONO-5334 doses). Levels of B-ALP and PINP were suppressed in all groups (including placebo) for 6 months but then increased for ONO-5334 to near baseline by 12-24 months. On treatment cessation, there were increases above baseline in uCTX-I, uNTX, and TRAP5b, and decreases in ICTP and fDPD.

Engelke et al investigated the effect of 2 years of ONO-5334 in a randomized, double-blind, placebo, and active controlled parallel group study of 147 subjects (age 55-75 years) (14). Subjects were randomized to placebo; 50 mg bd (BID); 100 mg/d (qd); ONO-5334 300 mg qd; or ALN 70 mg once weekly (qw). After 24 months, ONO-5334 produced increases vs. placebo for integral, trabecular, and cortical BMD at the spine and hip measured using QCT (for ONO-5334 300 mg QD, BMD increases were 10.5%, 7.1%, and 13.4% for integral, cortical, and trabecular BMD at the spine, respectively, and 6.2%, 3.4%, and 14.6% for integral, cortical, and trabecular total femur BMD, respectively). Changes in cortical and trabecular BMD in the spine and hip were similar for ALN and ONO-5334. There was no evidence of periosteal apposition. Cortical thickness did not change for ONO-5334 in the spine or hip, with exception of a 2.1% increase after month 24 in the intertrochanter for 300 mg qd.

Bisphosphonates

Risedronate

Bala et al recruited 161 younger (Group 1, ≤55 years) and 163 older (Group 2, ≥55 years) women randomized to risedronate 35 mg/week or placebo (15). In the younger group, distal radius compact-appearing cortex porosity increased by 4.2% ± 1.6% in controls ($p=0.01$). This increase was prevented by risedronate. Trabecular vBMD decreased by 3.6% ± 1.4% ($p=0.02$) in controls and decreased by about half that, 1.6% ± 0.6% ($p=0.005$) with risedronate. In the older group, changes did not achieve significance apart from a reduction in compact-appearing cortex porosity in the risedronate treated group (0.9% ± 0.4%, $p=0.047$). Risedronate slows microstructural deterioration in younger and partly reverses it in older postmenopausal women.

The work illustrates that the effect of therapy in part depends on the pattern of remodeling. In early menopause, accelerated bone loss is due to perturbed remodeling at the surface level where many resorption cavities are excavated and this accelerated loss is slowed but not stopped with therapy. Later, when remodeling has returned to steady state at a high remodeling rate, the drug can reduce porosity,

not only just lessen its continued increase.

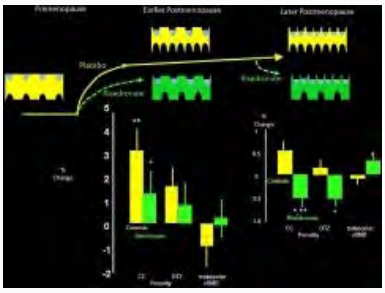


Figure 9. In early menopause, women given placebo (yellow) had increased porosity of the compact cortex (CC) and outer transitional zone (OTZ) and a decrease in trabecular vBMD. In later menopause women also had increased porosity but no detectable fall in trabecular vBMD. Risedronate (green) reduced the rise in porosity and fall in trabecular vBMD during early menopause and reduced porosity in later menopausal women and increased trabecular vBMD. Adapted from J Bone Miner Res 2014;29:380-8 with permission of the American Society of Bone and Mineral Research.

Zoledronic acid

Grey et al report that 180 postmenopausal women with osteopenia were randomized double-blind in a 2 year placebo-controlled trial to a single dose of intravenous zoledronic acid (1, 2.5 or 5 mg), or placebo (16). The change in spine BMD was greater in the zoledronate groups than placebo; mean (95% CI) difference vs. placebo: 1 mg 4.4%; 2.5 mg 5.5%; 5 mg 5.3% (all p<0.001). Change in total hip BMD was greater in each group than the placebo 1 mg 2.6%; 2.5 mg 4.4%; 5 mg 4.7% (all p<0.001). β-CTX and P1NP were lower in the 2.5 mg and 5 mg groups than the placebo (all p<0.001). Changes were similar in the 2.5 mg and 5 mg groups, changes in the 1 mg group were smaller than in the other zoledronate groups. The study makes the important point that this potent agent is likely to be effective at lower doses. There is evidence that a single dose may be as effective in reducing fracture rates as annual administration.

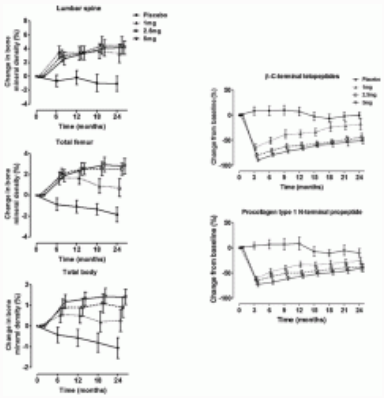


Figure 10. Left panels: BMD at the spine, total hip and total body during 2 years were highter in each dose than placebo throughout the study. Right panels: CTX and P1NP during 2 years were lower using 2.5 and 5 mg zoledronic acid than placeo. The levels using 1 mg were lower up to 18 months. Reproduced from J Bone Miner Res 2014;29:166-72 with permission of the American Society of Bone and Mineral Research.

Ibandronate

Miller et al conducted a post hoc analysis using individual patient data from the 2-year monthly oral ibandronate in ladies (MOBILE, 150 mg, n=176)), the dosing intravenous administration (DIVA) studies, and the 3-year long-term extensions (LTEs, iv ibandronate every 2 months 2 mg, n=253, or quarterly 3 mg, n=263) to assess fracture risk during 5 years (17). Three-year placebo data (n=1924) were obtained from the ibandronate osteoporosis vertebral fracture trial in North America and Europe (BONE) and iv Fracture Prevention trials. Ibandronate regimens with annual cumulative exposure ≥10.8 mg were associated with a longer time to fracture for all clinical fractures, nonvertebral fractures, and clinical vertebral fractures vs. placebo (P=0.005). For all fracture types, the rate of fracture appeared stable during the 5-year treatment period. Credibility of post hoc analyses like this is difficult to evaluate.

Meier et al report that observational studies suggest beneficial effects of bisphosphonates in osteonecrosis (ON) of the knee (18). In this randomized, double-blind, placebo-controlled trial, 30 patients (mean age, 57.3±10.7 years) with ON of the knee were assigned to ibandronate (cumulative dose, 13.5 mg) or placebo intravenously (divided into five doses 12 weeks). Patients were followed for 48 weeks. After 12 weeks, mean pain score was reduced in ibandronate-treated (mean change, -2.98; 95% CI, -4.34 to -1.62) and placebo-treated (-3.59; 95% CI, -5.07 to -2.12) subjects. Except for significant decrease in bone resorption marker (CTX) in ibandronate-treated subjects (p<0.01), adjusted mean changes in all functional and radiological outcome measures were comparable between treatment groups after 24 and 48 weeks. IV ibandronate has no beneficial effect over and above anti-inflammatory medication.

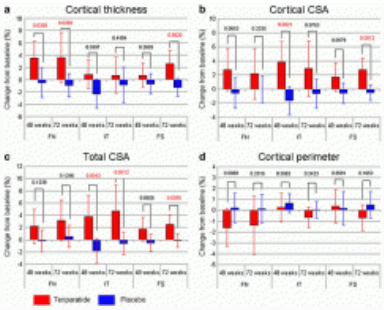
Anabolic Agents

Parathyroid hormone peptides

Fujita et al report the results of a randomized, double-blind trial of 28.2 μg teriparatide vs. placebo (1.4 μg teriparatide) in 316 subjects (19). Incident vertebral fractures occurred in 3.3% of the teriparatide group and 12.6% of the placebo group during 78 weeks. Kaplan-Meier estimates of risk after 78 weeks 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 teriparatide group increased by 4.4±4.7 %, higher than in the placebo (P=0.001).

Ito et al administered weekly teriparatide [human PTH (1-34)] to 29 postmenopausal women with osteoporosis (74.2±5.1 years) and placebo (n=37, 74.8±5.3 years) (20). CT data were obtained at baseline, 48 and 72 weeks. Once weekly teriparatide increased cortical thickness/cross-sectional area and total area, and improved biomechanical properties at the femoral neck and shaft, not cortical perimeter.

Figure 11. Percent changes in cortical thickness (a), cross-sectional area (CSA) (b), total CSA (c), and cortical perimeter (d) at 48 and 72 weeks. Changes at the femoral neck (FN), intertrochanter (IT), and femoral shaft (FS) are shown. Values on top of each panel indicate p values (between teriparatide and



placebo group). Red and blue bars correspond to teriparatide and placebo groups, respectively. Reproduced from Osteoporos Int 2014;25:1163-72 with permission from Springer.

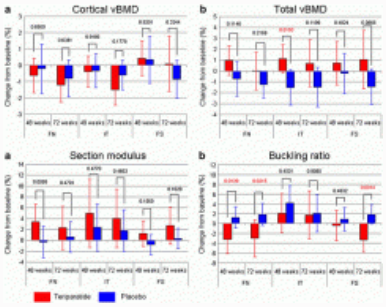
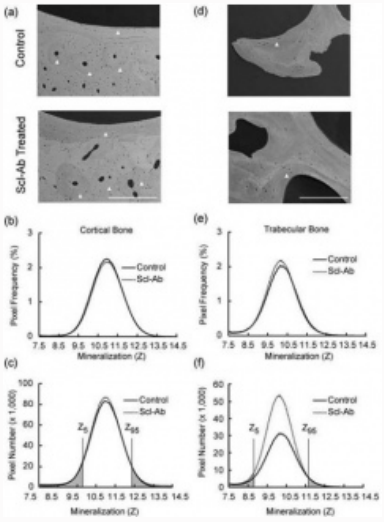


Figure 12. Upper panels: Percent changes in cortical vBMD (a) and total vBMD (b) at 48 and 72 weeks. Changes at the femoral neck (FN), intertrochanter (IT), and femoral shaft (FS) are shown. Red and blue bars correspond to teriparatide and placebo groups, respectively. Lower panels. Percent changes in SM (a) and BR (b) at 48 and 72 weeks. Changes at the FN, IT and FS are shown. Reproduced from Osteoporos Int 2014;25:1163-72 with permission from Springer.

Antisclerostin antibody

Ross et al report up to 54% increases in the bone volume following Scl-Ab without change in mean global matrix mineralization of trabecular or cortical bone (21). However, there was an increase in the number of pixels with a low mineralization and a decrease in the standard deviation of the distribution. Scl-Ab did not affect the mineral-to-matrix ratio, crystallinity or collagen crosslinking in the endocortical, intracortical, or trabecular compartments. There was a trend toward accelerated mineralization intracortically and a nearly 10% increase in carbonate substitution for tissue older than 2 weeks in the trabecular compartment.

Figure 13. Representative bSEM images of (a) cortical and (d) trabecular bone from primates treated for 10 weeks with either saline (controls) or Scl-Ab (scale bar=200 μm). Newly remodeled or relatively young tissue is highlighted with arrow heads. Representative normalized BMDDs of (b) cortical and (e) trabecular bone. Representative nonnormalized BMDDs of (c) cortical and (f) trabecular bone. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2188 with permission of the American Society of Bone and Mineral Research.



McColm et al report two clinical studies conducted to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple doses (iv and sc) of blosozumab in postmenopausal women (22). Subjects received escalating doses of blosozumab: single iv doses up to 750 mg, single sc doses of 150 mg, multiple iv doses up to 750 mg every 2 weeks (Q2W) for 8 weeks, multiple sc doses up to 270 mg Q2W for 8 weeks, or placebo. Six subjects were randomized to each dose in the single-dose study (12 to placebo) and up to 12 subjects to each arm in the multiple-dose study. Blosozumab was well tolerated. There was up to a 3.41% (p=0.002) and up to a 7.71% (p<0.001) change from baseline in lumbar spine BMD at day 85 after single or multiple administrations of blosozumab, respectively. Prior BP did not have an impact on the effects of single doses of blosozumab. Antibodies to blosozumab were detected with no effect on PD responses were identified.

PTH and Alendronate
Two is better than one

Altman et al treated 30 female rats with vehicle (Veh), ALN, PTH, or both (23). Individual trabecula segmentation (ITS)-based analyses using in vivo microcomputed tomography showed an increase in BV/TV with all treatments and the highest in the combined group. Tb.Th increased with PTH and PTH+ALN beyond that of the Veh or ALN. SMI decreased in all treatments with PTH+ALN having the greatest tendency toward platelike structures. Increased plate Tb.N and increased plate-to-rod ratio was most pronounced in the PTH+ALN group. Stiffness increased in all treatment groups with the largest increase in the PTH+ALN group. PTH+ALN increased bone formation and suppressed resorption. PTH+ALN has an additive effect on trabecular bone.

Figure 14. Changes in BV/TV, trabecular thickness, structural model index (SMI) and trabecular stiffness in each group. Reproduced from Bone, 61:149-57, Copyright (2014), with permission from Elsevier.

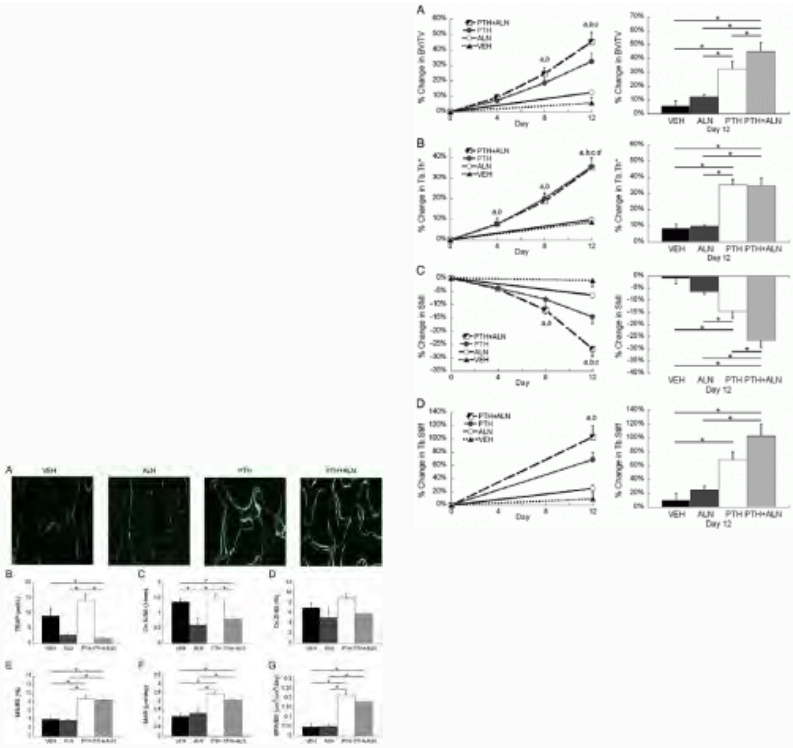
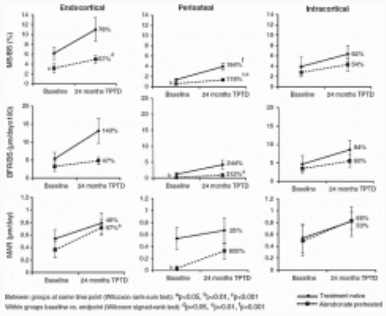


Figure 15. (A) Calcein labelling in trabecular bone in each group, (B) serum TRAP, Osteoclast number and surface, mineralizing surface, MAR and BFR. Reproduced from Bone, 61:149-57, Copyright (2014), with permission from Elsevier.

Ma et al analyzed the effects of 24 months teriparatide in 29 ALN-pretreated and 16 treatment niave (TN) women (24). At baseline, reduced remodeling was evident the ALN group. Following teriparatide, forming and resorbing osteons increased. Teriparatide increased MAR in the endocortical, and MS/BS% in the periosteal compartment in the ALN-pretreated group. Most indices of bone formation remained lower in the ALN-pretreated group. Endocortical wall width was increased in both groups. Cortical porosity and cortical thickness increased in the ALN-pretreated group after teriparatide. 24 months of teriparatide increases cortical bone formation and cortical turnover in patients either TN or had previous ALN therapy.

Figure 16. Cortical changes in MS/BS, BFR and MAR upon the endocortical, periosteal and intracortical surface after 24 months in mineralizing surface. Reproduced from Bone, 59:139-47, Copyright (2014), with permission from Elsevier.



Remodeling Independent Mechanisms
Strontium ranelate

Chavassieux et al report a multicenter, international, double-blind, controlled study of 387 postmenopausal women with osteoporosis having transiliac bone biopsies at baseline and after 6 or 12 months of strontium ranelate (SrRan) 2 g/day (n=256) or alendronate 70 mg/week (n=131) (25). No deleterious effect on mineralization of SrRan or ALN was observed. In the intention-to-treat (ITT) population (268 patients with paired biopsy specimens), greater changes in static and dynamic bone formation parameters were observed with ALN than SrRan. Static parameters of formation were maintained between baseline and the last value with SrRan reflecting continued remodeling upon the endosteal surface, except for osteoblast surfaces, which decreased at M6. Decreases (not increases) in the dynamic parameters of formation (mineralizing surface, bone formation rate, adjusted apposition rate, activation frequency) were noted at M6 and M12 in SrRan. Compared with ALN, the bone formation parameters at M6 and M12 were higher ($p<0.001$) with SrRan. ALN, not SrRan, decreased resorption parameters. Compared with the baseline, wall thickness was decreased at M6 but not at M12 and cancellous bone structure parameters (trabecular bone volume, trabecular thickness, trabecular number, number of nodes/tissue volume) were decreased at M12 with SrRan; none of these changes were different from ALN.

This study provides compelling evidence that SrRan is not an anabolic agent and indeed, it does not really have substantive effects on bone remodeling. Bone formation surfaces remains higher than alendronate precisely because remodeling is not suppressed – the statement does not mean bone formation is higher – this refers to the surface extent of bone formation; there is no evidence that the volume of bone deposited by each BMU is increased. There is less diminution of the bone remodeling

with SrRan vs. ALN because SrRan does not suppress surface level remodeling, alendronate does because it is a classic antiresorptive agent.

Abrahamsen et al report that the European Medicines Agency (EMA) recently warned that SrRan should be avoided in patients with ischaemic heart disease (IHD), peripheral vascular disease (PVD) or cerebrovascular disease (CVD), and in patients with uncontrolled hypertension (26). Using the Danish National Prescription Database, 3252 patients aged 50+ who began SrRan and 35,606 users of other osteoporosis drugs (controls) were studied. Patients starting SrRan were older and more likely to suffer from IHD, PVD or CVD. The adjusted risk of MI: HR 1.05 (0.79-1.41, p=0.73) in women and 1.28 (0.74-2.20, p=0.38) in men. For stroke, the adjusted HR was 1.23 (0.98-1.55, p=0.07) in women and 1.64 (0.99-2.70, p=0.05) in men. All-cause mortality was higher (women: adjusted HR 1.20 [1.10-1.30, p<0.001]; men: adjusted HR 1.22 [1.03-1.45, p<0.05]). A large proportion of patients currently treated with strontium ranelate have conditions that would now be considered contraindications according to EMA.

Cooper et al report that of 112,445 women with treated postmenopausal osteoporosis, 6487 received SrRan (27). Annual incidence rates for first myocardial infarction (1352 cases), myocardial infarction with hospitalisation (1465 cases), and cardiovascular death (3619 cases) were 3.24, 6.13 and 14.66 per 1000 patient-years, respectively. Current or past use of SrRan was not associated with increased risk for first myocardial infarction (OR 1.05, 0.68-1.61 and OR 1.12, 0.79-1.58, respectively), hospitalization with myocardial infarction (OR 0.84, 0.54-1.30 and OR 1.17, 0.83-1.66), or cardiovascular death (OR 0.96, 0.76-1.21 and OR 1.16, 0.94-1.43) vs. patients who had never used SrRan.

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Progress in Osteoporosis

CRITICAL REVIEW JOURNAL

OVERVIEW, VOL 14, ISSUE 2

Ego Seeman
Editor

By Ego Seeman Thu, 08/14/2014 - 10:13

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."

We invite readers to comment on and discuss this journal entry at the bottom of the page.

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Denosumab

Denosumab is the most powerful remodeling suppressant available. Remodeling removes old or damaged bone and so it is beneficial provided that each remodeling transaction carried out by each basic multicellular unit (BMU) removes and replaces the same volume of bone. However, when BMU balance becomes negative, as occurs around midlife, each remodeling event produces structural decay. So, it can be argued that *any* remodeling is bad for the structure of bone. However, the price that may be paid for remodeling suppression is the potential for compromising the material composition of bone, especially in persons with low baseline remodeling who may assemble a bone with a mean bone matrix mineral density at the upper part of the normal distribution for this trait.

In the presence of little or no remodeling, microdamage is unlikely to be removed. As more and more of the unremodeled matrix undergoes secondary mineralization, a process that takes months to years to reach completion, adjacent osteons become similarly and homogeneously mineralized. The increased homogeneity, i.e., reduced heterogeneity, in matrix mineralization density and increase pentosidine crosslinking of collagen are likely to reduced ductility of bone matrix – its ability to deform without cracking. This leads to microdamage as the matrix becomes stiff so that when a load is imposed, instead of matrix deforming, changing length and absorbing energy in that way, the energy is released as a microcrack. If these accumulate, or one major crack progresses in length, catastrophic structural failure may occur.

The question is what is worse; to allow some remodeling and sacrifice structure while maintaining material composition of the slowly decaying bone, or to suppress remodeling as much as possible and preserve structure but allow deterioration in material composition. There is an answer to this question. There needs to be a measure pretreatment material composition and structure and monitoring of the relative effects of treatment on the material composition, structure and whole bone strength. From this, it may be possible to administer and titrate therapies accordingly.

Four papers published recently address the effects of denosumab on bone histomorphetry, structure, comparisons with bisphosphonates and the effects on intrauterine development. **Brown et al** evaluated 41 subjects (13 crossover from placebo and 28 long-term denosumab groups representing up to 5 years denosumab treatment) (1). The mean (SD) duration from the last denosumab dose to the first dose of tetracycline was 5.7 (0.5) months. Qualitative histology showed normal mineralized lamellar bone. Bone remodeling decreased as reflected by eroded surface in crossover and long-term subjects. 11/13 (85%)

Supported by an unrestricted educational grant from
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crossover subjects and 20/28 (71%) long-term subjects had double or single tetracycline label in trabecular and/or cortical compartments; specimens from 5 crossover subjects and 10 long-term subjects were evaluable for dynamic trabecular bone parameters; remodeling indices were low, consistent with reduced remodeling. Information on the material composition of bone and its consequences in the longer term on bone strength were not studied. I find this disappointing because we need information regarding the material composition of bone with longer term denosumab therapy given its very efficient remodeling suppressant effects, we need to know if there is a risk of increased tissue mineralization and glycosylation and so, an increased risk for atypical fractures.

Brown et al report that postmenopausal women ≥55 years suboptimally adherent to bisphosphonate (BP) were randomized to denosumab 60 mg subcutaneously every 6 months (N=852) or oral 150 mg monthly ibandronate or risedronate (N=851) for 12 months (2). Denosumab produced greater gains in BMD at 12 months than monthly ($p<0.0001$ all). In higher risk subjects, denosumab led to greater gains in BMD than oral BPs at the total hip (2.2 vs. 0.8 %), femoral neck (1.8 vs. 0.3 %), and lumbar spine (3.7 vs. 1.4 %). Denosumab also led to greater decreases in sCTX-1 in the whole group and higher risk subjects (all $p<0.0001$). There are no surprises here given how powerfully denosumab reduces remodeling. What is of interest is where is the remodeling continuing in the skeleton. It is likely that this is intracortical remodeling that continues with the BPs. This needs formal study but has been reported. Zebaze et al report greater suppression of remodeling and a greater reduction in porosity with denosumab than alendronate (3). If denosumab suppresses intracortical remodeling more than alendronate, could this drug have greater antifracture efficacy than alendronate? We don't know. No comparator studies have been done, but it is clearly one of the great challenges for the new leaders in the field. A 20% reduction in nonvertebral fracture efficacy reported in most trials is not good enough.

Poole et al used 3D cortical bone mapping of the proximal femur in 80 postmenopausal women with osteoporosis to determine the timing and location of effects of denosumab (4). Cortical 3D bone thickness and surface density maps of both hips were created from CT scans at baseline, 12, 24 and 36 months. After registration of each bone to an average femur shape model followed by statistical parametric mapping to identify differences between denosumab and control. Denosumab increased cortical mass surface density and thickness by 12 months and by 5.4% over 3 years, and by up to 12% relative to placebo at locations such as the lateral femoral trochanter. The authors report one third of the increase came from increasing cortical density, and two thirds from increasing cortical thickness relative to placebo.

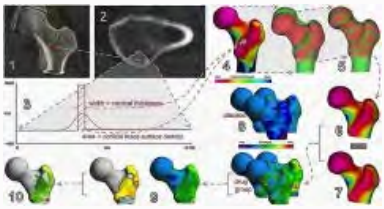

Figure 1. Summary of the steps involved in 3D cortical bone mapping and analysis of changes over time using statistical parametric mapping (SPM). (1) Triangulated 3D surface of a left proximal femur (one individual) and corresponding coronal CT plane after segmentation with Stradwin software. (2) An axial CT slice to demonstrate sampling the CT data along an 18mm cyan trans-cortical line at the surface location indicated by the red circular dot. (3) Parametric fit (red curve) and original CT data (cyan curve), superimposed on a graph of distance (x axis) vs. Hounsfield units (y axis) along the 18 mm transcortical line. The cortical thickness is the distance between the red arrows. (4) Many thousands of cortical thickness estimates painted by reference to a colour scale onto the femoral surface of same individual. (5) Registration (morphing) of the individual's femoral surface shape to the canonical femur shape, CFS. (6) Resultant map displaying cortical thickness for the individual now on the CFS after left and right femurs are averaged to give a single map per participant at each visit. (7) Subtracting the baseline cortical thickness map from the 36 month map in an individual to create a difference map. (8) After unblinding, there are two groups; cortical thickness difference maps from the placebo (upper), and denosumab groups (lower). (9) Typical results from one arm of the study (in this case, the denosumab group) using the statistical parametric mapping process to find and quantify where the 36 month maps differ from baseline maps. The left image shows a yellow p-value map displayed on the CFS. The yellow foci are vertices where cortical thickness changed significantly between baseline and 36 months, ranging from grey (non-significant) via orange to increasingly bright yellow as the p value decreases. The right image shows the amount of change as a colour scale on the CFS. In this hypothetical case we see increasing thickness with denosumab. (10) Final result showing the magnitude of increase in cortical thickness on the CFS with only areas of statistically significantly greater cortical thickness retained, the rest greyed out. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2325 with permission of the American Society of Bone and Mineral Research.

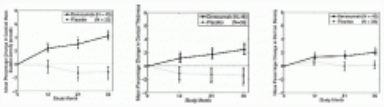

Figure 2. Percentage changes in overall cortical mass surface density (left), overall* cortical thickness (middle) and overall* cortical density (right) during 3 years treatment with denosumab or placebo. These results are averaged across the entire femoral cortical surface. *By 'overall', we denote the mean value for all femurs, each averaged over the entire canonical femur surface; i.e., the average of approximately 6000 points per femur from 78 femurs (every femur). The values are shown for each of 4 visits (baseline, 12 months, 24 months, 36 months). Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2325 with permission of the American Society of Bone and Mineral Research.*

As discussed by the authors, it is possible that cortical thickening is produced by infilling of porosity with subendocortical cortex. It is difficult to explain this by any other means. Antiresorptives are not anabolic, they do not increase bone mass by depositing bone upon the endocortical surface to thicken the cortex. At best, they allow partial refilling of endocortical resorption cavities excavated before treatment – these excavated sites partly refill while newly excavated sites are virtually abolished, so at best, if a hemiosteon is dug on the endocortical surface it may be about 100 microns in depth and then refills to about 97% of its starting value – this cannot build bone unless the resorption cavity dug was reduced by denosumab; this is possible but remains unproven. Another mechanism of cortical thickening may be continued bone modeling that becomes detectable because it is no longer obscured by high remodeling which is now suppressed (5).

Boyce et al report subcutaneous 50 mg/kg/month denosumab was given to pregnant cynomolgus monkeys from gestation day (GD) 20 to parturition (6). For up to 6 months postpartum (birth day [BD] 180/181), remodeling markers decreased at birth day. Spontaneous long bone fractures were detected in 4 denosumab-exposed infants at BD28 and BD60. BD1 infants exposed to denosumab in utero had decreased bone length; increased radio-opacity of the axial and appendicular skeleton and base of the skull with decreased marrow cavities, widened growth plates, flared metaphyses, altered jaw/skull shape, reduced jaw length; delayed secondary ossification centers, increased trabecular BMD, decreased cortical

BMD. Bones with endochondral ossification consisted of dense primary spongiosa with reduced marrow space. Retained woven bone was observed in bones formed by intramembranous ossification. Reductions in toughness at the femur diaphysis and lack of correlation between energy and bone mass at the vertebra were observed. Tooth eruption was unimpaired, the reduced growth and increased bone density of the mandible resulted in tooth malalignment and dental dysplasia. Radiographic changes at BD1 persisted at BD28, with evidence of resumption of resorption and remodeling in most infants at BD60 and/or BD90. There was recovery from bone-related changes in infants necropsied at BD181 where exposure to denosumab had been below limits of quantitation for 3 months. The phenotype resembles infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL.

Cathepsin K Inhibition

Cathepsin K (CatK) inhibition prevents bone resorption by preventing collagen degradation (7). There are many fascinating aspects concerning the mechanisms of action of this class of drug. The most consistent and credible effect is the reduction in the size of the resorption cavities excavated. Antiresorptives like the BPs and denosumab probably do this too but it is well documented experimentally with CatK inhibitors and other models perturbing collagen degradation (8).

After this, the data becomes challenging to interpret. BPs and denosumab reduce the rate of bone remodeling – they reduce the number of resorption sites appearing per unit bone volume per unit time and this reduction in activation frequency is clearly identifiable in the reduction in circulating remodeling markers. CatK inhibition also reduces remodeling rate but this appears to be site-, surface- and species-specific. The trabecular and intracortical surface extent of remodeling, as measured by the mineralizing surface per unit bone surface is reduced but not necessarily upon the endocortical surface, at least in monkeys (9).

If remodeling removes a larger volume of bone than is subsequently deposited upon the endocortical surface, this will erode and thin the cortex. If remodeling is slowed, as it appears to be upon intracortical and trabecular surfaces, then structural decay will still occur at these locations but more slowly and will produce cortical porosity and trabecular thinning respectively, provided there is a negative BMU balance.

If the depth of resorption produced by each BMU is lessened using a CatK inhibitor, and the volume of bone deposited is now equal to the volume resorbed, then there will be no net bone loss despite continued remodeling. If the volume of bone deposited exceeds the volume resorbed then this may produce a positive BMU balance. Under these circumstances, high remodeling rate is an advantage because each remodeling event will add bone. This desirable scenario remains unproven experimentally.

Several studies have been published recently, but the data need to be examined carefully. **Ochi et al** report that vehicle, ONO-5334 (3, 10 or 30 mg/kg) or alendronate (0.5 mg/kg) were administered for 8 months to sham and OVX monkeys (10). Alendronate prevented OVX-induced increase in remodeling rate, but it did not appear to reduce remodeling markers; this is surprising as virtually all studies in animals and humans demonstrate a convincing and easily visualized reduction in remodeling with alendronate. ONO-5334 at 30 mg/kg did not suppress remodeling, again this is quite different to studies done in human subjects. In this study, remodeling upon periosteal, osteonal and endocortical surfaces continued as determined by histomorphometry. If remodeling continued, then bone structure should deteriorate if BMU balance is negative. However, the higher dose maintained urinary CTX near zero and kept serum osteocalcin around the level of the sham animals. So, the drug prevented a rise in remodeling markers, but it did not prevent remodeling at the surface of bone. ONO-5334 reversed the effect of OVX on vertebral BMD with improvement in strength. Both ONO-5334 and alendronate prevented OVX-induced changes in vertebral microstructure. Femoral neck pQCT showed that ONO-5334 increased total and cortical BMD and strength. I don't understand this work.

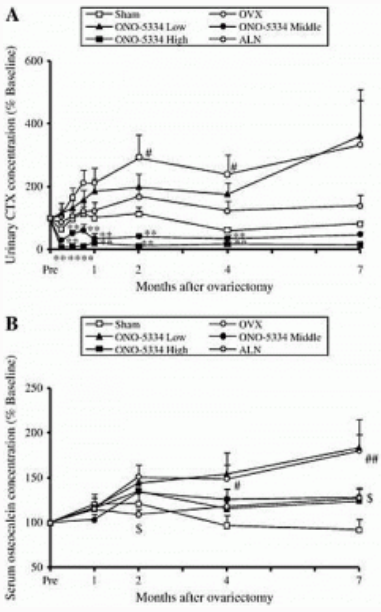

*Figure 3. Changes in urinary CTX (A) and serum osteocalcin (B) in ovariectomized cynomolgus monkeys. Monkeys orally received ONO-5334 (0.3, 3 and 30 mg/kg), alendronate (0.5 mg/kg) or vehicle for 8 months. Serum was collected 4 h after administration on each sampling day for determination of osteocalcin level. 24-h cumulated urine was collected on each sampling day for determination of CTX level. Data are presented as % baseline (mean+SE, n=6–8). #, ##: p<0.05, 0.01 vs. sham group, respectively (Student t test). **: p<0.01 vs. OVX group (Dunnett test). $: p<0.05 vs. OVX group (Student t test). Reproduced from Bone, 65:1-8, Copyright (2014), with permission from Elsevier.*

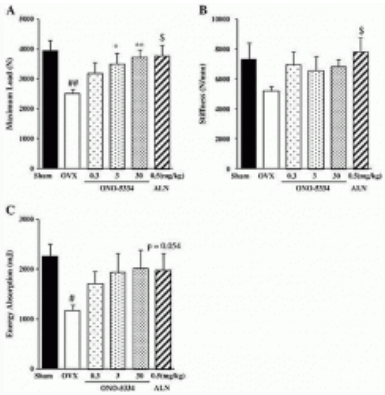

*Figure 4. Bone mechanical strength, maximum load (A), stiffness (B) and energy absorption (C) in the 4th lumbar vertebra. Monkeys orally received ONO-5334 (0.3, 3 and 30 mg/kg), alendronate (0.5 mg/kg) or vehicle for 8 months. Compression test of the isolated 4th lumbar vertebra was conducted after necropsy. Data are presented as mean+SE (n=6-8). #, ##: p<0.05, 0.01 vs. sham group, respectively (Student t test). *, **: p<0.05, 0.01 vs. OVX group, respectively (Dunnett test). $: p<0.05 vs. OVX group (Student t test). Reproduced from Bone, 65:1-8, Copyright (2014), with permission from Elsevier.*

Engelke et al report a double-blind, placebo-controlled, 2-year trial involving postmenopausal women randomized to odanacatib (ODN) 50 mg weekly or placebo; hip QCT scans were available for 158 women (11). The ODN minus placebo effects were significant for total hip integral (5.4%), trabecular (12.2%) and cortical vBMD (2.5%), not integral bone volume. A small but statistically significant increase in cortical volume (1.0-1.3%) and thickness (1.4-1.9%) was reported. The proportions of total bone mineral content (BMC) gain attributed to cortical gain ranged from 40-52% depending on the location. ODN improved integral, trabecular and cortical vBMD and BMC relative to placebo. Cortical volume and thickness increased in all regions except the femoral neck. The increase in cortical volume and BMC paralleled the increase in cortical vBMD, demonstrating a consistent effect of ODN on cortical bone. These data are difficult to interpret. One possibility is cortical volume within the periosteal and endocortical surfaces increased, but there was no report of either an increase in periosteal perimeter or a decrease in endocortical perimeter. The other possibility is that there is infilling of pores with matrix which then mineralizes. A third possibility is that there is no increase in matrix volume at all, but the existing matrix undergoes more complete secondary mineralization producing this increase in cortical vBMD. Whether these methods have the resolution to accurately quantify small changes in volume and to distinguish these alternatives is not clear.

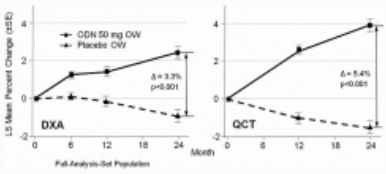

Figure 5. Total hip least squares (LS) mean percentage changes of bone mineral density over 24 month in the ODN and PBO groups. Left: aBMD measured by DXA; right: integral vBMD measured by QCT. Error bars indicate standard error. OW: once weekly. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2292 with permission of the American Society of Bone and Mineral Research.

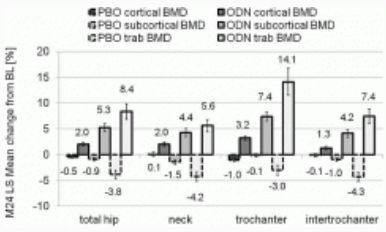

Figure 6. Least squares (LS) mean percentage change from baseline (BL) after 24 months for cortical, subcortical and trabecular vBMD. ODN-PBO differences were significant for all VOIs and compartments shown in the graph. The numbers indicate percentage change of the corresponding parameter versus baseline. Error bars indicate standard error. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2292 with permission of the American Society of Bone and Mineral Research.

Cheung et al randomized 214 postmenopausal women (mean age 64.0±6.8 years and baseline lumbar spine T-score -1.81±0.83) to oral ODN 50 mg or placebo, weekly for 2 years (12). Increases from baseline in total vBMD occurred at the distal radius and tibia. At both sites, differences from placebo were also found in trabecular vBMD, cortical vBMD, cortical thickness, cortical area, and strength estimated using finite element analysis (treatment differences at radius and tibia = 2.64% and 2.66%). At the distal radius, ODN improved trabecular thickness and bone volume/total volume (BV/TV) vs. placebo. At a more proximal radial site, ODN attenuated the increase in cortical porosity found with placebo (treatment difference = -7.7%, p=0.066). At the distal tibia, odanacatib improved trabecular number, separation, and BV/TV vs. placebo.

Figure 7. Two-year percent changes from baseline in other HR-pQCT parameters at (A) radius and (B) tibia. The distal radius and tibia (to the left of the vertical line) were scanned for trabecular number, trabecular separation, trabecular thickness, trabecular bone volume/total volume (BV/TV), cortical area, and cortical porosity. The more proximal regions (to the right of the vertical line) were scanned for assessment of cortical porosity. LS: least squares. Reproduced from J Bone Miner Res 2014;29:1786-94 with permission of the American Society of Bone and Mineral Research.

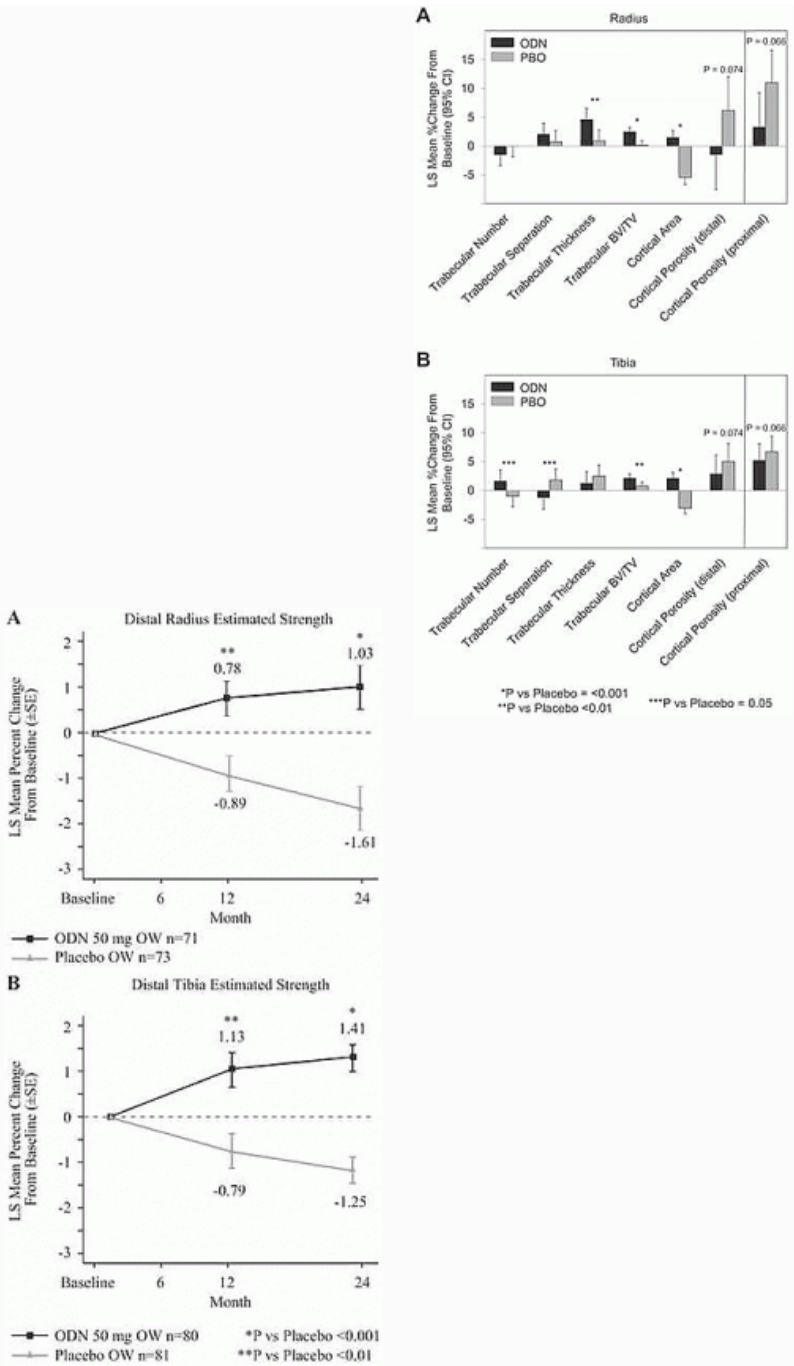

Figure 8. Percent changes from baseline in estimated strength at (A) the distal radius and (B) the distal tibia, based on finite element analysis of HR-pQCT scans. LS: least squares. Reproduced from J Bone Miner Res 2014;29:1786-94 with permission of the American Society of Bone and Mineral Research.

Pennypacker et al report that adult OVX rhesus monkeys were treated with vehicle or ODN (6 or 30 mg/kg, once per day [q.d., p.o.]) for 21 months. Calcein and tetracycline double-labeling were given at 12 and 21 months, and the femoral cross-sections were subjected to dynamic histomorphometric and cement line analyses (13). ODN increased periosteal and endocortical bone formation (BFR/BS) with increased endocortical mineralizing surface (102%, $p<0.01$) with the 6 mg/kg dose. Both doses reduced remodeling hemiosteon numbers by 51% and 66% ($p<0.05$), respectively, and ODN 30 mg/kg numerically reduced activation frequency without affecting wall thickness. On the same endocortical surface, ODN increased all modeling-based parameters, while reducing intracortical remodeling, consistent with the observed no treatment effects on cortical porosity. ODN 30 mg/kg increased cortical thickness (CtTh,

p<0.001), reduced marrow area (p<0.01) and increased femoral structural strength (p<0.001). Peak load correlated with the increases in BMC (r2=0.9057, p<0.0001) and CtTh (r2=0.6866, p<0.0001). The authors claim that treatment reduced cortical remodeling and stimulating modeling-based bone formation, improved cortical dimension and strength in OVX monkeys. These are interesting observations, but they have not been reproduced or reported yet in the bone biopsy data presented at ASBMR last week (see next issue of PIO).

Discontinuing BPs after 5 years is regarded as a viable option to avert adverse events of long term remodeling suppression. However, remodeling rate eventually increases and will erode the skeleton if there is a negative remodeling balance. **Bauer et al** tested methods of predicting fracture risk among women discontinuing alendronate after 4-5 years in the prospective Fracture Intervention Trial Long-term Extension (FLEX) study, which randomized women aged 61-86 years previously treated with 4-5 years of alendronate to 5 more years of alendronate or placebo (14). The analysis included only the placebo group. Hip and spine DXA were measured when placebo was begun (FLEX baseline) and after 1-3 years of follow-up. Urinary type I collagen crosslinked N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP), were measured at FLEX baseline and after 1 and 3 years. During 5 years of placebo, 94 of 437 women (22%) had 1 or more symptomatic fractures; 82 had fractures after 1 year. One-year changes in hip DXA, NTX, and BAP were not related to fracture, but older age and lower hip DXA at time of discontinuation were related to increased fracture risk (lowest tertile of baseline femoral neck DXA vs. other 2 tertiles relative hazard ratio: 2.17 [1.38-3.41]; total hip DXA relative hazard ratio: 1.87 [1.20-2.92]). The authors infer that age and hip BMD at discontinuation predict clinical fractures during the next 5 years.

The authors' inference from this work is "Follow-up measurements of DXA 1 year after discontinuation and of BAP or NTX 1-2 years after discontinuation are not associated with fracture risk and cannot be recommended." Women with BMD<-3.5 SD, those with BMD below the baseline in the fracture intervention (FIT) trial, those losing bone rapidly, and 12 women sustaining fractures before repeat measurements of BMD and bone remodeling markers, were excluded. Bone remodeling markers were measured in only ~90 women, and 83 women discontinuing the placebo "took bone-active medications". It is possible that that these features truncated the extremes of these traits producing limited power to detect an association with fracture.

Three questions leave uncertainties as to 'how long' to treat. First, does 10 years treatment confer continued antifracture efficacy? There was no randomized untreated control group in the FLEX trial, nor in the 10-year follow-up of the study by Bone et al (15), so this question cannot be answered. Second, if treatment is stopped, do fracture rates increase? It is *implied* that fractures in the second 5 years of FLEX when placebo is given is due to stopping alendronate, but that inference depends on whether covariates were equally distributed at rerandomization of the 1099 women into placebo or one of two alendronate doses, and whether retention and compliance during the further 5 years were high; ~20% of participants discontinued the allotted treatment (16). Third, is any benefit from 5 years treatment sustained? It is also *implied* (but not stated) that the *absence* of fractures during the second 5 years is, in part, due to prior alendronate, but this inference requires demonstration of a lower fracture rate than in a control group. So, the data in FLEX trial is difficult to interpret.

Thus, even though the evidence base is limited, stopping treatment or poor compliance increase remodeling rate, bone loss, and fractures (17). We know this. More 'typical' fractures result from stopping than atypical fractures produced by continuing treatment (18). We know this too. Treatment guidelines pay no attention to remodeling rate, material composition or structure. Perhaps there are factors (low remodeling, high tissue mineralization density, high collagen crosslinking, severe microstructural decay) that signal risk for atypical femoral fractures and identify those at risk. We won't know until we look.

Jaw and PTH

Kim et al report that in 24 cases of osteonecrosis of the jaw associated with BP use (BRONJ), 15 subjects were assigned to 20 µg teripartide (TPTD) for 6 months and 9 were assigned to the none (19). All continued calcium and vitamin D. While 60% of the non-TPTD group showed one stage of improvement in BRONJ, 40.0% did not show any improvement. In the TPTD group, 62.5% showed one stage of improvement and 37.5% demonstrated a marked improvement, including two stages of improvement or complete healing. All TPTD cases improved. Patients with higher baseline serum 25(OH)D levels showed better clinical therapeutic outcomes with TPTD.

Vitamin D May Not Increase Calcium Absorption

Gallagher et al report that 198 white and African American women aged 25-45 years with serum 25(OH)D <20 ng/mL were randomized double-blind to vitamin D3 400, 800, 1600, 2400 IU, or placebo plus calcium supplement (20). Calcium absorption was measured at baseline and 12 months using radiocalcium-45 and 100 mg of calcium. Mean baseline serum 25OHD was 13.4 ng/mL (33.5 nmol/L) and increased to 40 ng/mL (100 nmol/L) with 2400 IU without an increase in calcium absorption. There was no relationship between 12-month calcium absorption and final serum 25(OH)D. There was no evidence of a threshold suggesting that active transport of calcium is saturated at 25(OH)D levels <5 ng/mL. There is no need to recommend vitamin D for increasing calcium absorption in normal subjects.

Milk Supplements

Sahni et al report 830 men and women completed a food frequency questionnaire in 1988-89. Energy adjusted intakes of milk, yogurt, cheese, cream and milk+yogurt (servings/wk) were calculated (21). The mean age at baseline was 77 y (68-96). 97 hip fractures occurred over 11.6 y (0.04-21.9). OR for medium (>1 and <7 servings/wk) or higher (≥7 servings/wk) milk intake vs. low intake (≤1 serving/wk) intake was 0.58 (0.31-1.06), P=0.078. OR for medium vs. low intake: 0.61 (0.36-1.08), P=0.071; P trend: 0.178]. Hip fracture risk was 40% lower among those with medium/high milk intake, compared to those with low intake (P=0.061). A similar threshold was observed for milk+yogurt intake (P=0.104). Greater intakes of milk and milk+yogurt may lower risk for hip fracture. While of borderline significance, this study does support the possibility that calcium supplementation by dietary means may reduce the risk of hip fracture. It is a case-control study and so it is hypothesis generating, not hypothesis testing – what is needed are randomized controlled trials with both fracture outcomes and cardiac outcomes measured.

Radavelli-Bagatini et al evaluated the association between dairy food and bone in 564 elderly women aged 80-92 y (mean 84.7) who attended the 10-year follow-up to tertiles of dairy intake: first tertile (≤1.5 servings/d), second tertile (1.5-2.2 servings/d) and third tertile (≥2.2 servings/d) (22). pQCT at the 15% tibia showed that compared with those in the first tertile of dairy intake, women in the third tertile had 5.7% greater total bone mass (p=0.005), principally because of higher cortical and subcortical bone mass (5.9%, p=0.050), resulting in a 6.2% higher total vBMD (p=0.013). Trabecular, but not cortical and subcortical, vBMD was also higher (7.8%, p=0.044). DXA assessment showed that women in the third tertile of dairy intake had greater appendicular bone mass (7.1%, p=0.007) and skeletal muscle mass (3.3%, p=0.014) compared with tertile 1. The associations with bone measures were dependent on dairy protein and calcium intakes, whereas the association with appendicular muscle mass was not totally dependent on dairy protein intake.

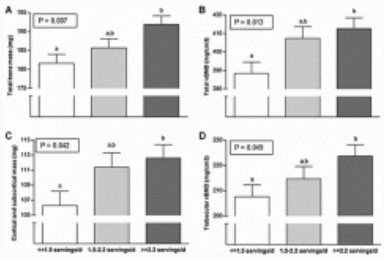

Figure 9. pQCT assessments at 15% tibia according to dairy intake. (A) Total bone mass. (B) Total vBMD. (C) Cortical and subcortical mass. (D) Trabecular vBMD. Values are expected mean and SEM. Means without a common letter differ, p<0.05, multivariate adjusted for age, BMI, physical activity, alcohol consumption, smoking habit, calcium supplementation during the intervention phase, current calcium supplementation, current vitamin D supplementation, and current osteoporosis medication (ANCOVA with Bonferroni post hoc test). Reproduced from J Bone Miner Res 2014;29:1691-700 with permission of the American Society of Bone and Mineral Research.

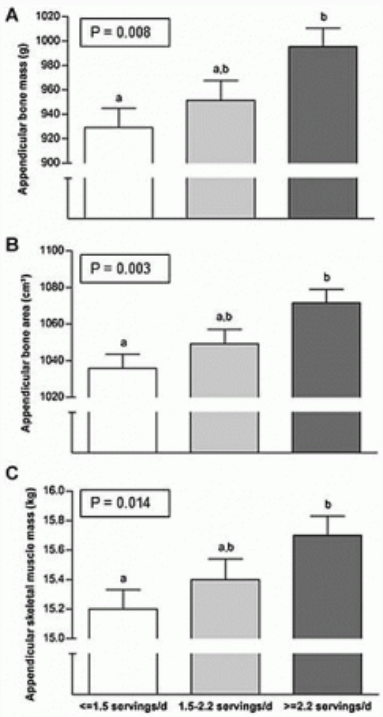

Figure 10. Appendicular bone and muscle mass according to dairy intake. (A) Appendicular bone mass. (B) Appendicular bone area. (C) Appendicular skeletal muscle mass. Values are expected mean and SEM. Means without a common letter differ, p<0.05; A and B were multivariate adjusted for age, BMI, physical activity, alcohol consumption, smoking habit, calcium supplementation during the intervention phase, current calcium supplementation, current vitamin D supplementation, and current osteoporosis medication; C was adjusted for age, BMI, physical activity, smoking habit, calcium supplementation during the intervention phase, and current vitamin D supplementation (ANCOVA with Bonferroni post hoc test). Reproduced from J Bone Miner Res 2014;29:1691-700 with permission of the American Society of Bone and Mineral Research.

Calcium Supplements During Growth

Zhang et al randomly assigned to 40 g of milk powder with 300 mg (Low-Ca group), 600 mg (Mid-Ca group) or 900 mg of calcium (High-Ca group) for 2 years in 111 girls and 109 boys (aged 12-14 y) enrolled, 91 girls and 91 boys completed the trial (23). The girls in the High-Ca group (1110 mg/d) had 2.3%, 2.7% and 2.6% greater BMD accretion at the total hip, femoral neck and shaft (P<0.05) than those in the Low-Ca group (655 mg/d). A significant effect of higher intake was also observed for percentage change of size-adjusted BMC at femur neck (P=0.047). No differences in the percentage changes in BMD, BMC or size-adjusted BMC between the Mid- and Low-Ca groups and between the High- and Mid-Ca groups. Extra calcium had no observable additional effect in the boys.

Calcium Supplements and Cardiovascular Risk Much ado about nothing?

Lewis et al report an ancillary study of 1103 women, 75.2±2.7 y, assessed common carotid artery intimal medial thickness (CCA-IMT) and carotid atherosclerosis at year 3 of CAIFOS (24). By intent to treat, women randomized to calcium had no higher mean CCA-IMT (calcium 0.778±0.006 mm, placebo 0.783±0.006 mm, p=0.491) and maximum CCA-IMT (calcium 0.921±0.007 mm, placebo 0.929±0.006 mm, p=0.404). Women randomized to calcium did not have increased carotid atherosclerosis (calcium 47.2%, placebo 52.7%, p=0.066). Women taking >80% supplements had reduced carotid atherosclerosis in unadjusted but *not* in multivariate adjusted models (p=0.033 and p=0.064, respectively). Participants in the highest tertile of total calcium (diet and supplements) had reduced carotid atherosclerosis in unadjusted and multivariable adjusted analyses compared with participants in the lowest tertile (OR=0.67, 0.50-0.90, p=0.008, and OR=0.70, 0.51-0.96, p=0.028, respectively). These findings do not support that calcium supplementation increases carotid artery intimal medial thickness or carotid atherosclerosis, and high calcium intake may reduce this surrogate cardiovascular risk factor.

Paik et al found no independent associations between supplemental calcium intake and risk of incident coronary heart disease (CHD) and stroke in a prospective cohort study of 74,245 women in the Nurses' Health Study with 24 years of follow-up (25). During 24 years of follow-up, 4565 cardiovascular events occurred (2709 CHD and 1856 strokes). At baseline, women who took calcium supplements had higher levels of physical activity, smoked less, and had lower trans fat intake compared with those who did not take calcium supplements. After multivariable adjustment, the relative risk of cardiovascular disease for women taking >1000 mg/d of calcium supplements compared with none was 0.82 (95% CI 0.74-0.92; p

for trend <0.001), the multivariable adjusted relative risk for CHD was 0.71 (0.61-0.83; p for trend <0.001) and for stroke was 1.03 (0.87-1.21; p for trend = 0.61).

Lewis et al undertook a meta-analysis of randomized controlled trials with placebo or no-treatment control groups to determine if these supplements increase myocardial infarction (MI), angina pectoris and acute coronary syndrome, and chronic CHD. 18 studies met the inclusion criteria and contributed 63,563 participants with 3390 CHD events and 4157 deaths (26). Five trials contributed CHD events with pooled relative RR of 1.02 (0.96-1.09; P=0.51). Seventeen trials contributed all-cause mortality data with pooled RR of 0.96 (0.91-1.02; P=0.18). The RR for MI was 1.08 (0.92-1.26; P=0.32), angina pectoris and acute coronary syndrome 1.09 (0.95-1.24; P=0.22) and chronic CHD 0.92 (0.73-1.15; P=0.46). The authors infer that current evidence does not support the hypothesis that calcium supplementation with or without vitamin D increase coronary heart disease or all-cause mortality risk in elderly women. However, a glance at Figure 11 shows that the duration of most of the studies was 1-3 years. If calcium supplementation has an adverse effect, unless acute, it is unlikely to be detected in brief studies such as this. How many lung cancers will be observed in smokers of 1 pack of cigarettes per year?

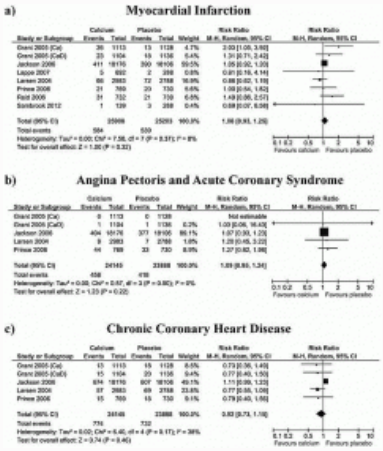

Figure 11. Random effects estimates of calcium supplementation with or without vitamin D for a) myocardial infarction, b) angina pectoris and acute coronary syndrome and c) chronic coronary heart disease compared to no calcium. For Grant et al (2005), events were reported in those who received calcium cf. placebo (Ca) and calcium plus vitamin D cf. vitamin D only (CaD). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2311 with permission of the American Society of Bone and Mineral Research.

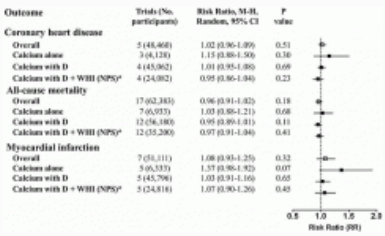

*Figure 12. Sensitivity analyses based on type of supplementation. *Post hoc subgroup analysis of the Women's Health Initiative (WHI) in participants with no personal supplements at baseline (NPS) using the trial investigators internal dataset (28). M-H: Mantel-Haenszel, this method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result. Reproduced from J Bone Miner Res 2014;doi:10.1002/jbmr.2311 with permission of the American Society of Bone and Mineral Research.*

Sclerostin Deficiency and Stronger Bone

The prospect of a new anabolic agent in antisclerostin antibodies requires demonstration that the new bone will be healthy bone. **Hassler et al** studied cortical bone of Sost-knockout (KO) mice (n=9, 16-week-old) and sclerosteosis patients (young [4-14 y], n=4 and adults [24 and 43 y], n=2) (27). In Sost-KO mice, endocortical bone had reduced matrix mineralization -1.9%, p<0.0001 (younger tissue age) and -1.5%, p<0.05 (older tissue age), and relative proteoglycan content was increased. Bone matrix mineralization density distribution was shifted towards lower matrix mineralization in samples of compact bone of sclerosteosis patients associated with increased mineralization heterogeneity in the young population. The relative proteoglycan content was increased. The altered bone composition may contribute to increased strength.

Sclerostin Antibody

Roschger et al assessed once-weekly intravenous Sost-ab injections for 4 weeks in male Col1a1Jrt/+mice, a model of severe dominant osteogenesis imperfecta (OI), starting either at 4 weeks (growing mice) or at 20 weeks (adult mice) of age. Sost-ab had no effect on weight or femur length (28). In OI mice, no treatment-associated differences in remodeling markers. µCT analyses at the femur showed that Sost-ab was associated with higher trabecular bone volume and higher cortical thickness in wildtype mice at both ages and in growing OI mice, but not in adult OI mice. Three-point bending tests of the femur showed that in wildtype but not in OI mice, Sost-ab was associated with higher ultimate load and work to failure. Quantitative backscattered electron imaging of the femur did not show any effect of Sost-ab on CaPeak regardless of genotype, age or measurement location. Thus, Sost-ab had a larger effect in wildtype than in Col1a1Jrt/+mice. The data suggest that Sost-ab is less effective in severe OI mouse model.

Ross et al report that in rats and nonhuman primates treated with vehicle or sclerostin antibody (Scl-Ab), despite up to 54% increases in the bone volume after Scl-Ab, the mean global mineralization of trabecular and cortical bone was unaffected (29). However, in BMDD in the primate trabecular bone had an increase in the number of pixels with a low mineralization value and a decrease in the standard deviation of the distribution. Tissue age-specific measurements in the primate model showed that Scl-Ab did not affect the mineral-to-matrix ratio, crystallinity, or collagen crosslinking in the endocortical, intracortical, or trabecular compartments. Scl-Ab was associated with a nonsignificant trend toward accelerated mineralization intracortically and a nearly 10% increase in carbonate substitution for tissue older than 2 weeks in the trabecular compartment (p<0.001). Scl-Ab does not negatively impact matrix quality.

Bone formation may be remodeling-based (RBF) or modeling-based (MBF), the former coupled to bone resorption and the latter occurring directly on quiescent surfaces. Scl-Ab increases bone formation while decreasing bone resorption. **Ominsky et al** tested the hypothesis that Scl-Ab produces a modeling based anabolic response by examining bones from OVX rats and male cynomolgus monkeys (cynos) (30). Histomorphometry was performed to quantify and characterize bone surfaces in OVX rats administered vehicle or Scl-Ab (25 mg/kg) subcutaneously (sc) twice/week for 5 weeks and in adolescent cynos administered vehicle or Scl-Ab (30 mg/kg) sc every 2 weeks for 10 weeks. Fluorochrome-labeled surfaces in L2 vertebra and femur endocortex (cynos only) were considered to be MBF or RBF based on characteristics of their associated cement lines. In OVX rats, Scl-Ab increased MBF by 8-fold (from 7% to 63% of bone surface, compared to vehicle). In cynos, Scl-Ab increased MBF on trabecular (from 0.6% to 34%) and endocortical surfaces (from 7% to 77%) relative to vehicle. Scl-Ab did not affect RBF in rats or cynos despite decreased resorption surface in both species. In cynos, Scl-Ab resulted in a greater proportion of RBF and MBF containing sequential labels from week 2, indicating an increase in the lifespan of the formative site. This extended formation period was associated with robust increases in the percent of new bone volume formed. Scl-Ab increased bone volume by increasing MBF and prolonged the formation period at both modeling and remodeling sites while reducing bone resorption.

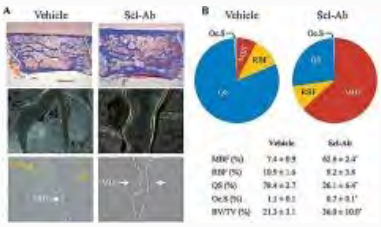

*Figure 13. Effects of Scl-Ab on modeling bone formation on trabecular surfaces in OVX rats. Histomorphometry was performed on LV2 from OVX rats treated twice weekly with sc Vehicle or Scl-Ab (25 mg/kg) for 5 weeks. (A) For each group, images are shown of the whole sagittal section stained with Goldner's trichrome (top panel) and with magnified epifluorescent images (middle panel) showing the fluorochrome labels administered on day 0 (xylenol orange, red), days 22–23 (calcein, green), and days 32–33 (tetracycline, orange). Red arrows indicate the locations of faint xylenol orange labels. The corresponding polarized light micrographs (bottom panel) show the collagen orientation, reflecting changes in the cement lines used for assessment of modeling (white dashed lines) and remodeling (orange dotted lines), and showing the lamellar architecture of the newly formed bone. (B) Bone surfaces were characterized as modeling-based formation (MBF), remodeling-based formation (RBF), quiescent (QS), or osteoclastic (OcS), and are expressed as a percentage of the total surface. Trabecular bone volume/total volume (BV/TV) was also measured. Data are expressed as mean±SEM; *p<0.05 vs. vehicle by two-tailed t test. Reproduced from J Bone Miner Res 2014;29:1424-30 with permission of the American Society of Bone and Mineral Research.*

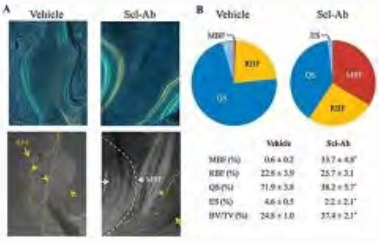

*Figure 14. Effects of Scl-Ab on modeling bone formation on trabecular surfaces in cynomolgus monkeys. Histomorphometry was performed on LV2 from male cynos treated sc every 2 weeks with vehicle or Scl-Ab (30 mg/kg) for 10 weeks. (A) For each group, epifluorescent images (top panel) reflect a pair of tetracycline labels (orange) injected on days 14 and 24 and calcein labels injected on days 56 and 66 (green). The corresponding polarized light micrographs (bottom panel) show the collagen orientation, reflecting changes in the cement lines used for assessment of modeling (white dashed lines) and remodeling (orange dotted lines), and showing the lamellar architecture of the newly formed bone. (B) Bone surfaces were characterized as modeling-based formation (MBF), remodeling-based formation (RBF), quiescent (QS), or eroded (ES), and are expressed as a percentage of the total surface. Trabecular bone volume/total volume (BV/TV) was also measured. Data are expressed as mean±SEM; *p<0.05 vs. vehicle by two-tailed t test. Reproduced from J Bone Miner Res 2014;29:1424-30 with permission of the American Society of Bone and Mineral Research.*

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Progress in Osteoporosis

CRITICAL REVIEW JOURNAL

OVERVIEW, VOL 14, ISSUE 3

Ego Seeman
Editor

By Ego Seeman Tue, 12/02/2014 - 07:51

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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Bone's Material Composition

The strength of bone is determined by the amount of material, the constituents of this material, and its architectural design. The term bone 'quality' is often used to capture bone's material properties but this term is ambiguous, so ambiguous that it ensures no two people can be quite sure that they are talking about the same thing.

If this word is to be used then it is better stated in the plural, bone's 'qualities', because this forces us to define each component. The material composition of bone includes the collagen, the mineral, noncollagenous proteins and water. Several recent studies deal with some of these qualities of bone and I summarize several of these papers in this issue.

To establish trabecular bone quality in 54 healthy individuals between 1.5-23 years, **Gamsjaeger et al** studied three tissue ages defined by three fluorescent double labels representing early bone formation and maturation (days 3, 12, 20) and a fourth representing mature tissue at the center of trabeculae (1). Mineral/matrix ratio, mineral maturity/crystallinity index and relative pyridinoline collagen crosslink content index increased by 485%, 20% and 14%, respectively, between days 3 and 20 while relative proteoglycan content index was unchanged but was 121% higher in the old compared to young tissue. The relative lipid content decreased within days 3 to 20 by -22%.

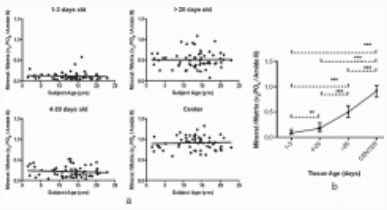

*Figure 1. (a) Scatter plots show that mineral/matrix ratio, expressed as the ratio of the integrated areas of the v_2PO_4 and amide III bands, was independent of subject age at all 4 tissue ages investigated in the present study. The linear regression line is also shown for the 4 different tissue ages considered. (b) On the other hand, the mineral/matrix ratio significantly increased as a function of tissue age (**p<0.01, ***p<0.0001). Reproduced from Bone, 69C:89-97, Copyright (2014), with permission from Elsevier.*

Figure 2. (a) Scatter plots indicate that the mineral maturity/crystallinity, estimated from the inverse of the Full Width at Half Height (FWHH) of the v PO

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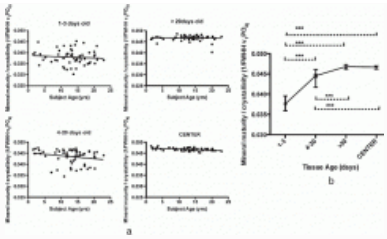


*band was independent of subject age at the 3 younger tissue ages analyzed. It was however dependent on subject age only at the oldest of the ages examined, namely at the trabecular center (Spearman r=0.360, p=0.005). It was also significantly dependent on tissue age. The linear regression line is also shown for the different 4 tissue ages considered. (b) As can be seen, this parameter significantly increases as a function of tissue age (b) (***p<0.0001). Reproduced from Bone, 69C:89-97, Copyright (2014), with permission from Elsevier.*

The mineral/matrix ratio reflects the amount of mineral normalized for the amount of organic matrix. This ratio is sensitive to tissue age and increases from days 1-3 to day 20 and was highest in the oldest tissue at the centre of the trabeculae reflecting slower secondary mineralization. The mineral maturity/crystallinity reflects crystal size; the larger the crystals the greater the fragility.

Pyridinoline is a mature, nonreducible trivalent collagen crosslink present in mineralizing type I collagen which increases early consistent with the very rapid primary mineralization that takes place within a week or so of osteoid deposition. From day 20 on to older tissue in the centre of the trabeculae little further change occurs subsequently.

Crosslinking contributes to tensile strength and viscoelasticity independent of mineral content or composition. Proteoglycans inhibit mineralization and are present in perilacunar matrix and around the canaliculi where they may prevent mineralization in the pericellular space of the lacuna-canalicular network to ensure interstitial fluid movement. Differences between the oldest tissue and the 3 younger ones in the above study may reflect different proteoglycans or differences in post-translational modifications including addition of glycosaminoglycan chains as well as N- and O-linked oligosaccharides. The relevance of changes in type and amount to bone strength require further research. Lipid content is implicated in mineral nucleation responsible for mineralization. Calcium-acidic phospholipid-phosphate complexes increase concentration during cartilage calcification and early bone formation. The relative lipid content was dependent on tissue age, with the highest values encountered in youngest bone.

Misof et al analyzed bone mineralization density distribution (BMDD) in transiliac crest biopsy samples from healthy premenopausal women (n=73) aged 25-48 years (2). Cortical (Ct.) and cancelleous (Cn.) BMDD correlated (r=0.42 to 0.73, all p<0.001). Mineralization density heterogeneity (Ct.CaWidth), and cortical porosity (Ct.Po) was greater at a lower degrees of mineralization (Ct.CaMean). Ct.Po correlated inversely with the percentage of highly mineralized bone areas and positively with the percentage of lower mineralized bone areas.

These observations are likely to reflect coordinated regulation of bone remodeling between cortical and trabecular compartments. When remodeling rate is high the proportion of new osteons with younger and less completely mineralized osteons increases and the proportion of older osteons that are more completely mineralized decreases. In the presence of a negative BMU balance, when less osteoid is deposited incompletely refilling the excavated cavity, the resultant Haversian canal is larger leaving a more porous cortex. This produces the association between higher porosity and less mineralized bone matrix. The challenge is to deteremine the net effect on bone strength. Higher porosity predisposes to fracture but lower levels of tissue mineralization may produce a matrix that is more ductile; better able to deform when loaded.

Collagen crosslinks are associated with bone disease and confer fracture risk independent of mineral content. **McNerny et al** produced lathyrism (inhibition of lysyl oxidase) by subcutaneous injection of 150 or 350 mg/kg β-aminopropionitrile during 3 weeks in young growing mice (3). Reduced pyridinoline crosslink content and reduced cortical toughness resulted. Newly deposited bone had lower mineral/matrix, carbonate/phosphate and amide I crosslink (matrix maturity) ratios. Ratios reflecting relative crosslink maturity were associated with toughness [HP/(DHLNL+HLNL) r^2=0.208, p<0.05; (HP+LP)/(DHNL+HLNL) r^2=0.196, p<0.1], whereas mature pyridinoline crosslinks were associated with tissue strength (lysyl pyridinoline r^2=0.159, p=0.014; hydroxylysyl pyridinoline r^2=0.112, p<0.05).

Hassler et al studied cortical bone of Sost-knockout (KO) mice (n=9, 16 wk old) and patients with sclerosteosis (4-14 yr, n=4, adults 24 and 43 yr) (4). In Sost-KO mice mineralization of endocortical matrix was reduced by -1.9% (p<0.0001, younger tissue age) and -1.5% (p<0.05, older tissue age). The matrix also had increased proteoglycan content. Similarly, patients with sclerosteosis had lower tissue mineralization, greater heterogeneity in tissue mineralization and higher proteoglycan content; alterations that may contribute to increased bone strength in sclerostin deficiency.

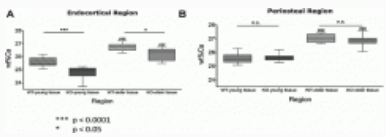
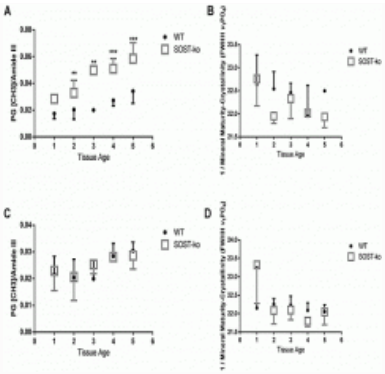


*Figure 3. Degree of mineralization (wt%Ca) in Sost KO mice and wildtypes. (A) Regions of young tissue age (5-15 days) as well as older regions (55-65 days) exhibit significantly lower mineralization (-1.9% [-0.47 wt%Ca] and -1.5% [-0.39 wt%Ca], respectively) at the site of endocortical bone apposition. (B) At the site of periosteal bone apposition no changes in mineralization were observed between Sost KO and wildtype mice, when comparing the same tissue age. Consistently, older tissue is significantly higher mineralized than younger tissue in both genotypes (significance levels not indicated). Two way ANOVA revealed no interaction between genotype and tissue age for both anatomical sites. ***p<0.0001, *p<0.05, ###p<0.0001 vs. young tissue of the same genotype. wt%Ca=weight percent Ca; KO=knockout; WT=wildtype; n.s.=not significant. Reproduced from J Bone Miner Res 2014;29:2144-51 with permission of the American Society of Bone and Mineral Research.*

*Figure 4. Raman parameters measured in Sost KO mice and wildtypes. The relative proteoglycan content (expressed by the PG(CH3)/Amide III ratio) data are presented as median and interquartile range. It was significantly lower at the tissue ages 2 to 5 at the endocortical envelope, **p<0.01, ***p<0.001 per unpaired t test. Two way ANOVA revealed an impact of both tissue age and genotype.*



(B) At the site of periosteal bone apposition the relative proteoglycan content was dependent on tissue age exclusively. The mineral maturity/crystallinity inversely related to the FWHH of the v_1PO_4 band at both endocortical (C) and periosteal (D) surfaces was significantly dependent on tissue age. It was also dependent on genotype at endocortical surfaces exclusively, although post hoc analysis did not reveal significant differences at any of the individual tissue ages considered. KO=knockout; FWHH=full width half height; v_1PO_4 band=930-980 cm^{-1}. Reproduced from J Bone Miner Res 2014;29:2144-51 with permission of the American Society of Bone and Mineral Research.

Acerbo et al reported changes in collagen and mineral properties of cortical bone associated with osteoporosis and treatments as quantified by small- and wide-angle X-ray scattering microbeam mapping (5). Adult rats (age 6 mos) were ovariectomized and treated with alendronate, PTH, or sodium fluoride. Porotic tibial cortical bone had increased collagen alignment, an effect attenuated by alendronate (ALN) and sodium fluoride. Mineral crystal lengths in newly formed cortical bone were smaller in animals with osteoporosis, but existing cortical bone was not altered. ALN mitigated changes in crystal lengths.

Chen et al reported that noncollagenous proteins, including osteocalcin and bone sialoprotein, may contribute to mineralization of collagen (6). Osteocalcin is present at the surface of, outside and within type I collagen while bone sialoprotein localizes at the surface of or outside type I collagen. Osteocalcin is located along the a4-1, b1, c2 and d bands defining in part the hole and overlap zones within type I collagen. While type I collagen is a stereochemical guide for intrafibrillar mineral nucleation and deposition, osteocalcin bound may mediate nucleation, growth and development of platelet-shaped apatite crystals as studied here in avian tendon.

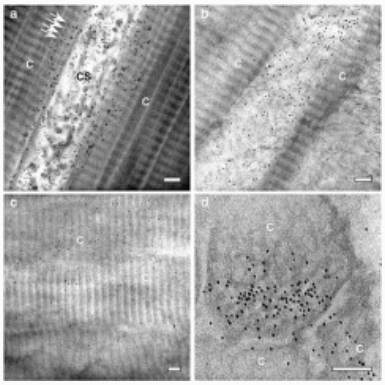


Figure 5. TEM images of immunolocalized OC stained with uranyl acetate. (a) Longitudinal tendon section with partial decalcification using 0.2% EDTA for 8 min shows immunolabeling of OC along collagen periodicity (arrows) as well as within interfibrillar collagen spaces (CS). (b, c) Longitudinal tendon sections with complete decalcification using 1% EDTA for 20 min illustrate OC immunolabeling between (b) and within (c) collagen; the labeling in (c) appears to be specific along the collagen periodicity and images such as this were carefully analyzed to determine the distribution of gold particles associated with collagen bands comprising the periodicity of the protein. (d) Transverse tendon section with complete decalcification using 1% EDTA for 20 min demonstrates OC labeling within the profiles of collagen fibrils. For (b), (c), and (d), antibody solutions contained 2 mM Ca^{2+}. Collagen (C). Scale bar=100 nm for all images. Reproduced from Bone, 71:7-16, Copyright (2014), with permission from Elsevier.

Gamsjaeger et al reported that HLA-B27 transgenic rats have colitis and accelerated alveolar bone loss (7). Bone fragility may be the result of changes in material composition, not only deficits in mineralized bone matrix. HLA-B27 transgenic rats had a significant negative correlation between alveolar bone loss and long bone BMD as well as mineral/matrix ratio at active bone-forming trabecular surfaces. A lower mineral/matrix ratio and higher relative proteoglycan and advanced glycation endproduct (-N-carboxymethyl-L-lysine) content and pyridinoline/divalent collagen crosslink ratio were observed compared with wildtype.

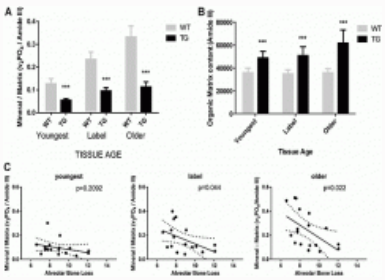


*Figure 6. (A) Mineral/matrix ratio at three distinct tissue ages at actively forming trabecular surfaces. TG animals had a significantly (***p<0.0001) lower ratio at all three. (B) Organic matrix content was significantly increased (***p<0.0001) in the TG animals at all three tissue ages considered. (C) The mineral/matrix ratio significantly correlated with alveolar bone loss (ABL) at the two older tissue age sites (p=0.044 and 0.022, respectively). Reproduced from J Bone Miner Res 2014;29:2382-91 with permission of the American Society of Bone and Mineral Research.*

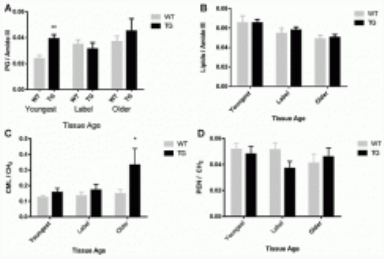


*Figure 7. (A) Relative proteoglycan content. TG animals had a higher content at the youngest tissue age (**p<0.001). (B) Relative lipids content. There were no differences between the WT and TG animals. (C) Relative CML content. The TG animals had elevated content at the oldest tissue age compared with WT (*p<0.05). (D) Relative PEN content. No differences between WT and TG animals were evident. Reproduced from J Bone Miner Res 2014;29:2382-91 with permission of the American Society of Bone and Mineral Research.*

Ural et al investigated the relationship between nonenzymatic glycation, resorption, and microdamage generated in vivo in cortical bone (8). Total fluorescent advanced glycation endproducts (AGEs) were

measured in 96 human cortical bone samples from 83 donors. Resorption pit density, average resorption pit area, and percent resorption area were quantified in samples from 48 common donors with AGE measurements. Linear microcrack density and diffuse damage were measured in 21 common donors with AGE and resorption measurements. Average resorption pit area and percent resorption area decreased with increasing AGEs independently of age. Resorption pit density and percent resorption area demonstrated negative age-adjusted correlation with diffuse damage. Average resorption pit area, resorption pit density, and percent resorption area decreased with age. There is a negative correlation between AGEs and resorption independent of age. AGEs alter the resorption process and/or accumulate in the tissue as a result of reduced resorption and may lead to bone fragility by adversely affecting fracture resistance through altered bone matrix properties.

Hassler et al evaluated material properties in patients receiving ALN for 5 or 10 years using Raman microspectroscopic analysis of iliac crest biopsies in women treated with ALN for 5 years then rerandomized to placebo (N=14), 5 mg/d ALN (N=10), or 10 mg/d ALN (N=6) for another 5 years (9). The parameters monitored and expressed as a function of tissue age were (i) the mineral/matrix ratio, (ii) the relative proteoglycan content, (iii) the relative lipid content, (iv) the mineral maturity/crystallinity, and (v) the relative pyridinoline content. 10-year ALN results in minimal, transient changes in tissue composition compared to 5 years use that were confined to actively forming trabecular surfaces. Prolonged reduction in bone turnover during 10 years of therapy with ALN by itself is unlikely to be associated with adverse effects on material properties.

Xiang et al analyzed parameters from 72 fetuses recovered at day 153 gestation (54% term) and identified six principal components (PC1-6) explaining 80% of skeletal variation (10). Parental genomes accounted for most variation in bone wet weight (PC1, 72.1%), limb ossification (PC2, 99.8%), flat bone size (PC4, 99.7%), and axial growth (PC5, 96.9%). Limb length showed less effect of parental genomes (PC3, 40.8%) and a nongenetic maternal effect (gestational weight gain, 29%). Fetal sex affected bone wet weight (PC1, $p<0.0001$) and limb length (PC3, $p<0.05$). Maternal genome effects were strong for wet weight (74.1%, $p<0.0001$) and axial growth (93.5%, $p<0.001$), growth plate height (98.6%, $p<0.0001$) and trabecular thickness (85.5%, $p<0.0001$) in distal femur, fetal serum 25-hydroxyvitamin D (96.9%, $p<0.001$). Paternal genome controlled limb ossification (95.1%, $p<0.0001$), alkaline phosphatase (90.0%, $p<0.001$). Bone wet weight and flat bone size correlated with muscle weight ($r=0.84$ and 0.77, $p<0.0001$) and negatively with muscle H19 expression ($r=-0.34$ and -0.31, $p<0.01$).

Calcium Supplements in Men and Rodents

Kalluru et al randomized 323 healthy men to calcium 600 mg/d (n=108), calcium 1200 mg/d (n=108), or placebo (n=107) over 2 years, 85 placebo and 87 treated men were followed for 1-2 years off medication (11). In the core trial, BMD increased at all sites by 1.0-1.5% at 2 years in the group receiving calcium 1200 mg/d, compared to placebo. In post-trial follow-up, the calcium group had a 0.41% higher total body BMD than controls (P=0.04) but there was no between-group differences at other sites. There is a small residual benefit in total body BMD, but not at the hip or spine.

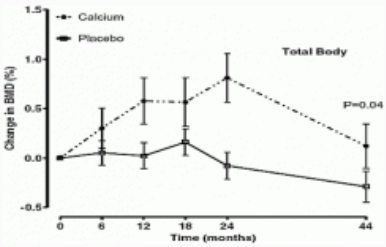


Figure 8. Change in total body BMD throughout the core trial period (up to year 2) and after discontinuation of intervention in men randomized to calcium 1200 mg/d or placebo. P values are for the between-group comparison of percent change from core trial baseline to 44 months. Data are mean ±SEM. In the period after discontinuation of intervention, the rate of bone loss was 0.0016 g/cm^2/year in the placebo group and 0.0060 g/cm^2/year in the calcium group (P=0.0017). Reproduced from Osteoporos Int 2014;doi:10.1007/s00198-014-2896-x with permission from Springer.

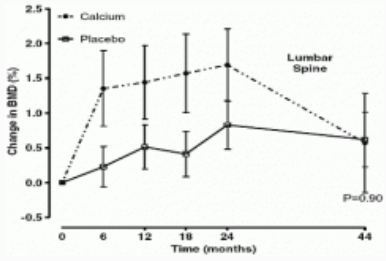


Figure 9. Change in BMD at spine throughout the core trial period (up to year 2) and after discontinuation of intervention in men randomized to calcium 1200 mg/d or placebo. P values are for the between-group comparison of percent change from core trial baseline to 44 months. Data are mean ±SEM. In the period after discontinuation of intervention, the rate of bone loss was 0.0016 g/cm^2/year in the placebo group and 0.0090 g/cm^2/year in the calcium group (P=0.03). Reproduced from Osteoporos Int 2014;doi:10.1007/s00198-014-2896-x with permission from Springer.

There are no surprises here. When a weak antiresorptive like calcium supplements is administered, there is a modest 10-20% reduction in remodeling rate so that more cavities excavated prior starting calcium refill while simultanously 10-20% fewer new cavities are created. The net effect is a modest rise in BMD in the first 12-24 months of treatment. After this, steady state is restored at the modestly higher BMD and remodeling now continues but at a slower rate than prior treatment. Bone loss resumes but more slowly because the negative BMU balance is not restored so remodeling continues at 80-90% of the pretreatment rate and bone loss and structural decay occur but more slowly. When supplementation stops the reversion to higher remodeling rate eventually occurs and benefits are eventually eroded. This is why calcium supplements alone are not sufficient treatment of bone fragility.

Viguet-Carrin et al assessed the effects of 4 weeks calcium supplementation in rats, age 28 days using high (1.2%), adequate Ca (0.5%) or low Ca intakes (0.2%) (12). Compared to the adequate Ca intake, low-Ca intake had a detrimental impact on bone growth (33.63 vs. 33.68 mm), strength (-19.7% for failure load), architecture (-58% for BV/TV) and peak mass accrual (-29% for BMD). Higher than adequate Ca intake improved peak strength (106 vs. 184 N/mm for the stiffness and 61 vs. 89 N for the failure load) and material properties (467 vs. 514 mPa for tissue hardness) without changes in bone mass, size, microarchitecture or turnover. Compared to the adequate level of Ca, IGF-I level was lower in the low-Ca intake group and higher in the high-Ca intake group.

Risk Factors for Fractures

Byberg et al investigated the association between fruit and vegetable intake and hip fracture in 40,644 men and 34,947 women who answered questionnaires in 1997 (age 45-83 yrs) (13). The follow-up time was 14.2 years. One third of the participants reported an intake of fruit and vegetables of >5 servings/d, one third >3 to ≤5 servings/day, 28% >1 to ≤3 servings/d, and 6% reported ≤1 serving/d. During 1,037,645 person-years 3644 hip fractures (2266, 62%, in women), those with zero consumption had 88% higher rate of hip fracture compared with those consuming 5 servings/d; HR, 1.88 (95%CI 1.53-2.32). The rate was lower with higher intakes; HR for 1 vs. 5 servings/d, 1.35 (95%CI 1.21-1.58). More than 5 servings/d did not confer lower HRs. An intake below 5 servings/d confers higher rates of hip fracture.

Jamal et al reported results from the MrOS study which enrolled 5122 community dwelling men aged ≥65 years from six centers across the United States (14). Subjects were followed for fractures for up to 9 years. Hyponatremia was observed in 64 men (1.2% of the cohort). After adjustment, compared to men with serum sodium ≥135 mmol/L, those with serum sodium <135 mmol/L, had an increased risk hip fracture (HR=3.04; 95%CI 1.37-6.75), prevalent (OR=2.46; 95%CI 1.22-4.95) and incident (OR=3.53; 95%CI 1.35-9.19) morphometric spine fractures but not nonspine fractures (OR=1.44; 95%CI 0.85-2.44). Adjusting for BMD did not change the findings.

Antifracture Efficacy of Weekly PTH

Fujita et al reported a randomized, double-blind trial to assess the antifracture efficacy of 28.2 µg teriparatide vs. placebo (1.4 µg teriparatide) in 316 subjects studied for 131 weeks (15). Vertebral fractures occurred in 3.3% of subjects in the 28.2 µg teriparatide-treated group and 12.6% in placebo during 78 weeks; Kaplan-Meier estimates of risk after 78 weeks 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% (P=0.001 relative to placebo).

Antifracture Efficacy of Clodronate

Frediani et al reported a meta-analysis of 18 trials, 13 in patients with cancer, 4 in osteoporosis/low BMD, and 1 in elderly women (16). A placebo arm was available in 13 trials. Follow-up ranged from 3 months to 5 years. Clodronate reduced fractures (OR=0.572, 95%CI 0.465-0.704 for vertebral; OR=0.668, 95%CI 0.494-0.905 for nonvertebral fractures).

Antifracture Efficacy of Denosumab

Nakamura et al reported a phase three fracture study to examine the antifracture efficacy and safety of denosumab 60 mg in 1262 Japanese women and men with osteoporosis compared with placebo (17). Subjects were assigned to denosumab 60 mg sc every 6 months (n=500), placebo (n=511), or oral ALN 35 mg weekly (n=251). All received calcium and vitamin D. Denosumab reduced vertebral fracture by 65.7%, with incidences of 3.6% in denosumab and 10.3% in placebo at 24 months (HR 0.343; 95%CI 0.194-0.606, P=0.0001). No difference in adverse events was found between denosumab and placebo during the first 24 months of the study. No comparisons with the alendronate arm were presented for reasons that are not apparent.

Targeting Anabolic Therapy to Bone Using a Bisphosphonate

Liu et al reported that a C1 conjugate drug chemically links ALN with the anabolic agent prostanoid EP4 receptor agonist (EP4a) through a linker molecule (LK) to form a conjugate (18). This enables the bone-targeting ability of ALN to deliver EP4a to bone sites. Using an OVX model, 3-month-old female Sprague Dawley rats were allowed to lose bone for 7 weeks, then treated for 6 weeks. Treatment groups consisted of C1 conjugate at low and high doses, vehicle-treated OVX and sham, prostaglandin E2, and mixture of unconjugated ALN-LK and EP4a. Weekly administration of the C1 conjugate dose-dependently increased trabecular bone volume, which partially or completely reversed OVX-induced bone loss in the vertebra and improved vertebral strength. The conjugate also stimulated endocortical woven bone formation and intracortical resorption, with high dose treatment increasing the mechanical strength but compromising the material properties.

Anabolic Therapy
Blosozumab

Recker et al randomized 120 postmenopausal women (mean age 65.8 y) with a spine T-score -2.0 to -3.5 to subcutaneous blosozumab 180 mg 4 weekly, 180 mg Q2W, 270 mg Q2W, or placebo for one year (19). Blosozumab increased spine BMD (17.7%), total hip BMD (6.2%), and formation markers. The formation markers trended toward pretreatment levels by study end. BSAP remained higher than placebo in the highest dose group. CTx decreased early to less than placebo by 2 weeks, and remained reduced.

Morse et al investigated long-term sclerostin deficiency on mechanotransduction in unloaded 10 week old female $Sost^{-/-}$ induced by 0.5 U botulinum toxin injections into the right quadriceps and calf muscles (20). Increased loading was performed on the left tibiae in other mice through unilateral cyclic axial compression of equivalent strains (+1200 µe) at 1200 cycles/d, 5 d/wk. Loaded/unloaded and normal load tibiae were assessed at day 14. Loss of BV was seen in the unloaded tibiae of wildtype, not unloaded $Sost^{-/-}$ tibiae. An increase in BV was seen in the loaded tibiae of wildtype and $Sost^{-/-}$ mice associated with increased midshaft periosteal mineralizing surface/bone surface (MS/BS), mineral apposition rate (MAR), and bone formation rate/bone surface (BFR/BS), and endosteal MAR and BFR/BS. Loading induced a greater increase in periosteal MAR and BFR/BS in $Sost^{-/-}$ mice than in wildtype. Long-term sclerostin deficiency inhibits the bone loss induced with decreased loads, but augments the increase in bone formation with loading.

Morden et al studied a cohort of 1.64 million beneficiaries: 87.9% women, mean age, 76.8 with a mean

follow-up of 39.6 months; 38.1% received oral bisphosphonates (21). Cumulative bisphosphonate receipt ranged from 4-252 pills (5th to 95th percentile). There were 2308 upper gastrointestinal cancers (0.43/1000 person years) but no association between bisphosphonate pills and cancer was dectected (OR for each additional pill 1.00 (95%CI 1.00, 1.00). In subcohorts, compared to none, lowest cumulative bisphosphonate use (1-9 pills) was associated with higher risk of endoscopy (OR 1.11, 95%CI 1.08-1.14) and antacid initiation (OR 1.13, 95%CI 1.10-1.16).

Gibson-Smith et al evaluated secular trends (2000-2010) for major (humerus, vertebral, or forearm) and any (nonhip) fracture after hip fracture in 30,516 subjects (22). Within one year following hip fracture, 2.7 and 8.4% of patients sustained a major or any (nonhip) fracture. After 5 years the, 14.7 and 32.5% had these respective fractures. The most important risk factors were the female sex (aHR 1.90, 95%CI 1.51-2.40) and a history of secondary osteoporosis (aHR 1.54, 95%CI 1.17-2.02). The annual risk increased during the study period for both subsequent major (2009-2010 vs. 2000-2002: aHR 1.44, 95%CI 1.12-1.83) and any (nonhip) facture (2009-2010 vs. 2000-2002: aHR 1.80, 95%CI 1.58-2.06).

Binkley et al randomized women to oral recombinant salmon calcitonin tablets or placebo once daily for one year. 129 women were randomized, 86 to calcitonin and 43 to placebo (23). Calcitonin recipients experienced a significant increase from baseline in lumbar spine BMD; the difference compared with placebo was significant. Dosing at bedtime or with dinner was equally effective. CTx-1 was suppressed with calcitonin. Gastrointestinal adverse events were common, but the overall safety profile was comparable between groups.

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