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Ego Seeman
Editor

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

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

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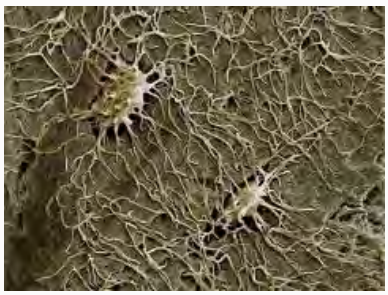
Osteocytes
The galaxy within

Buenzli PR, Sims NA. Quantifying the osteocyte network in the human skeleton. Bone 2015;75:144-50.

Buenzli and Sims present a fascinating insight into the intergalactic vastness of the osteocyte-canalicular network. If you integrate the content of this paper into your thinking, you will never 'see' bone in quite the same way again. The authors estimate that the total number of osteocytes within the skeleton is ~42 billion, the total number of dendritic projections is ~3.7 trillion forming a total length of 175,000 km. These cells form 23 trillion connections with each other and with bone surface cells. The total surface area of the lacunocanalicular system is 215 m^2 but within there is only enough space for 24 mL of extracellular fluid. The authors suggest 9.1 million osteocytes are replenished daily.

Figure 1. Osteocytes communicate with each other by interconnecting canaliculi. Image with permission from authors.



Hesse B, Varga P, Langer M, Pacureanu A, Schrof S, Männicke N, Suhonen H, Maurer P, Cloetens P, Peyrin F, Raum K. Canalicular network morphology is the major determinant of the spatial distribution of mass density in human bone tissue: evidence by means of synchrotron radiation phase-contrast nano-CT. J Bone Miner Res 2015;30:346-56.

Hesse et al hypothesized that mineral exchange is achieved by the diffusion of mineral from the lacunar-

canalicular network (LCN) to the bone matrix, resulting in a gradual change in tissue mineralization. The aim of this study was, therefore, to investigate the spatial distribution of mass density in the perilacunar and pericanalicular bone matrix and to explore how these densities are influenced by tissue aging. This is achieved by analyzing human jaw bone specimens from four healthy donors and four treated with high-dosage bisphosphonate using synchrotron radiation phase-contrast nano-CT (50-nm voxel). Mass density in the vicinity of lacunae ($p<0.001$) and canaliculi ($p<0.001$) is different from the mean matrix mass density, resulting in gradients with respect to the distance from both pore-matrix interfaces, which diminish with increasing tissue age. The density gradients are more pronounced around the lacunae than canaliculi.

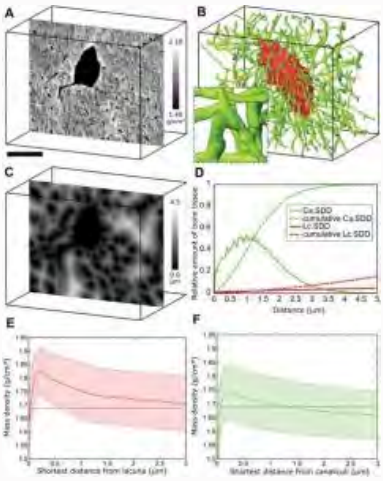


Figure 2. Perilacunar and pericanalicular bone tissue mass densities. (A) One slice of a volume of interest containing one osteocyte lacuna cropped from the 3D reconstructed phase nano-CT image. The volume of interest (VOI) dimensions are 800x600x630 pixels. The gray scale corresponds to mass density, and the scale bar=10 µm. (B) Surface representations of the lacunar (red) and canalicular (green) compartments segmented from the same image volume. (C) Distance transform image showing the shortest distance from each point in matrix to the lacunar-canalicular network. (D) Histogram of the 3D distance map (shortest distance distribution [SDD]) of the canalicular (green) and the lacunar (red) boundaries shown together with their cumulative functions for the same VOI. From the solid lines, 50% of the bone tissue is within 1.2-µm to the canalicular boundaries, whereas at this distance the cumulative function of the histogram of the distances considering the lacuna is only about 10 times smaller. (E, F) Average mass density and standard error bands as a function of the shortest distance to the osteocyte lacuna (E) and canaliculi (F), shown for the same VOI. The gray horizontal lines represent the mean mass density within the VOI. Reproduced from J Bone Miner Res 2015;30:346-56 with permission of the American Society of Bone and Mineral Research.

The Bone Remodeling Compartment
Where the action is

Jensen PR, Andersen TL, Hauge EM, Bollerslev J, Delaisse JM. A joined role of canopy and reversal cells in bone remodeling – Lessons from glucocorticoid-induced osteoporosis. Bone 2015;73:16-23.

The endosteal surface is covered by flattened osteoblast cells. At points of initiation of remodeling upon an endosteal surface, these lining cells lift and form the ‘canopy’ or ‘roof’ of a bone remodeling compartment (BRC) within which the remodeling cycle takes place. **Jensen et al** report that coupling between resorption and formation phases of the remodeling cycle requires an intact canopy overlying the surface upon which osteoclasts remove, and then osteoblasts deposit, bone during remodeling. Disruption of the canopy in myeloma, postmenopausal- and glucocorticoid-induced osteoporosis is associated with the absence of progression to the formation phase, i.e., uncoupling. Long-term glucocorticoid treatment is associated with arrested remodeling and lack of canopy coverage correlated with a deficiency in forming surfaces. The reason for the lack of canopies is not apparent but the reason this lack of canopies contributes to uncoupling may relate to the role of this layer or multilayered structure in providing a reservoir of osteoprogenitors.

Jean-Marie Delaisse and his group of investigators have pioneered this a fascinating area of research. A reading of a few of their papers is highly recommended because it provides important insights into bone remodeling. Remodeling is initiated at points upon the three (intracortical, endocortical and trabecular) components of bone’s inner or endosteal surface.

Coupling Between Bone Resorption and Formation Within the BRC

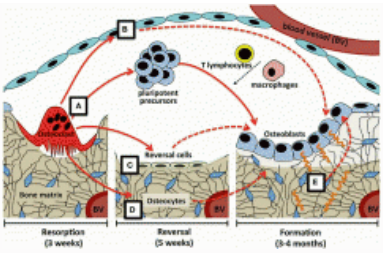
**Sims NA, Martin TJ. Coupling signals between the osteoclast and osteoblast: How are Messages transmitted between these temporary visitors to the bone surface?
Front Endocrinol (Lausanne) 2015;6:41.**

This short opinion piece is required reading for all of us. **Sims and Martin** present an elegant synthesis of the complex coordination of the volumes of bone resorbed and formed during bone remodeling; a coordination commonly referred to as coupling.

One of the challenges in understanding coupling mediated by local factors (from resorbed matrix, osteoclasts or by osteoclasts and osteoblast contact) is that these cells are not present at the same time. Resorption by osteoclasts occurs over a few weeks. Initiation of bone formation is delayed by a reversal phase of about a week or more during which neither osteoclasts or osteoblasts are present! Bone formation then proceeds with deposition of matrix during three months.

The authors suggest that osteoclast-derived coupling factors released from the matrix, secreted from the osteoclast, or expressed on the cell membrane initiate differentiation of early osteoblast progenitors with the level of osteoblast activity and numbers of differentiated cells refined by other factors released by a range of cells within the BMU.

Figure 3. Possible coupling mechanisms that overcome the delay between resorption and formation. (A) Osteoclast-derived factors (released from the matrix, secreted from the osteoclast, or expressed on the osteoclast membrane) initiate



differentiation of very early osteoblast progenitors. Osteoblast activity and numbers of differentiated cells may be refined by factors from a range of cells within the BMU. Osteoclast-derived factors may act directly on cells that transmit signals (dashed lines) to osteoblast precursors and mature osteoblasts; these transmitting cells may be (B) osteoblast-lineage cells in the remodeling canopy, (C) reversal cells on the surface, and (D) osteocytes. (E) Physical changes brought about by the osteoclast such as the resorptive pit and mechanical strain detected by osteocytes may provide signals (in part mediated by sclerostin regulation) required for initiation and completion of the correct volume of matrix formed by mature osteoblasts. Reproduced from Front Endocrinol 2015;6:41 under the terms of the Creative Commons Attribution License (CC BY).

Coadministration of Antiresorptive and Anabolic Therapy
Is two better than one?

de Bakker CM, Altman AR, Tseng WJ, Tribble MB, Li C, Chandra A, Qin L, Liu XS. µCT-based, in vivo dynamic bone histomorphometry allows 3D evaluation of the early responses of bone resorption and formation to PTH and alendronate combination therapy. Bone 2015;73:198-207.

de Bakker et al report a µCT-based in vivo dynamic histomorphometry technique for tracking changes during therapy. There are many interesting aspects to this study and its worth a quiet evening thorough reading. Two aspects are of particular interest are first that these investigators validate a method of quantifying bone remodeling by µCT and second that they examine and provide evidence for net benefits of combining anabolic and antiresorptive therapy, rather than the blunting usually reported leading to the unfortunate neglect of the value of combined therapy for patients (Seeman and Martin, J Bone Miner Res 2015;30:753-64). The investigators report increased rate of bone formation in rats treated with PTH and PTH+alendronate (ALN) with no evidence of bluniting of the response relative to PTH despite a , decrease in measures of bone resorption with ALN and PTH+ALN. PTH induced bone formation *despite* bone resorption suppression. The reason adding an antiresorptive might blunt the anabolic effect of PTH is that the anabolic effect is believed to be mediated mainly by remodeling based bone formation rather than modeling based bone formation. If so, then the anabolic effect should be blunted but this is not observed. The study did not evaluate bone strength. This is important. While there may be no blunting of the anabolic effect, evidence is needed that there is an advantage in terms of biomechanical strength by combining therapy over either drug alone. At present I am not convinced that such evidence exists. More work is needed.

Cortical Porosity
The void within

Nirody JA, Cheng KP, Parrish RM, Burghardt AJ, Majumdar S, Link TM, Kazakia GJ. Spatial distribution of intracortical porosity varies across age and sex. Bone 2015;75:88-95.

Nirody et al evaluated porosity of cortex adjacent to the medullary canal, of midcortical and subperiosteal regions using HR-pQCT of the distal tibia from 145 individuals. The elderly (65-78 years, n=22) had higher porosity than young subjects (20-29 years, n=29) with the greatest difference in midcortical porosity (+344%, p<0.001) due to more (+243%, p<0.001) and bigger pores (+28%, p<0.001). Females had greater age-related changes in porosity and pore number than males. Females and males displayed comparable nonsignificant changes with age in pore size.

This work raises a number of issues. First, the greater difference across age in midcortical porosity is contrary to most published work suggesting that there is a gradient of increasing in porosity across the cortex with the highest porosity in advanced age being in inner cortex adjacent to the medullary canal, and progressively less porosity towards the periosteal surface.

This discrepancy is likely to be the result of problems in distinguishing fragmented inner cortex, which looks like trabecular bone, from true trabecular bone in the medullary compartment. What is inner cortex has probably been trabecularized leaving the rise in porosity in this inner cortex underestimated; the porosity and fragments of cortex produced by intracortical remodeling are erroneously calculated as being part of the medullary canal seemingly enlarged by these contents.

Second, the age-related increase in porosity is reported to be the result of more pores than bigger pores. This is also contrary to most literature which suggests that the increase in porosity is the result of progressive enlargement of *existing* pores. There is really no such thing as ‘porosity’. Over 80% of pores are cross sections of the canals traversing the cortex formed during skeletal growth, the remaining porosity is the result of remodeling units in either their resorption, reversal or excavation phases (only about 10-15% of the bone is being remodelled annually), while the remainder is formed by the osteocyic lacunocanalicular system and voids in collagen.

The reason why porosity increases more by enlargement of existing pores than formation of new pores is that all intracortical remodeling is initiated at points upon the lining of the canals and when the matrix around the canal is excavated, less matrix is deposited producing *focal* canal enlargement. With time, more and more enlargement of existing canals occurs until they coalesce forming large irregularly shaped ‘pores’. However, it is plausible that a new canal is dug from an existing canal. More work is needed to resolve this issue. Finding nonsignificant age related increases in pore size in either sex is problematic. I suggest that most pores remain undetected using threshold based segmentation.

Tong X, Burton IS, Isaksson H, Jurvelin JS, Kroger H. Cortical bone histomorphometry in male remoral neck: The investigation of age-association and regional differences. Calcif Tissue Int 2015;96:295-306.

Tong et al report enormous heterogeneity in cortical osteonal size and porosity as well as heterogeneity in

cortical thicknesses. These authors investigated age-association differences in corticl morphology of the femoral neck in (n=20, aged 18-82 years, males). While the sample size was small, the findings are of interest to at least note the magnitude of the heterogeneity in these traits and think about what they might mean.

Mean Ct.Wi, inferior Ct.Wi, and superior Ct.Wi were negatively associated with age. The inferior cortex was the thickest and the superior cortex was the thinnest. Osteonal size and pore area were negatively associated with age. Osteonal area and number were higher in the antero-inferior area (P<0.002) and infero-posterior area (P=0.002) compared to the postero-superior area. The Haversian canal area was higher in the infero-posterior area compared to the postero-superior area (P=0.002). Moreover, porosity was higher in the antero-superior area (P<0.002), supero-anterior area (P<0.002) and supero-posterior area (P<0.002) compared to the infero-anterior area. Eroded endocortical perimeter (E.Pm/Ec.Pm) correlated with superior cortical width.

Bone Formed During Anabolic Treatment is Slowly Lost After Stopping

Recknor CP, Recker RR, Benson CT, Robins DA, Chiang AY, Alam J, Hu L, Matsumoto T, Sowa H, Sloan JH, Konrad RJ, Mitlak BH, Sipos AA. The effect of discontinuing treatment with blosozumab: Follow-up results of a phase 2 randomized clinical trial in postmenopausal women with low bone mineral density. J Bone Miner Res 2015;doi:10.1002/jbmr.2489.

Blosozumab, a humanized monoclonal antibody that binds sclerostin, increases bone formation and is one of the new kids on the horizon for anabolic therapy. **Recknor et al** studied women enrolled in a 1-year randomized, placebo-controlled phase 2 trial for an additional year after treatment stopped. Of the 106 women completing treatment; 88 completed 1-year follow-up. At the end of one year after discontinuing treatment, spine BMD remained greater than placebo in women treated with blosozumab 270 mg every 2 weeks (Q2W), and blosozumab 180 mg Q2W (6.9% and 3.6% above baseline, respectively). Total hip BMD also declined but remained greater than placebo in women treated with those two doses of blosozumab (3.9% and 2.6% above baseline, respectively).

As with teriparatide therapy and with antiresorptive therapy, when treatment is stopped, the benefits are progressively lost. The rate of loss varies from drug to drug but whatever the case, presumably, with return of remodeling, benefits are eroded and like teriparatide, it is likely that antiresorptive therapy will be needed at the end of a course of this class of anabolic therapy.

Recker RR, Benson CT, Matsumoto T, Bolognese MA, Robins DA, Alam J, Chiang AY, Hu L, Krege JH, Sowa H, Mitlak BH, Myers SL. A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. J Bone Min Res 2015;30:216-24.

Recker et al report the results of a randomized, double-blind, placebo-controlled multicenter phase 2 clinical trial of blosozumab, a humanized monoclonal antibody targeted against sclerostin in postmenopausal women with low BMD randomized to subcutaneous blosozumab 180 mg every 4 weeks (Q4W), 180 mg every 2 weeks (Q2W), 270 mg Q2W, or matching placebo for 1 year, with calcium and vitamin D. Overall, 120 women were enrolled in the study (mean age 65.8 years, mean lumbar spine T-score –2.8). Blosozumab increased spine, femoral neck, and total hip BMD as compared with placebo. In the highest dose group, BMD increases from baseline reached 17.7% at the spine, and 6.2% at the total hip. Biochemical markers of bone formation increased and trended toward pretreatment levels by study end. However, bone specific alkaline phosphatase remained higher than placebo at study end in the highest dose group. CTx, a biochemical marker of bone resorption, decreased early in blosozumab treatment to a concentration less than that of the placebo group by 2 weeks, and remained reduced throughout.

Modeling Based Bone Formation Detected by Suppressing Remodeling

Ominsky MS, Libanati C, Niu QT, Boyce RW, Kostenuik PJ, Wagman RB, Baron R, Dempster DW. Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. J Bone Miner Res 2015; doi:10.1002/jbmr.2480.

Denosumab (DMAb) administration is associated with continued BMD increases through 8 years. Secondary mineralization may occur for several years after deposition of bone matrix. However, the increase in BMD should become asymptotic as more and more complete mineralization is achieved. For this reason, it is difficult to explain a continued increase in BMD during 8 years of DMab therapy. **Ominsky et al** report that the increase in BMD may be the result of continued accrual of bone matrix via modeling-based bone formation that occurs in the untreated state but is either obscured or removed by remodeling. When remodeling is suppressed, this has allows the continued slow modeling to be detected and influence bone morphology.

The authors examined fluorochrome labeling patterns in sections from ovariectomized (OVX) cynomolgus monkeys (cynos) treated with DMAb for 16 months. Mature OVX or Sham cynos were treated with vehicle while other OVX cynos received monthly 25 or 50 mg/kg DMAb. DMAb groups had low remodeling biomarkers and near-absent fluorochrome labeling in proximal femur cancellous bone. Femoral neck BMD continued to rise in DMAb-treated cynos , from a 4.6% increase at month 6 to 9.8% above baseline at month 16. Further examination showed labeling on the superior endocortex and the inferior periosteal surface, typically containing multiple superimposed labels from month 6 to 16 over smooth cement lines, consistent with modeling-based bone formation. Quantitative analysis at the ninth rib, demonstrated that DMAb did not alter modeling-based labels suggesting that this effect depended in part upon loading circumstances. These observations are indeed novel and require further investigation, particularly in human subjects.

Denosumab, Alendronate and Remodeling Suppression

Kostenuik PJ, Smith SY, Samadfam R, Jolette J, Zhou L, Ominsky MS. Effects of denosumab, alendronate, or denosumab following alendronate on bone turnover, calcium homeostasis, bone mass and bone strength in ovariectomized cynomolgus monkeys. J Bone Miner Res 2015;30:657-69.

Kostenuik et al report the effect of transitioning from ALN to DMAb was examined in mature OVX cynos. One day after OVX, cynos (7-10/group) were treated with vehicle (VEH, s.c.), ALN (50 µg/kg, i.v., twice monthly) or DMAb (25 mg/kg/month, s.c.) for 12 months. Other animals received VEH or ALN for 6 months and then transitioned to 6 months of DMAb. DMAb produced a greater reductions in serum CTx than ALN, and transition from ALN to DMAb produced further reductions relative to continued ALN. Compared with ALN, DMAb caused greater reductions in osteoclast surface, eroded surface, cortical porosity and fluorochrome labeling, and transition from ALN to DMAb reduced these parameters relative to continued ALN. Destructive biomechanical testing revealed significantly greater vertebral strength in all three groups receiving DMAb, including those receiving DMAb after ALN, relative to VEH controls.

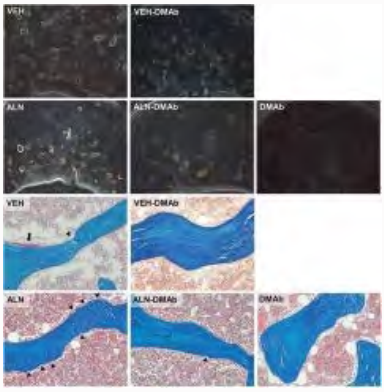


Figure 4. Upper panels are fluorescent photomicrographs of tibial diaphysis cross-sections from the VEH, ALN, ALN-DMAb and DMAb groups. VEH controls exhibited the greatest cortical porosity and intracortical remodeling, while the ALN-DMAb and DMAb groups exhibited the least. Lower panels are Goldner's trichrome-stained photomicrographs of trabecular bone from L2. VEH control depicts remodeling with a large scalloped resorption pit on the upper trabecular surface (arrowhead), and its refilling by osteoblasts (arrow). Minimal remodeling is seen in the treatment groups. Shallow but increased eroded surfaces are evident in the ALN example (arrowheads), whereas eroded surfaces were minimal in ALN-DMAb and DMAb examples. Reproduced from J Bone Miner Res 2015;30:657-69 with permission of the American Society of Bone and Mineral Research.

Raloxifene and Skeleton Hydration

Allen MR, Territo PR, Lin C, Persohn S, Jiang L, Riley AA, McCarthy BP, Newman CL, Burr DB, Hutchins GD. In vivo UTE-MRI reveals positive effects of raloxifene on skeletal bound water in skeletally mature beagle dogs. J Bone Miner Res 2015;doi:10.1002/jbmr.2470.

Allen et al report that raloxifene affects mechanical properties in part through modification of skeletal bound water. Skeletal hydration was measured in vivo using ultrashort echotime magnetic resonance imaging (UTE-MRI) in 12 skeletally female beagle dogs (n=6/group) treated for 6 months with vehicle (VEH, 1 ml/kg/d) or raloxifene (RAL, 0.5 mg/kg/d). Following six months, animals underwent in vivo UTE-MRI of the proximal tibial cortical bone. UTE-MRI signal intensity versus echotime curves were analyzed. Raloxifene-treated animals had higher bound water (+14%; p=0.05) and lower free water (-20%) compared to controls.

Bisphosphonates Do Not Increase Cortical Thickness

Niimi R, Kono T, Nishihara A, Hasegawa M, Matsumine A, Kono T, Sudo A. Cortical thickness of the femur and long-term bisphosphonate use. J Bone Miner Res 2015;30:225-31.

Niimi et al enrolled 142 patients (mean 79 years) taking bisphosphonate (BP) for more than 5 years, and enrolled 426 BP free osteoporosis patients as controls. There were no differences in cortical thickness between long-term BP users and controls. In addition, after further use of BP for a minimum of 1 year, no differences in the changes in cortical thickness of the femur were observed.

There is no rational basis for there to be cortical thickening. This may occur by greater periosteal apposition but antiresorptives do not stimulate periosteal deposition of bone, nor do they inhibit it. Antiresorptives at best reduce the number of remodeling sites resorbing bone upon the endocortical surface, reduce them, not abolish them, so they slow cortical thinning but they do not restore cortical thickness nor to they promote bone formation in the endocortical surface.

Odanacatib and Altered Ductility

Khan MP, Singh AK, Singh AK, Shrivastava P, Tiwari MC, Nagar GK, Bora HK, Parameswaran V, Sanyal S, Bellare JR, Chattopadhyay N. Odanacatib restores trabecular bone of skeletally mature female rabbits with osteopenia but induces brittleness of cortical bone: a comparative study of the investigational drug with PTH, estrogen and alendronate. J Bone Miner Res 2015;doi:10.1002/jbmr.2520.

Khan et al report that mature New Zealand rabbits were OVX and following induction of bone loss were given odanacatib (ODN) (9 µM/d) for 14 weeks. Sham operated and OVX rabbits treated with ALN, 17β-estradiol (E2) or PTH served as controls. Between the sham and ODN-treated osteopenic groups, lumbar and femur metaphyseal BMD, Ca/P ratio, trabecular microstructure and geometric indices, vertebral compressive strength, trabecular lining cells, femoral BMD, cortical area and thickness, and periosteal deposition and serum P1NP were comparable. Skeletal improvements in ALN or E2-treated groups were less than that of the sham/ODN/PTH group. However, the ODN group displayed reduced ductility and enhanced brittleness of central femur, which might have been contributed by higher crytallinity and tissue mineralization. ODN did not suppress remodeling but inhibited osteoclast activity more than ALN. ODN reverses BMD, skeletal architecture and compressive strength in osteopenic rabbits however, increases crystallinity and tissue mineralization thus leading to increased cortical brittleness.

Heterogeneity in Trabecular Matrix Mineral Density

Wang J, Kazakia GJ, Zhou B, Shi XT, Guo XE. Distinct tissue mineral density in plate and rod-like trabeculae of human trabecular bone. J Bone Miner Res 2015;doi:10.1002/jbmr.2498.

Wang et al report tissue mineralization in individual trabeculae of different trabecular types and orientations. Individual trabecula mineralization (ITM) analysis was used to determine tissue mineral density (TMD) distributions in plate- and rod-like trabeculae and to compare the TMD of trabeculae along various orientations from the femoral neck, greater trochanter, and proximal tibia. Trabecular plates had higher TMD than rods. TMD in trabecular plates was lowest in longitudinal plates and the highest TMD in transverse plates. Conversely, there was a relatively uniform distribution of TMD among trabecular rods with respect to trabecular orientation. TMD distribution revealed that trabecular plates had higher mean and peak TMD, whereas trabecular rods had a wider TMD distribution and a larger portion of low mineralized trabeculae. Comparison of apparent Young's moduli derived from microfinite element models demonstrated that heterogeneous TMD in trabecular plates had a significant influence on the elastic mechanical property of trabecular bone.

Familial Resemblance in Microarchitecture

Nagy H, Chapurlat R, Sornay-Rendu E, Boutroy S, Szulc P. Family resemblance of bone turnover rate in mothers and daughters-the MODAM study. Osteoporos Int 2015;26:921-30.

Nagy et al studied bone turnover markers (BTM) and microarchitecture (using HR-pQCT) in 171 postmenopausal women and their 210 premenopausal daughters. After adjustment for age, weight, lifestyle factors, hormones, and mother's fracture status, BTM levels correlated between mothers and daughters (intraclass correlation coefficient = 0.22-0.27, $p<0.005$). Average BTM levels were 0.6 SD higher among daughters of mothers in the highest BTM quartile vs. the ones in the lowest BTM quartile. The variability of BTM levels explained 10 and 14% of variability of bone microarchitecture in the daughters and mothers, respectively. Cortical density was lower by 2.3-2.9% (0.6 SD, $p<0.05$ to <0.005) in the daughters from the mother-daughter pairs with high BTM levels than in the daughters from the pairs with low BTM levels. Corresponding differences for the mothers were 4.5-4.8 % (0.5 SD, $p<0.05$ to <0.01).

Fractures, Osteopenia and Mortality

Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: The Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res 2015;30:637-46.

Half of all fragility fractures occur in individuals BMD T-score>–2.5. **Bliuc et al** examined adverse events of subsequent fracture and mortality following initial fracture according to BMD level in community-dwelling participants aged 60+ years from the Dubbo Osteoporosis Epidemiology Study. There were 528 low-trauma fractures in women and 187 in men. Of these, 12% occurred in individuals with normal BMD (38 women, 50 men) and 42% in individuals with osteopenia (221 women, 76 men). The risk of subsequent fracture was >2.0-fold for all levels of BMD in women and men. With subsequent fracture risk, postfracture mortality was increased in individuals with low BMD (age-adjusted standardized mortality ratio for osteopenia 1.3 [1.1-1.7] and 2.2 [1.7-2.9] for women and men, respectively, and osteoporosis 1.7 [1.5-2.0] and 2.7 [2.0-3.6] for women and men, respectively).

Bliuc D, Nguyen ND, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Accelerated bone loss and increased post-fracture mortality in elderly women and men. Osteoporos Int 2015;26:1331-9.

Bliuc et al report that in 341 women and 106 men, survival was lowest for the highest quartile of bone loss. The association of bone loss with mortality was observed for vertebral in both sexes and nonhip nonvertebral fractures in women ($p<0.0001$). Bone loss did not contribute to mortality risk following hip fractures. Rapid bone loss was associated with 44-77% increased mortality risk after multiple variable adjustment. It remains to be determined whether bone loss is a marker or plays a role in the mortality associated with fractures.

Sclerostin Inhibition Preserves Bone Mass in Paralysis

Beggs LA, Ye F, Ghosh P, Beck DT, Conover CF, Balaez A, Miller JR, Phillips EG, Zheng N, Williams AA, Aguirre J, Wronski TJ, Bose PK, Borst SE, Yarrow JF. Sclerostin inhibition prevents spinal cord injury-induced cancellous bone loss. J Bone Miner Res 2015;30:681-89.

Beggs et al report that sclerostin, an osteocyte-derived glycoprotein that negatively regulates intraskeletal Wnt signaling, is elevated after SCI and may contribute to bone loss. 55 (n=11-19/group) skeletally mature male Sprague Dawley rats were randomized to: (A) sham surgery (T8 laminectomy), (B) moderate-severe (250 kilodyne) SCI, (C) 250 kilodyne SCI + TE (7.0 mg/wk, im), or (D) 250 kilodyne SCI + Scl-Ab (25 mg/kg, twice weekly, sc) for 3 weeks. Twenty-one days post-injury, SCI animals exhibited reduced hindlimb cancellous bone volume at the proximal tibia and distal femur, characterized by reduced trabecular number and thickness. SCI also reduced trabecular connectivity and platelike trabecular structures, and deficits in cortical bone strength. Scl-Ab and TE both prevented SCI-induced cancellous bone loss. Scl-Ab increased osteoblast surface and bone formation whereas TE reduced osteoclast surface with minimal effect on bone formation. The deleterious microarchitectural alterations in the trabecular network were also prevented in SCI + Scl-Ab and SCI + TE animals, whereas only Scl-Ab prevented the reduction in cortical bone strength.

Atrial Fibrillation and Alendronate

Herrera L, Leal I, Lapi F, Schuemie M, Arcoraci V, Cipriani F, Sessa E, Vaccheri A, Piccinni C, Staniscia T, Vestri A, Di Bari M, Corrao G, Zambon A, Gregori D, Carle F, Sturkenboom M, Mazzaglia G, Trifiro G. Risk of atrial fibrillation among bisphosphonate users: A multicenter,

population-based, Italian study. Osteoporos Int 2015;26:1499-506.

Herrera et al report results of a nested case-control study using the databases of drug-dispensing and hospital discharge diagnoses from five Italian regions involving new users of bisphosphonates aged 55 years and older. Patients were followed from the first BP prescription until an occurrence of an atrial fibrillation (AF) diagnosis (index date, i.e., ID), cancer, death, or the end of the study period, whichever came first. For the risk estimation, any AF case was matched by age and sex to up to 10 controls from the same source population. BP exposure was classified into current (<90 days prior to ID), recent (91-180), past (181-364), and distant past (≥365) use. Compared with distant past users of BP, current users of BP showed increased risk of AF: OR=1.78 and 95%CI=1.46-2.16. ALN use was associated with AF as compared with distant past use of BP (OR, 1.97; 95%CI, 1.59-2.43).

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Progress in Osteoporosis

CRITICAL REVIEW JOURNAL

OVERVIEW, VOL 15, ISSUE 2

Ego Seeman
Editor

By Ego Seeman Fri, 08/21/2015 - 11:00

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

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

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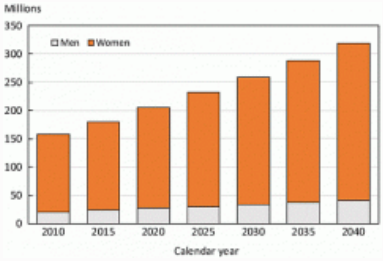
The Burden of Fractures is Increasing

Oden A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: Secular increases 2010-2040. Osteoporos Int 2015;26:2243-8.

Oden et al quantified the number of individuals worldwide aged 50 years or more at high risk of fracture in 2010 and 2040. A threshold of high fracture probability was set at the age-specific 10-year probability of a major fracture (clinical vertebral, forearm, humeral or hip fracture) equivalent to that of a woman with a BMI of 24 kg/m^2 and a prior fragility fracture. The prevalence of high risk was determined worldwide, and by continent, and applied to the demography for each country. Twenty-one million men and 137 million women had a fracture probability at or above the threshold in the world for the year 2010. The greatest number of men and women at high risk were from Asia (55%). Worldwide, the number of high-risk individuals is expected to double over the next 40 years.

Figure 1. Number of individuals (millions) having a 10-year probability of a major osteoporotic fracture calculated without BMD above the fracture threshold for the years 2010-2040. Reproduced from Osteoporos Int 2015;26:2243-8 with permission from Springer.



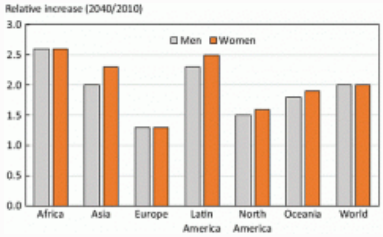


Figure 2. The increase in the number of men and women with a10-year probability of a major osteoporotic fracture above the fracture threshold between the years 2010-2040. Reproduced from Osteoporos Int 2015;26:2243-8 with permission from Springer.

Karampampa K, Ahlbom A, Michaelsson K, Andersson T, Drefahl S, Modig K. Declining incidence trends for hip fractures have not been accompanied by improvements in lifetime risk or post-fracture survival – A nationwide study of the Swedish population 60 years and older. Bone 2015;78:55-61.

Karampampa et al report that the Swedish population 60 years old and above was followed between 1987-2010 in the National Patient Register and the Cause of Death Register. The age-specific hip fracture incidence decreased between 1995-2010 in all ages by 1% per year. The lifetime risk remained stable between 9-11% for men, and between 18-20% for women. The expected mean age of a first hip fracture increased by 2.5 years for men and by 2.2 years for women. No improvements over time were observed for the 3-month survival for men, while for women a 1% decrease per year was observed. The 1-year survival increased over time for men (0.4% per year), while no improvement was observed for women. The age-specific hip fracture incidence has decreased but the lifetime risk has not decreased because life expectancy has increased. Survival after hip fracture has not improved.

Sobolev B, Sheehan KJ, Kuramoto L, Guy P. Excess mortality associated with second hip fracture. Osteoporos Int 2015;26:1903-10.

Sobolev et al retrieved 42,435 hospitalization records of patients aged 60 years or older discharged after admission for hip fracture between 1990-2005 in British Columbia, Canada. The average monthly death rate (per 1000 patient-months) was 16.2 (95%CI 16.0-16.4) for those without second hip fracture vs. 21.1 (95%CI 20.2-22.1) for those with second hip fracture. The hazard of death was 55% higher for patients with second hip fracture (HR=1.55, 95%CI 1.47-1.63). The hazard of death was 58% higher for men with second hip fracture (HR=1.58, 95%CI 1.42-1.75). The hazard of death was 54% higher for women with second hip fracture (HR=1.54, 95%CI 1.46-1.63).

Microdamage
Location and mechanisms

Goff MG, Lambers FM, Nguyen TM, Sung J, Rimnac CM, Hernandez CJ. Fatigue-induced microdamage in cancellous bone occurs distant from resorption cavities and trabecular surfaces. Bone 2015;79:8-14.

Goff et al subjected human vertebral cancellous bone to cyclic compressive loading (10 male donors, 6 female donors, mean age 76). The 10% largest microdamage sites accounted for 70% of all microdamage. The large microdamage sites predicted reductions in Young's modulus better than overall volume of damage. Most microdamage volume (~69%) was located >30 µm from trabecular surfaces suggesting microdamage occurs within interstitial regions, not near resorption cavities as sources of stress concentration.

Crack Crack and the Hierarchical Design of Bone

Katsamenis OL, Jenkins T, Thurner PJ. Toughness and damage susceptibility in human cortical bone is proportional to mechanical inhomogeneity at the osteonal-level. Bone 2015;76:158-68.

Katsamenis et al investigated cortical osteonal-, micro- and tissue-level mechanical behaviour from young and elderly donors. Toughness and crack growth resistance at the tissue-level correlate with damage susceptibility at the microlevel, and mechanical inhomogeneity between lamellae and interlamellar areas at the osteonal level. Reduced nanoelasticity inhomogeneity of lamellar/interlamellar layers in osteons correlated with increased indentation depth at the microlevel and an overall reduction in crack-growth toughness and fracture toughness of the tissue. The reduction in nanoelasticity inhomogeneity is responsible for the inability of the microstructure to effectively adapt to the applied load by redistributing strains preventing damage formation and propagation. Failure of tougher bone specimens is governed by increased deflection of the crack path and broadly spread damage around the crack-tip. In contrast, shorter and more direct crack paths as well as less distributed damage were evidenced during failure of the weaker specimens.

Collagen Structure and Mineralization

Quan BD, Sone ED. Structural changes in collagen fibrils across a mineralized interface revealed by cryo-TEM. Bone 2015;77:42-9.

Quan et al compared cryo-TEM images of rat tail tendon collagen. Across a mineralized interface, mineralization results in axial contraction of the fibril in the more flexible gap region with lateral expansion. The features of the banding pattern are not changed, indicating that the axial arrangement of molecules remains intact. Collagen fibrils accommodate mineral without disruption of their molecular packing, leading to synergy of mechanical properties.

Trabecular BV/TV
An important determinant of stiffness

Maquer G, Musy SN, Wandel J, Gross T, Zysset PK. Bone volume fraction and fabric anisotropy are better determinants of trabecular bone stiffness than other morphological variables. J Bone Miner Res 2015;30:1000-8.

Maquer et al studied individual trabeculae segmentation and trabecular bone score in 743 µCT reconstructions of cubic trabecular bone samples from femur, radius, vertebrae, and iliac crest. Their stiffness tensor (CFE) was computed using microfinite element analyses. Bone volume fraction (BV/TV) is the best determinant of CFE (r^2 adj = 0.889), especially with fabric anisotropy (r^2 adj = 0.968). Including the other predictors hardly affected variance. BV/TV explained 87% of the variance in elastic properties. Fabric anisotropy further described 10% of the bone stiffness. BV/TV and fabric anisotropy are the best determinants of trabecular stiffness.

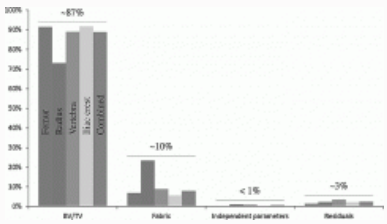


Figure 3. The relative contribution of each variable. Bone volume fraction (BV/TV) and fabric anisotropy explained most of the elastic properties of bone. The contribution of the other parameters found independent (SMI, Tb.Th.SD, Tb.Sp.SD, pTb.Th, rTb.Th, p.Tb.S, r.Tb.l, RR.Junc.D, and TBS) was less than the residuals. Reproduced from J Bone Miner Res 2015;30:1000-8 with permission of the American Society of Bone and Mineral Research.

Treatment of Structural Deterioration in Renal Disease

Newman CL, Chen NX, Smith E, Smith M, Brown D, Moe SM, Allen MR. Compromised vertebral structural and mechanical properties associated with progressive kidney disease and the effects of traditional pharmacological interventions. Bone 2015;77:50-6.

Newman et al studied animals with kidney disease left untreated, treated with calcium, zoledronic acid, antisclerostin antibody, or antisclerostin antibody plus calcium. Chronic kidney disease with high PTH resulted in 6-fold higher remodeling, reduction in trabecular and cortical bone, and compromised mechanical properties in the vertebra. Treatments that reduced remodeling were effective in normalizing vertebral structure and mechanical properties if the treatment reduced PTH. Similarly, treatment with antisclerostin antibody was effective in enhancing bone mass and mechanical properties only if combined with PTH-suppressive treatment.

Antisclerostin Antibody Prevents Structural Decay After Spinal Cord Injury

Qin W, Li X, Peng Y, Harlow LM, Ren Y, Wu Y, Li J, Qin Y, Sun J, Brown T, Feng JQ, Ke HZ, Bauman WA, Cardozo CC. Sclerostin antibody preserves the morphology and structure of osteocytes and blocks the severe skeletal deterioration after motor-complete spinal cord injury in rats. J Bone Miner Res 2015;doi:10.1002/jbmr.2549.

Qin et al reported that spine cord injury was induced in rats. they were administered Scl-Ab (25 mg/kg/wk) or vehicle 7 days after injury then weekly for 7 weeks. SCI decreases distal femur BMD (-25%) and trabecular bone volume (-67%); Scl-Ab prevented this deterioration with increased bone formation. Spinal cord injury reduced osteocytes and dendrites with a change from a spindle to round shape; Scl-Ab corrected these abnormalities. In ex vivo cultures of marrow cells, Scl-Ab inhibited osteoclastogenesis and promoted osteoblastogenesis with increases in mRNA levels of LRP5, OPG and the OPG/RANKL ratio,

and a decrease in DKK1 mRNA.

Atypical Fractures and Femoral Bowing

Schilcher J, Howe TS, Png MA, Aspenberg P, Bee JK. Atypical fractures are mainly subtrochanteric in Singapore and diaphyseal in Sweden: A cross-sectional study. J Bone Miner Res 2015;doi:10.1002/jbmr.2547.

Schilcher et al reported that atypical fractures (AFF) occur along the femoral shaft in Swedish patients and are mainly subtrochanteric in patients from Singapore. Subtrochanteric fractures comprised 48% of all fractures in Singapore, and 17% in Sweden (p=0.0001). In Singapore, femoral bow was associated with more fractures in the diaphyses (P=0.0001). This was not seen in Sweden.

Chou AC, Ng AC, Png MA, Chua DT, Ng DC, Howe TS, Koh JS. Bone cross-sectional geometry is not associated with atypical femoral fractures in Asian female chronic bisphosphonate users. Bone 2015;79:170-5.

By contrast, **Chou et al** reported that in 31 patients with AFF age-matched to 31 patients with any femoral fracture (NFF) and 49 patients with osteoporotic femoral fracture (OFF). There were no differences in parameters between patients with AFF and patients with NFF. Patients with AFF and NFF had higher BMD, cross-sectional area (CSA), section modulus (SM), average cortical thickness (ACT) values and lower buckling ratio values at the narrow neck and intertrochanteric (IT) regions than patients with OFF. Additionally, patients with NFF had higher SM values at the IT region than patients with OFF, while patients with AFF had higher BMD, CSA, and ACT values at the femoral shaft region. All other measured parameters were not different between the groups. Varus neck shaft angles were not f associated with AFF in Asian females.

PTH Remodels Bisphosphonate Out of Bone

Murphy CM, Schindeler A, Cantrill LC, Mikulec K, Peacock L, Little DG. PTH(1-34) treatment increases bisphosphonate turnover in fracture repair in rats. J Bone Miner Res 2015;30:1022-9.

PTH(1-34) increases bone turnover. **Murphy et al** hypothesized PTH may increase bisphosphonate (BP) turnover in the skeleton and so improve healing of microfractures. Fluorescent labeled pamidronate (Pam) and radiolabeled ^{14}C-ZA (zoledronic acid). were dosed to Wistar rats in models of normal growth and closed fracture repair. Rats were treated with saline or 25 µg/kg/d PTH(1-34) and the effects on BP liberation and bone healing were examined. There was a decrease in fluorescence in long bones and fracture callus in treated animals. This was confirmed by autoradiography for ^{14}C-ZA. Callus bone volume (BV) was increased in fractured limbs, and although decreases in callus-bound BP with PTH(1-34) was noted, these were not sufficient to alter BV. However, increased intracellular BP was noted in resorbing osteoclasts, confirming that, in principle, PTH(1-34) increases bone turnover as well as BP turnover.

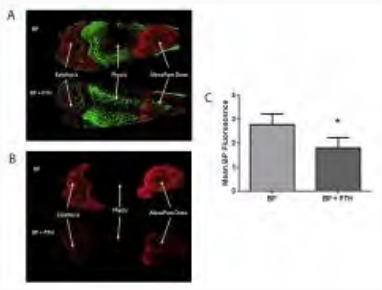


*Figure 4. (A) An overlay of labeled AlexaPam647 (red) and calcein (green) in rats receiving saline or daily PTH(1-34) intervention. AlexaPam647 was given 6 weeks before harvest, and calcein 10 and 7 days before harvest. AlexaPam647 signal was reduced in the PTH(1-34)-treated group, and no change was observed within the growth plate (physis) indicative of BP release and rebinding. (B) Representation of the image in panel A without the calcein overlay. This emphasizes the reduction in the bone as a result of PTH(1-34) treatment. (C) Quantification of fluorescent signal from capture images showed a significant reduction in signal with PTH(1-34) treatment (*p<0.001 in relation to BP). Reproduced from J Bone Miner Res 2015;30:1022-9 with permission of the American Society of Bone and Mineral Research.*

How Do Osteoclast Precursors Speak to Osteoblast Lineage Cells?

Deng L, Wang Y, Peng Y, Wu Y, Ding Y, Jiang Y, Shen Z, Fu Q. Osteoblast-derived microvesicles: A novel mechanism for communication between osteoblasts and osteoclasts. Bone 2015;79:37-42.

The maintenance of remodeling balance by the BMU depends on cellular communication between osteoclasts and osteoblasts. **Deng et al** reported that microvesicles containing RANKL protein shed from osteoblasts may mediate intercellular communication by transfering this protein to osteoclast precursors to facilitate ostoclast formation.

How Do Osteoclasts Become Multinucleated?

Levaot N, Ottolenghi A, Mann M, Guterman-Ram G, Kam Z, Geiger B. Osteoclast fusion is initiated by a small subset of RANKL-stimulated monocyte progenitors, which can fuse to RANKL-unstimulated progenitors. Bone 2015;79:21-8.

Levaot et al reported that osteoclasts are formed by fusion of monocyte progenitors, a process initiated by a small subset of precursors, 'fusion founders', capable of fusing with other founders or with nonstimulated progenitors ('fusion followers'). Fusion between a founder and a follower cell consists of an pairing for 5-35 min, then the fusion event occurs requiring a transfer of fluorescent reporter proteins from nucleus to nucleus suggesting crosstalk between the founder and follower progenitors via the cytoplasm as well as overall transcriptional regulation in the developing heterokaryon.

Macrophage Cells
A neglected participant in the cellular machinery of bone

Vi L, Baht GS, Whetstone H, Ng A, Wei Q, Poon R, Mylvaganam S, Grynpas M, Alman BA. Macrophages promote osteoblastic differentiation in-vivo: Implications in fracture repair and bone homeostasis. J Bone Miner Res 2015;30:1090-102.

Macrophages are activated in inflammation and during early repair. Interestingly and are present in bone during development. **Vi et al** explored the function of macrophages using transgenic mice. Depletion of macrophages led to growth retardation and osteoporosis. By 3 months of age, macrophage-deficient mice displayed a 25% reduction in BMD and a 70% reduction in the number of trabeculae. Functional osteoclasts were still present in bones, lining trabecular bone and the endosteal surface of the cortical bone. There was a 60% reduction marrow mesenchymal progenitor cells and a decrease in the ability of these cells to differentiate to osteoblasts. When macrophages were depleted during fracture repair, bone union was impaired. Calluses from macrophage-deficient animals were smaller, and contained less bone and more fibrotic tissue deposition. Macrophages are crucial for maintaining bone homeostasis and promoting fracture repair by enhancing the differentiation of mesenchymal progenitors.

TGFβ
One of many factors coupling resorption and formation

Weivoda MM, Ruan M, Pederson L, Hachfeld C, Davey RA, Zajac JD, Westendorf JJ, Khosla S, Oursler MJ. Osteoclast TGFβ receptor signaling induces Wnt1 secretion and couples bone resorption to bone formation. J Bone Miner Res 2015;doi:10.1002/jbmr.2586.

Osteoclasts release and activate TGFβ from the bone matrix. **Weivoda et al** reported that osteoclast-specific inhibition of TGFβ receptor signaling in mice results in osteopenia due to reduced osteoblast numbers not osteoclast number or activity. TGFβ induced osteoclast expression of Wnt1 and this was blocked by impaired TGFβ receptor signaling. Osteoclasts in aged murine bones had lower TGFβ signaling and Wnt1 expression in vivo. Ex vivo stimulation of osteoclasts derived from young or old mouse bone marrow macrophages showed no difference in TGFβ induced Wnt1 expression. However, young osteoclasts expressed reduced Wnt1 when cultured on aged mouse bone chips compared to young mouse bone chips, consistent with decreased skeletal TGFβ availability with age. Osteoclast responses to TGFβ are essential for coupling resorption to formation.

Sphingosine-1-phosphate in Osteocytic Mechanotransduction

Zhang JN, Zhao Y, Liu C, Han ES, Yu X, Lidington D, Bolz SS, You L. The role of the sphingosine-1-phosphate signaling pathway in osteocyte mechanotransduction. Bone 2015;79:71-8.

Osteocytes translate loading into biochemical signals. **Zhang et al** reported that sphingosine-1-phosphate (S1P) participates mechanotransduction by activation of osteocytes in response to loading-induced oscillatory fluid flow (OFF). OFF (1 Pa, 1 Hz) applied to osteocyte-like MLO-Y4 cells decreased endogenous S1P and suppressed the OFF-induced intracellular calcium response. Addition of S1P to MLO-Y4 cells enhanced the synthesis and release of PGE2 and amplified OFF-induced PGE2 release. The stimulatory effect of OFF on the gene expression of OPG and RANKL was S1P dependent. The S1P2 receptor subtype was involved in OFF-induced PGE2 synthesis and release, as well as downregulation of RANKL/OPG gene expression ratio.

Vestibular Signals and Bone Remodeling
An unlikely coupling

Vignaux G, Ndong JD, Perrien DS, Elefteriou F. Inner ear vestibular signals regulate bone remodeling via the sympathetic nervous system. J Bone Miner Res 2015;30:1103-11.

The vestibular system has projections to brain centers that regulate sympathetic outflow which inhibits bone formation and promotes bone resorption. **Vignaux et al** demonstrated that bilateral vestibular lesions in mice cause low bone mass with decreased bone formation and increased bone resorption. This reduction in bone mass is prevented by the propranolol and by genetic deletion of the β2-adrenergic receptor, globally or specifically in osteoblasts. Patients with inner ear pathologies might be at risk for fracture.

Bisphosphonates and Denosumab

Anastasilakis AD, Polyzos SA, Gkiomisi A, Saridakis ZG, Digkas D, Bisbinas I, Sakellariou GT, Papatheodorou A, Kokkoris P, Makras P. Denosumab versus zoledronic acid in patients previously treated with zoledronic acid. Osteoporos Int 2015;doi:10.1007/s00198-015-3174-2.

Anastasilakis et al compared yearly changes in BMD, turnover markers, free soluble RANKL (sRANKL) and sclerostin with denosumab or zoledronic acid in postmenopausal women with low bone mass previously treated with zoledronic acid for 1 year assigned to denosumab (n=32) or zoledronic acid infusion (n=26). The lumbar spine increase was 4.5 and 4.4 % with denosumab and zoledronic acid, respectively (NS). Denosumab caused a larger decrease in CTx at 3 months ($p<0.001$) and P1NP at 3 ($p<0.001$), 6 and 12 months ($p=0.042$). Denosumab decreased sRANKL by 87.4% at 3 months ($p<0.001$) and bone turnover more than zoledronic acid, but the increases in lumbar spine BMD are comparable.

Remodeling is reduced at one month with zoledronate, similar to that seen with denosumab, but after this the suppression of remodeling is greater with denosumab than zoledronic acid, or any other bisphosphonate for that matter. Remodeling markers reflect the number of remodeling sites turning over the skeleton and the relative volumes of bone resorbed and formed by each remodeling transaction. It is not possible to determine the source of the remodeling – whether it arises from cortical or trabecular bone or from the axial and appendicular skeleton. As zoledronic acid is bound avidly to mineral it is likely to not

access remodeling deep in cortical bone so the continued remodeling despite treatment is likely to reflect persisting intracortical remodeling. the similar risk in spine BMD is not surprising as all these patients received zolendronic acid for 12 months and the reduction in remodeling space transient achieved in that year accounts for this rise. The further reduction in remodeling is likely to arising from the appendicular skeleton in the now denosumab treated group.

Denosumab and Long-term Fracture Risk Reduction
A result seeking a control

Ferrari S, Adachi JD, Lippuner K, Zapalowski C, Miller PD, Reginster JY, Torring O, Kendler DL, Daizadeh NS, Wang A, O'Malley CD, Wagman RB, Libanati C, Lewiecki EM. Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. Osteoporos Int 2015;doi:10.1007/s00198-015-3179-x.

Ferrari et al evaluated if denosumab given beyond 3 years is associated with a further reduction in nonvertebral fracture rates. The analysis includes 4074 postmenopausal women with osteoporosis (n=2343 long-term; n=1731 cross-over) continued into the fourth year of treatment. Comparison of nonvertebral fracture rates during years 1-3 of denosumab with the fourth year and with the rate during years 4-7 was evaluated. For the combined group, the nonvertebral fracture rate per 100 participant-years was 2.15 for the first 3 years of denosumab (referent) and 1.36 in the fourth year (rate ratio [RR]=0.64; 95%CI=0.48- 0.85, p=0.003). Comparable findings were observed in the groups separately and when nonvertebral fracture rates during years 1-3 were compared to years 4-7 in the long-term group (RR=0.79; 95%CI=0.62-1.00, p=0.046). Fracture rate reductions in year 4 were most prominent in subjects with persisting low hip BMD. Without a control group, how do we know what determines fracture rates?

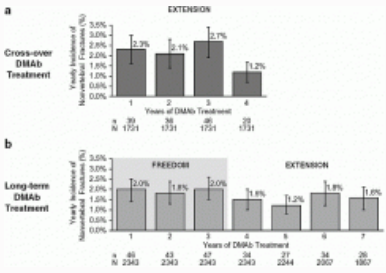


Figure 5. Yearly incidence of nonvertebral fractures in the post hoc analysis participants. (a) Yearly incidence of nonvertebral fractures through 4 years of denosumab treatment for the cross-over group. (b) Yearly incidence of nonvertebral fractures through 7 years for the long-term denosumab group in the long-term participants. Percentages for nonvertebral fractures are Kaplan-Meier estimates. DMAb=denosumab, n=number of subjects who have ≥1 nonvertebral fracture. Reproduced from Osteoporos Int 2015;doi:10.1007/s00198-015-3179-x with permission from Springer.

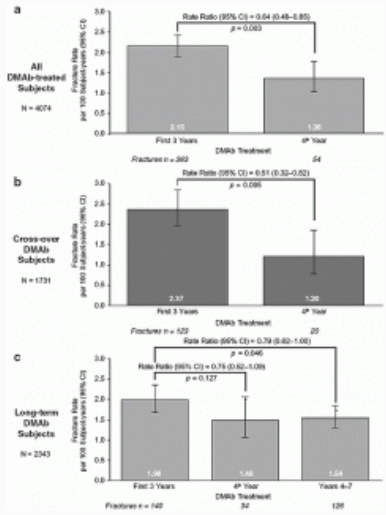
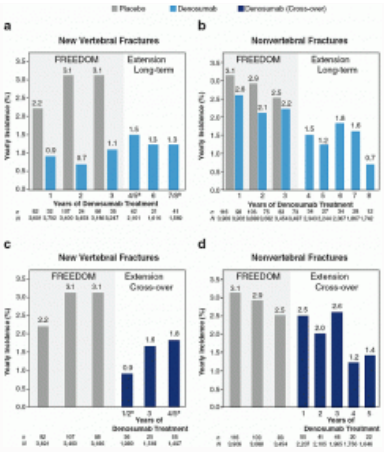


Figure 6. Nonvertebral fracture rate ratios. (a) All denosumab-treated participants. (b) Cross-over participants. (c) Long-term participants. N=number of subjects who completed FREEDOM (i.e., completed their 3-year visit and did not discontinue IP), missed ≤1 dose of IP in FREEDOM, and who enrolled in the extension. In addition, cross-over subjects completed 3 years of the extension and missed ≤1 dose of denosumab during the first 3 years of the extension. Fracture rates and rate ratios were obtained using generalized estimating equation Poisson models; fracture rates are per 100 participant-years. Rate ratios relative to the first 3 years of denosumab treatment were adjusted for age, total hip T-score, weight, and history of nonvertebral fracture. In addition, the treatment group variable was included in the model for the combined analysis only. Reproduced from Osteoporos Int 2015;doi:10.1007/s00198-015-3179-x with permission from Springer.

Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM, Brandi ML, Czerwinski E, Franek E, Lakatos P, Mautalen C, Minisola S, Reginster JY, Jensen S, Daizadeh NS, Wang A, Gavin M, Libanati C, Wagman RB, Bone HG. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: Results from the FREEDOM Extension study. Osteoporos Int 2015;doi:10.1007/s00198-015-3234-7.

Papapoulos et al reported the effects of denosumab for up to 8 years in 4550 women (2343 long-term; 2207 cross-over). In this analysis, women in the long-term and cross-over groups received denosumab for up to 8 and 5 years, respectively. Throughout the Extension, sustained reduction of bone turnover markers (BTMs) was observed. In the long-term group, mean BMD continued to increase for cumulative 8-year gains of 18.4 and 8.3% at the lumbar spine and total hip, respectively. In the cross-over group, mean BMD increased from the Extension baseline for 5-year cumulative gains of 13.1 and 6.2% at the lumbar spine and total hip, respectively. The yearly incidence of new vertebral and nonvertebral fractures remained low. The incidence of adverse and serious adverse events did not increase over time. Through Extension year 5, eight events of osteonecrosis of the jaw and two events of atypical femoral fracture were confirmed. Denosumab treatment for up to 8 years was associated with persistent reductions of BTMs, continued BMD gains, low fracture incidence, and a consistent safety profile.

Figure 7. Incidence of nonvertebral and new vertebral fractures during FREEDOM and the FREEDOM Extension. The yearly incidence of new vertebral and nonvertebral fractures in the long-term (a, b) and cross-over (c, d) groups are shown. For new vertebral fractures, percentages are crude incidence; lateral radiographs (lumbar and thoracic) were not obtained at Extension years 1 and 4 (long-term denosumab treatment years 4 and 7); n=number of women with ≥1 fracture; N=number of women with a spine X-ray evaluation during the time



period of interest. aAnnualized incidence (2-year incidence/2). For nonvertebral fractures, percentages are Kaplan-Meier estimates; n=number of women with ≥1 fracture; N=number of women who were still on study at the beginning of each period. Reproduced from Osteoporos Int 2015;doi:10.1007/s00198-015-3234-7 with permission from Springer.

Men Receiving Androgen Deprivation Therapy and Fracture Risk

Wu CT, Yang YH, Chen PC, Chen MF, Chen WC. Androgen deprivation increases the risk of fracture in prostate cancer patients: A population-based study in Chinese patients. Osteoporos Int 2015;26:2281-90.

Wu et al reported androgen deprivation therapy (ADT) using gonadotropin-releasing hormone (GnRH) agonists or orchiectomy in 17,359 subjects diagnosed with prostate cancer. The rates of fracture from 12 months after diagnosis until the last follow-up date were 8.7% for all patients, 7.1% for patients who did not receive ADT or orchiectomy, 9.8% for patients who received ADT, and 14.4% for patients who received orchiectomy with or without ADT (P<0.0001). A significant hazard ratio was observed in patients who received at least nine doses within 1 year after diagnosis and in those whose dose density exceeded two doses per year.

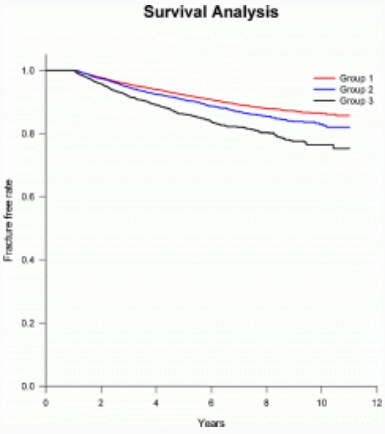


Figure 8. Kaplan-Meier plots of unadjusted estimates of fracture-free survival among the groups who did or did not receive ADT or orchiectomy. All subjects who survived at least 5 years after the diagnosis of prostate cancer were included in the analysis. Patients who incurred fractures during the first year after diagnosis were excluded. Those patients who did not receive GnRH agonists or orchiectomy (group 1) had the highest rate of fracture-free survival (5- and 10-year rates of 92.2 and 86.7 %, respectively). Those who received GnRH agonists alone (group 2) and orchiectomy with or without GnRH agonists (group 3) had lower rates of fracture-free survival (5- and 10-year rates of 90.0 and 83.4 % for group 2 and 85.6 and 76.7 % for group 3, respectively). The curves between any two of the three groups were significantly different (group 1 vs. group 2: P value=0.0009; group 1 vs. group 3: P value<0.0001; group 2 vs. group 3: P value<0.0001). Reproduced from Osteoporos Int 2015;26:2281-90 with permission from Springer.

Improved Initiation of Therapy After Hip Fracture

Klop C, Gibson-Smith D, Elders PJ, Welsing PM, Leufkens HG, Harvey NC, Bijlsma JW, van Staa TP, de Vries F. Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000-2010. Osteoporos Int 2015;26:1919-28.

To examine trends in anti-osteoporosis drug prescribing after hip fracture in the UK, **Klop et al** extracted data of 27,542 patients ≥50 years who had a first hip fracture between 2000-2010 to determine the probability being prescribed anti-osteoporosis drugs within 1 year of fracture. The probability of a prescription was 7% in 2000 and 46% in 2010. This was complemented by a similar increase in vitamin D/calcium. Cumulative incidence of receiving therapy was greater in women (8% in 2000, 51% in 2010) than men (4% in 2000, 34% in 2010). We are getting better but not that much better.

Bisphosphonate Antifracture Efficacy in Men

Chen L, Wang G, Zheng F, Zhao H, Li H. Efficacy of bisphosphonates against osteoporosis in adult men: A meta-analysis of randomized controlled trials. Osteoporos Int 2015;26:2355-63.

Chen et al reported that in 9 randomized controlled trials involving 2464 men, compared with placebo, the efficacy of bisphosphonates was the following: vertebral fracture, RR (95%CI) 0.36 (0.24, 0.56), P<0.01 and nonvertebral fracture, 0.52 (0.32, 0.84), P<0.01. Bisphosphonates reduced bone-specific alkaline phosphatase [MD (95%CI) -24.41 (-26.19, -22.62), P<0.01] and CTX [MD (95%CI) -34.51 (-41.03, -27.98), P<0.01].

Vitamin D Metabolites Are Weakly Associated With Bone Density

van Ballegooijen AJ, Robinson-Cohen C, Katz R, Criqui M, Budoff M, Li D, Siscovick D, Hoofnagle

A, Shea SJ, Burke G, de Boer IH, Kestenbaum B. Vitamin D metabolites and bone mineral density: The multi-ethnic study of atherosclerosis. Bone 2015;78:186-93.

van Ballegooijen et al reported that in 1773 adults, vitamin D metabolites were measured in White (n=714), Black (n=353), Chinese (n=249), and Hispanic (n=457) participants. Serum 25(OH)D and 24,25(OH2)D3 concentrations were highest among Whites and lowest among Blacks. BMD was greatest among Black participants. Higher serum 25(OH)D was only associated with higher BMD among Whites and Chinese participants. Comparing the lowest category of 25(OH)D (<20 ng/ml) to the highest (≥30 ng/ml), the adjusted mean difference in BMD was -8.1 g/cm^3 (95%CI -14.8, -1.4) for Whites; -10.2 g/cm^3 (-20.4, 0.0) for Chinese vs. 8.8 g/cm^3 (-2.8, 20.5) for Black and -1.1 g/cm^3 (-8.3, 6.2) for Hispanic. Serum PTH was not associated with BMD.

Combining Antiresorptives and Anabolics

Iwamoto J, Seki A. Effect of combined Tteriparatide and monthly risedronate therapy on cancellous bone mass in orchidectomized rats: A bone histomorphometry study. Calcif Tissue Int 2015;97:23-31.

Iwamoto et al reported that fifty 14-week-old male Sprague Dawley rats were randomized into the following: sham-operation + vehicle; ORX + vehicle; ORX + risedronate (90 µg/kg subcutaneous, every 4 weeks); ORX + teriparatide (30 µg/kg subcutaneous, three times per week); and ORX + risedronate + teriparatide. After 12 weeks, ORX decreased BV/TV and trabecular number (Tb.N), and increased trabecular separation (Tb.Sp). Risedronate increased BV/TV and Tb.N above the sham control values, while teriparatide prevented the ORX-induced decrease in BV/TV and increased trabecular width (Tb.Wi) above sham control levels. Risedronate decreased Tb.Sp below control values, while teriparatide prevented the ORX-induced increase in Tb.Sp. The combination of teriparatide and risedronate increased BV/TV and Tb.N and decreased Tb.Sp compared with teriparatide alone.

Tissue Mineral Density and PTH Administration

Misof BM, Roschger P, Dempster DW, Zhou H, Bilezikian JP, Klaushofer K, Rubin MR. PTH(1-84) administration in hypoparathyroidism transiently reduces bone matrix mineralization. J Bone Miner Res 2015;doi:10.1002/jbmr.2588.

PTH(1-84) increases low remodeling dynamics. **Misof et al** studied the effect of 1 year or 2 years PTH(1-84) treatment on cancellous and cortical bone mineralization density distribution (Cn. and Ct.BMDD) in paired transiliac bone biopsy samples in 30 adult hypoparathyroid patients (14 treated for 1 year/16 treated for 2 years). At baseline, Cn.BMDD was shifted to higher mineralization densities in both treatment groups (average degree of mineralization Cn.CaMean +3.9% and +2.7%, $p<0.001$). After 1 year PTH(1-84), Cn.CaMean was lower than that at baseline (-6.3%, $p<0.001$), while in the 2 years PTH(1-84) group Cn.CaMean did not differ from baseline. Significant changes of Ct.BMDD were observed in the 1 year treatment group only. PTH(1-84) treatment caused differential effects dependent on treatment. The greater increase in bone formation during the first year was associated with a decrease in bone matrix mineralization.

Bone Water
A guide to porosity

Seifert AC, Li C, Wehrli SL, Wehrli FW. A surrogate measure of cortical bone matrix density by long T2-suppressed MRI. J Bone Miner Res 2015;doi:10.1002/jbmr.2580.

Magnetic resonance has the potential to image and quantify free water within the Haversian pore system (transverse relaxation time, T2 >1 ms), and water hydrogen-bonded to matrix collagen (T2 approximately 300-400 µs). The objective of this study by **Seifert et al** was to evaluate a surrogate measurement for matrix density, single adiabatic inversion recovery (SIR) zero echo-time (ZTE) MRI, in human bone. Specimens of tibial cortical bone from 15 donors (27-97 years, 8 females and 7 males) were examined at 9.4T field strength using two methods: (1) ^{1}H ZTE MRI, to capture total ^{1}H signal, and (2) ^{1}H SIR-ZTE MRI, to selectively image matrix-associated 1H signal. Total water, bone matrix, and BMDs were quantified, and porosity was measured by µCT. ZTE apparent total water ^{1}H concentration was 32.7±3.2 M (range: 28.5-40.3 M), and correlated with porosity (R^2=0.80) and negatively with matrix and mineral densities (R^2=0.90 and 0.82, respectively). SIR-ZTE apparent bound water ^{1}H concentration was 32.9±3.9 M (range: 24.4-39.8 M), and its correlations were opposite to those of apparent total water: negative with porosity (R^2=0.73) and positive with matrix density (R^2=0.74) and mineral density (R^2=0.72). Porosity was correlated with gravimetric matrix density (R^2=0.91, negative) and total water density (R^2=0.92, positive). The strong correlations of SIR-ZTE-derived apparent bound water ^{1}H concentration with ground-truth measurements suggest that this quantitative solid-state MRI method provides a surrogate of matrix density.

Allen MR, Territo PR, Lin C, Persohn S, Jiang L, Riley AA, McCarthy BP, Newman CL, Burr DB, Hutchins GD. In vivo UTE-MRI reveals positive effects of raloxifene on skeletal-bound water in skeletally mature beagle dogs. J Bone Miner Res 2015;30:1441-4.

Allen et al reported that raloxifene positively affects mechanical properties of the bone matrix in part through modification of skeletal-bound water. To determine if raloxifene-induced alterations in skeletal hydration could be measured in vivo using ultrashort echotime MRI (UTE-MRI), 12 female beagle dogs were treated for 6 months with saline (1 mL/kg/d) or raloxifene (0.5 mg/kg/d). After 6 months, raloxifene-treated animals had higher bound water (+14%; $p=0.05$) and lower free water (-20%) compared with vehicle-treated animals.

Unal M, Akkus O. Raman spectral classification of mineral- and collagen-bound water's associations to elastic and post-yield mechanical properties of cortical bone. Bone 2015;81:315-26.

Unal et al reported bone hydration in 30 cortical samples was studied by short-wave infrared Raman spectroscopy. A dehydration method was developed to replace unbound (heat drying) and bound (ethanol treatment) water in bone. Four peaks were investigated: I3220/I2949, I3325/I2949 and I3453/I2949 reflect organic-matrix related water (collagen-related water), while I3584/I2949 reflects status of mineral-related water compartments. Collagen-water related biomarkers correlated with toughness (R^2=0.81 and R^2=0.79; p<0.001) and post-yield toughness (R^2=0.65 and R^2=0.73; p<0.001). Mineral-water related biomarker correlated negatively with elastic modulus (R^2=0.78; p<0.001) and positively with strength (R^2=0.46; p<0.001).

Toughness of Bone

Abraham AC, Agarwalla A, Yadavalli A, McAndrew C, Liu JY, Tang SY. Multiscale predictors of femoral neck in situ strength in aging women: Contributions of BMD, cortical porosity, reference point indentation, and nonenzymatic glycation. J Bone Miner Res 2015;doi:10.1002/jbmr.2568.

Abraham et al examined the correlation between femoral neck fracture strength in female cadaveric bone and areal BMD (aBMD), with cortical porosity (Ct.Po), reference point indentation (RPI), and advanced glycation endproducts (AGEs). All measurements predicted femoral neck fracture strength, with aBMD being the strongest correlate (aBMD: r=0.755, p<0.001; Ct.Po: r=-0.500, p<0.001; reference point indentation (RPI): r=-0.478, p<0.001; AGEs: r=-0.336, p=0.016). RPI-derived measurements were not correlated with tissue mineral density or cortical porosity. Inclusion of aBMD and any other factor improve the prediction of bone strength. Combining aBMD with tibial Ct.Po (r=0.835; p<0.001), tibial difference in indentation depth between the first and 20th cycle (r=0.883; p<0.001), or tibial AGEs (r=0.822; p<0.001) improves the prediction of femoral neck strength.

Granke M, Makowski AJ, Uppuganti S, Does MD, Nyman JS. Identifying novel clinical surrogates to assess human bone fracture toughness. J Bone Miner Res 2015;30:1290-300.

Granke et al investigated the role of ^{1}H nuclear magnetic resonance spectroscopy (NMR) and RPI to explain age-related variance in fracture toughness. Harvested from cadaveric femurs (62 human donors), single-edge notched beam specimens of cortical bone underwent fracture toughness testing (R-curve method). NMR-derived bound water showed the strongest correlation with fracture toughness (r=0.63 for crack initiation, r=0.35 for crack growth, and r=0.45 for overall fracture toughness; p<0.01). The age-related decrease in toughness properties were best explained by a combination of pore water and RPI-derived tissue stiffness (adj R^2=53.3%, 23.9%, and 35.2% for crack initiation, crack growth, and overall toughness, respectively; p<0.001). Improvements in fracture risk assessment could be achieved by accounting for water distribution (quantitative ultrashort echo time MRI) and by a local measure of tissue resistance to indentation, RPI.

Risedronate in Breast Cancer

Greenspan SL, Vujevich KT, Brufsky A, Lembersky BC, van Londen GJ, Jankowitz RC, Puhalla SL, Rastogi P, Perera S. Prevention of bone loss with risedronate in breast cancer survivors: A randomized, controlled clinical trial. Osteoporos Int 2015;26:1857-64.

Aromatase inhibitors (AIs), adjuvant endocrine therapy for postmenopausal women with hormone-receptor-positive breast cancer, are associated with bone loss and fractures. **Greenspan et al** conducted a 2-year double-blind, placebo-controlled, randomized trial in 109 postmenopausal women with low bone mass on an AI (anastrozole, letrozole, or exemestane) randomized to once weekly risedronate 35 mg or placebo, all received calcium plus vitamin D. 87% completed 24 months. BMD increased more in the treatment group compared to placebo with an adjusted difference at 24 months of 3.9±0.7 % at the spine and 3.2±0.5 % at the hip (both p<0.05). The adjusted difference between the active treatment and placebo groups were 0.09±0.04 nmol/LBCE for CTX and 23.3±4.8 µg/mL for P1NP (both p<0.05). Women with greater 12-month decreases in CTX and P1NP had a greater 24-month increase in spinal BMD (p<0.05).

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Progress in Osteoporosis

CRITICAL REVIEW JOURNAL

OVERVIEW, VOL 15, ISSUE 3

Ego Seeman
Editor

By Ego Seeman Tue, 11/10/2015 - 06:00

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

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

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Life Expectancy After Fracture

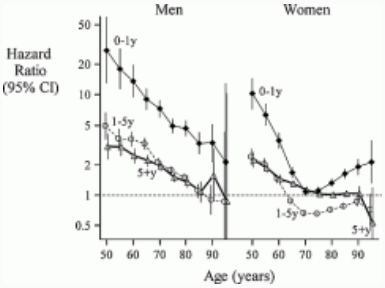
The need for long-term antifracture efficacy

Abrahamsen B, Osmond C, Cooper C. Life expectancy in patients treated for osteoporosis: Observational cohort study using national Danish prescription data. J Bone Miner Res 2015;30:1553-9.

Abrahamsen et al tracked scripts for osteoporosis drugs, comorbidity, and deaths in 58,637 patients and 225,084 controls with 10-17 y follow-up. In men <80 y and women <60 y, the risk of dying declined from being increased in the first year to a stable but elevated risk later. In women >65 y, the mortality risk was elevated in the first year of treatment and then was lower than background.

The residual life expectancy of a 50-y old man beginning treatment was 18.2 y and a 75-y old man was 7.5 y. Estimates in women were 26.4 y and 13.5 y, respectively. Thus, the average life expectancy is over 15 y in women younger than 75 y and in men younger than 60 y, highlighting the need for evidence of long-term efficacy.

Figure 1. Death hazard (shown as log HR) as a function of sex and age at beginning treatment, shown separately for the first year of treatment (0–1 y), years 1 to 5 (1–5 y), and years 5+. Conditional Cox proportional hazards model based on 58,637 patients beginning treatment for osteoporosis and 225,084 age- and sex-matched control subjects. Treatment was started in 1996-2003 and deaths tracked to the end of 2013. Reproduced from J Bone Miner Res 2015;30: 1553-9 with permission of the American Society of Bone and Mineral Research.



Elevated Incidence of Fractures in Women With Invasive Breast Cancer

Edwards BJ, Gradishar WJ, Smith ME, Pacheco JA, Holbrook J, McKoy JM, Nardone B, Tica S, Godinez-Puig V, Rademaker AW, Helenowski IB, Bunta AD, Stern PH, Rosen ST, West DP, Guise TA. Elevated incidence of fractures in women with invasive breast cancer. Osteoporos Int 2015; doi:10.1007/s00198-015-3246-3.

Edwards et al assessed 422 women with invasive breast cancer; 79 (28%) sustained fractures at multiple skeletal sites in 27 cases (116 fractures). The incidence of fractures was 40/1000 person-years. Women who sustained fractures had a family history of osteoporosis (36.9%, p=0.03) or history of a prior fracture (6/79, p=0.004). Fractures occurred 4.0 y (range 0-12 y) after cancer diagnosis. Fracture cases had femoral neck T-score of -1.2 SD. Fractures most commonly occurred in lower extremities, vertebral, and wrist. Hip fractures accounted for 11% of fractures, occurring at a median age of 61 y.

Lee SJ, Kim KM, Brown JK, Brett A, Roh YH, Kang DR, Park BW, Rhee Y. Negative impact of aromatase inhibitors on proximal femoral bone mass and geometry in postmenopausal women with breast cancer. Calcif Tissue Int 2015;97:551-9.

Lee et al reported 249 early breast cancer patients who underwent QCT in their fifties (mean age 54.3 y), cortical areal BMDs were lower in the aromatase inhibitor (AI) group than in the non-AI group (p<0.05). Cortical thickness of the femoral neck, trochanter, and total hip was lower in the AI group, especially in the superoposterior quadrant. Bone strength of the femoral neck (section modulus and cross-sectional moment of inertia) were lower in the AI group than in the non-AI group (p<0.05).

Exercise in Childhood and Fewer Fractures

Fritz J, Coster ME, Nilsson JA, Rosengren BE, Dencker M, Karlsson MK. The associations of physical activity with fracture risk-a 7-year prospective controlled intervention study in 3534 children. Osteoporos Int 2015; doi:10.1007/s00198-015-3311-y.

Fritz et al documented fractures in 3534 children aged 6-8 y at study start for up to 7 y; 1339 subjects did 40 min of moderate activity daily (intervention) and 2195 had 60 min activity weekly (controls). Incidence rate ratios (IRR) of fractures decreased with each year of the activity (r=-0.79; p=0.04). During the seventh year, IRR was halved [IRR 0.52 (0.27, 1.01)]. The intervention group had a greater gain in total spine aBMD with a mean group difference of 0.03 (0.00, 0.05) g/cm^2 and peak flexion torque 180° with a mean group difference of 5.0 (1.5, 8.6) Nm.

Is Any Association Between Testosterone and BMD Genetically Determined?

Shin J, Sung J, Lee K, Song YM. Genetic influence on the association between bone mineral density and testosterone in Korean men. Osteoporos Int 2015; doi:10.1007/s00198-015-3298-4.

Shin et al reported that in 1070 Korean men including, 144 pairs of monozygotic twins and their family members, total testosterone and calculated free testosterone (cFT) were positively associated with BMD. Monozygotic twins showed no association between pairwise difference of testosterone and pairwise difference of BMD. Bivariate variance component analysis showed that total testosterone and cFT had a positive additive genetic correlation with BMD at rib, spine, and arm, whereas SHBG had no significant genetic correlation with BMD. Inverse environmental correlations were seen between total testosterone and BMDs at the lumbar spine and arm.

Marrow Fat

Cohen A, Shen W, Dempster DW, Zhou H, Recker RR, Lappe JM, Kepley A, Kamanda-Kosseh M, Bucovsky M, Stein EM, Nickolas TL, Shane E. Marrow adiposity assessed on transiliac crest biopsy samples correlates with noninvasive measurement of marrow adiposity by proton magnetic resonance spectroscopy (^{1}H-MRS) at the spine but not the femur. Osteoporos Int 2015;26:2471-8.

Cohen et al evaluated premenopausal women, 9 with osteoporosis and 7 normal controls for marrow fat of the iliac crest by bone biopsy and at the lumbar spine (L3) and proximal femur by ^{1}H-MRS. At L3, fat fraction by ^{1}H-MRS correlated with marrow fat variables on iliac crest biopsies (r=0.5-0.8). There were no correlations between fat fraction at the femur and marrow fat on biopsies. Marrow fat was greater at the femur than at L3 and the iliac crest and correlated inversely with total hip and femoral neck BMD by DXA.

Diabetes and Bone Qualities

Farlay D, Armas L, Gineyts E, Akhter M, Recker R, Boivin G. Non-enzymatic glycation and degree of mineralization are higher in bone from fractured patients with type 1 diabetes mellitus. J Bone Miner Res 2015; doi:10.1002/jbmr.2607.

Farlay et al analyzed iliac crest bone biopsies from 5 patients with type 1 diabetes, diabetics without fractures and 5 healthy subjects, all age- and sex-matched. Trabecular bone from fracture cases had higher pentosidine than control (p=0.04) and was more mineralized than diabetics without fractures (p=0.04) and control (p=0.04). Trabecular and cortical bone were no different in pentosidine between diabetics without fractures and control. Positive correlations were found between HbA1c and Pentosidine (r'=0.79, p<0.003), and between HbA1c and DMB (r'=0.64, p<0.02).

Matrix Mineral Density of Trabecular Plates and Rods

Wang J, Kazakia GJ, Zhou B, Shi XT, Guo XE. Distinct tissue mineral density in plate- and rod-like trabeculae of human trabecular bone. J Bone Miner Res 2015;30:1641-50.

Wang et al reported an individual trabecula mineralization (ITM) analysis to determine tissue mineral density (TMD) in plate- and rod-like trabeculae. Plates had higher TMD than rods. The distribution of TMD in plates was lowest in longitudinal plates and the highest TMD in transverse plates. There was a uniform distribution of TMD among rods with respect to orientation. Plates had higher mean and peak TMD, whereas rods had a wider TMD distribution and a larger portion of low mineralized trabeculae. Heterogeneous TMD in trabecular plates influence elastic properties.

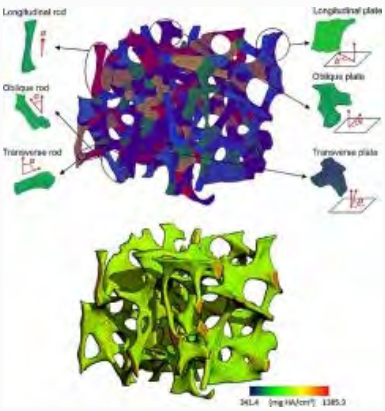


Figure 2. Illustration of ITM analysis. (Top) Decomposition of trabecular microstructure into individual trabecular plates and rods along various orientations. (Bottom) Grayscale image of trabecular bone to be mapped to the segmented trabecular microstructure to quantify the TMD of individualplates and rods. Reproduced from J Bone Miner Res 2015;30:1641-50 with permission of the American Society of Bone and Mineral Research.

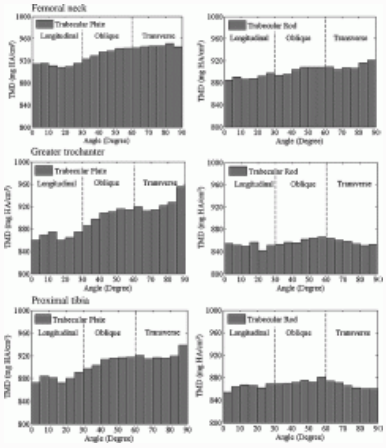


Figure 3. Distributions of individual trabecula TMD along trabecular orientation from the longitudinal to transverse direction for trabecular plates (left column) and rods (right column) and for femoral neck (top), greater trochanter (middle), and proximal tibia (bottom). Reproduced from J Bone Miner Res 2015;30:1641-50 with permission of the American Society of Bone and Mineral Research.

Amino Acid Intake and BMD

Jennings A, MacGregor A, Spector T, Cassidy A. Amino acid intakes are associated with bone mineral density and prevalence of low bone mass in women: Evidence from discordant monozygotic twins. J Bone Miner Res 2015; doi:10.1002/jbmr.2703.

Jennings et al reported analyses of female monozygotic twin-pairs discordant for amino acid intake (n=135). Twins with higher intakes of alanine and glycine had higher BMD at the spine than their co-twins, with within-pair differences in spine BMD of 0.012 g/cm^2 (SE 0.01; p=0.039) and 0.014 g/cm^2 (SE 0.01; p=0.026), respectively. Furthermore, in cross-sectional multivariable analyses of 3160 females aged 18-79 y, a higher intake of total protein was associated with higher BMD at the spine (quartile Q4 to quartile Q1: 0.017 g/cm^2, SE 0.01, p=0.035) and forearm (Q4 to Q1: 0.010 g/cm^2, SE 0.003, p=0.002). Intake of alanine, arginine, glutamic acid, leucine, lysine, and proline were associated with higher BMD at the spine and forearm with the strongest association observed for leucine (Q4 to Q1: 0.024 g/cm^2, SE 0.01, p=0.007). When intakes were stratified by source, vegetable or animal, prevalence of osteoporosis or osteopenia was 13% to 19% lower comparing extreme quartiles of vegetable intake for five amino acids (not glutamic acid or proline).

Adynamic Bone Disease in Renal Impaired Mice

Ng AH, Omelon S, Variola F, Allo B, Willett TL, Alman BA, Grynpas MD. Adynamic bone decreases bone toughness during ageing by affecting mineral and matrix. J Bone Miner Res 2015; doi:10.1002/jbmr.2702.

Ng et al studied young and old (4- and 16-months) Col2.3Deltatk mice treated with ganciclovir and pamidronate to create the adynamic bone condition. Ageing controls had a decline in bone formation and resorption with a corresponding deterioration in trabecular bone structure. Bone turnover was severely blunted at all ages in adynamic animals which preserved trabecular bone loss. However, the preservation of trabecular bone mass and structure in old adynamic mice did not rescue deterioration of bone mechanical properties. There was also a decrease in cortical bone toughness in old adynamic mice that was accompanied by a more mature collagen matrix and longer bone crystals.

Calcium Intake and Lower Fracture Risk and Mortality

Khan B, Nowson CA, Daly RM, English DR, Hodge AM, Giles GG, Ebeling PR. Higher dietary calcium intakes are associated with reduced risks of fractures, cardiovascular events, and mortality: A prospective cohort study of older men and women. J Bone Miner Res 2015;30:1758-66.

Khan et al followed 41,514 men and women aged 40-69 y for 12 (1.5) y. Primary outcome measures were time to death from all causes (n=2855), CVD-related deaths (n=557), cerebrovascular disease-related deaths (n=139), incident nonfatal CVD (n=1827), incident stroke events (n=537), and incident fractures (n=788); 12,097 participants eligible for fracture analysis and 34,468 for nonfatal CVD and mortality analyses. Highest and lowest quartiles of energy-adjusted dietary calcium intakes represented unadjusted means (SD) of 1348 (316) mg/d and 473 (91) mg/d, respectively. There were 788 (10.3%) incident fractures, 1827 (9.0%) incident CVD, and 2855 people (8.6%) died. Comparing the highest with the lowest quartile of calcium intake, HR were: all-cause mortality 0.86 (95%CI 0.76-0.98, p trend=0.01); nonfatal CVD and stroke, the OR was 0.84 (95%CI 0.70-0.99, p trend=0.04) and 0.69 (95%CI 0.51-0.93, p trend=0.02), respectively; and the OR for fracture was 0.70 (95%CI 0.54-0.92, p trend=0.004).

Porosity in Men With Fractures

Sundh D, Mellstrom D, Nilsson M, Karlsson M, Ohlsson C, Lorentzon M. Increased cortical porosity in older men with fracture. J Bone Miner Res 2015;30:1692-700.

Sundh et al reported that in 456 men, mean age 80.2 y, 87 (19.1%) had fractures at or after age 50 y, 52 (11.4%) had a fracture before the baseline exam and 35 (7.7%) had had an X-ray verified fracture between baseline and 5-y follow-up. Men in the all-fracture group and in the X-ray verified group had higher porosity, by 15.8% vs. 11.4% and 21.6%, respectively, than men in the nonfracture group. Cortical porosity was associated with fracture (OR per SD increase 1.49) and with any X-ray verified fracture alone (OR 1.73). Including aBMD (spine or hip, respectively). Porosity was associated with any fracture (OR 1.54) and with X-ray verified fracture alone (OR 1.49) even after adjustment for aBMD.

Sex Hormone Changes During Ageing in Men

Hsu B, Cumming RG, Seibel MJ, Naganathan V, Blyth FM, Bleicher K, Dave A, Le Couteur DG, Waite LM, Handelsman DJ. Reproductive hormones and longitudinal change in bone mineral density and incident fracture risk in older men: The Concord Health and Aging in Men Project. J Bone Miner Res 2015;30:1701-8.

Hsu et al studied 1705 men aged >70 y at baseline (2 and 5 y). Univariate analyses revealed inverse associations for serum SHBG, FSH, and LH and positive association for E1 but not DHT or E2 with BMD loss at the hip. Serum SHBG (β=-0.071), FSH (β=-0.085), LH (β=-0.070), and E1 (β=0.107) remained associated with BMD loss in multivariate models. Serum T, DHT, E2, and E1 levels were not associated with incident fractures in univariate or multivariate-adjusted analyses. In older men, lower serum SHBG, FSH, and LH and higher E1 levels protected against loss of BMD without increasing fracture rate. These variables may be biomarkers of bone health.

Serum Hormonal Binding Globulin and Fracture Risk in Men

Vandenput L, Mellstrom D, Kindmark A, Johansson H, Lorentzon M, Leung J, Redlund-Johnell I, Rosengren BE, Karlsson MK, Wang YX, Kwok T, Ohlsson C. High serum SHBG predicts incident

vertebral fractures in elderly men. J Bone Miner Res 2015; doi:10.1002/jbmr.2718.

Vandenput et al reported incident clinical vertebral fractures (n=242 cases) in 4324 men during follow-up of 9.1 y. In a subsample (n=2256), spine X-rays were obtained at baseline and 4.3 y to identify incident radiographic vertebral fractures (n=157 cases). Neither serum estradiol nor testosterone predicted incident clinical vertebral fractures. High serum SHBG, however, was associated with increased clinical vertebral fracture risk (1.24, 1.12-1.37). SHBG was also associated with increased incident radiographic vertebral fracture risk (combined data set; OR per SD increase, 95% CI: 1.23, 1.05-1.44).

Osteocalcin and Glucose

Jung KY, Kim KM, Ku EJ, Kim YJ, Lee DH, Choi SH, Jang HC, Shin CS, Park KS, Lim S. Age- and sex-specific association of circulating osteocalcin with dynamic measures of glucose homeostasis. Osteoporos Int 2015; doi:10.1007/s00198-015-3315-7.

Jung et al conducted a cross-sectional analysis from 719 participants aged 20-85 y: men <50 y (n=131), men ≥50 y (n=191), women <50 y (n=108), and women ≥50 y (n=279). Insulin resistance (HOMA-IR) and β cell function (HOMA-β) from a 75-g oral glucose tolerance test was assessed. The serum osteocalcin was higher in women aged ≥50 y than women <50 y (20.4±7.8 vs. 17.9±6.8 ng/ml, p<0.001), but there was no difference between men by age. The participants diagnosed with diabetes had lower serum osteocalcin levels than normal or prediabetic participants. Multivariable regression analyses indicated that serum osteocalcin had a negative and independent association with HbA1c levels in men and women aged <50 y, but not in women ≥50 y.

PTH Treatment and Gap Junctions

Pacheco-Costa R, Davis HM, Sorenson C, Hon MC, Hassan I, Reginato RD, Allen MR, Bellido T, Plotkin LI. Defective cancellous bone structure and abnormal response to PTH in cortical bone of mice lacking Cx43 cytoplasmic C-terminus domain. Bone 2015;81:632-43.

Connexin 43 (Cx43) forms gap junction channels and hemichannels that allow the communication among osteocytes, osteoblasts, and osteoclasts. Cx43 carboxy-terminal (CT) domain regulates channel opening and intracellular signaling by acting as a scaffold for structural and signaling proteins. **Pacheco-Costa et al** reported that in mice lacking the CT domain (Cx43DeltaCT/fl) had lower cancellous bone volume but higher cortical thickness than controls. PTH failed to increase endocortical bone formation or energy to failure, a mechanical property that indicates resistance to fracture in cortical bone in Cx43DeltaCT mice with or without osteocytic full length Cx43. Bone mass and bone formation markers were increased in all mouse models, regardless of whether full length or Cx43DeltaCT were or not expressed. Cx43 CT domain is involved in bone acquisition; and that Cx43 expression in osteocytes is dispensable for some but not all PTH anabolic actions.

Sclerostin Antibody Therapy in Glucocorticoid-induced Osteoporosis

Yao W, Dai W, Jiang L, Lay EY, Zhong Z, Ritchie RO, Li X, Ke H, Lane NE. Sclerostin-antibody treatment of glucocorticoid-induced osteoporosis maintained bone mass and strength. Osteoporos Int 2015; doi:10.1007/s00198-015-3308-6.

Yao et al evaluated the dose-dependent effects of glucocorticoids (GCs) (0, 0.8, 2.8, and 4 mg/kg/d) and Scl-Ab on autophagic osteoblasts, bone mass, and bone strength. GC treatment at 2.8 and 4 mg/kg/d of methylprednisolone lowered trabecular bone volume (Tb-BV/TV) at the lumbar vertebrae and distal femurs, cortical bone mass at the midshaft femur (FS), and cortical bone strength compared to placebo (PL). In mice treated with GC and Scl-Ab, Tb-BV/TV increased by 60-125 %, apparent bone strength of the lumbar vertebrae by 30-70 %, FS-BV by 10-18 %, and FS-apparent strength by 13-15%, as compared to GC vehicle-treated mice. GC treatment at 4 mg/kg/d reduced the number of autophagic osteoblasts by 70 % on the vertebral trabecular bone surface compared to the PL group (PL, GC 0 mg), and GC + Scl-Ab treatment.

Achiou Z, Toumi H, Touvier J, Boudenot A, Uzbekov R, Ominsky MS, Pallu S, Lespessailles E. Sclerostin antibody and interval treadmill training effects in a rodent model of glucocorticoid-induced osteopenia. Bone 2015;81:691-701.

Achiou et al studied male Wistar rats allocated to a control group (C) or one of 4 groups injected subcutaneously with methylprednisolone (5 mg/kg/d, 5 d/week) also given subcutaneously 2 d/week with vehicle (M) or Scl-Ab-VI (M+S: 25 mg/kg/d) and submitted or not to treadmill interval training exercise (1 h/d, 5 d/week) for 9 weeks (M+E, M+E+S). Methylprednisolone increased % fat mass and % apoptotic osteocytes, reduced whole body and femoral BMC, reduced femoral BMD and osteocyte lacunae occupancy. This effect was associated with lower trabecular bone volume (BV/TV) at the distal femur. Exercise increased BV/TV, osteocyte lacunae occupancy, while reducing fat mass, the bone resorption marker NTx, and osteocyte apoptosis. Exercise did not affect BMC or cortical microarchitecture. Scl-Ab increased osteocalcin and prevented the deleterious effects of M on bone mass, further increasing BMC, BMD and BV/TV to levels above the C group. Scl-Ab increased femoral cortical bone parameters at distal part and midshaft. Scl-Ab prevented the decrease in osteocyte lacunae occupancy and the increase in osteocyte apoptosis induced by M. The addition of exercise to Scl-Ab treatment did not result in additional improvements in bone mass or bone strength parameters.

Long-term Antiresorptive Therapy

Adler RA, Fuleihan GE, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greenspan SL, McKinney R, Jr., Pignolo RJ, Sellmeyer DE. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res 2015; doi:10.1002/jbmr.2708.

Adler et al reported that in the Fracture Intervention Trial Long-term Extension (FLEX), postmenopausal women receiving alendronate for 10 y had fewer clinical vertebral fractures than those switched to placebo after 5 y. In the HORIZON extension, women who received 6 annual infusions of zoledronic acid had fewer morphometric vertebral fractures compared with those switched to placebo after 3 y. Low hip T-score, between -2 and -2.5 in FLEX and below -2.5 in HORIZON extension, predicted a beneficial response to continued therapy. Hence, after 5 y of oral bisphosphonate (BP) or 3 y of intravenous BP, reassessment of risk should be considered. In women at high risk, for example, older women, those with a low hip T-score or high fracture risk score, those with previous major osteoporotic fracture, or who fracture on therapy, continuation of treatment for up to 10 y (oral) or 6 y (intravenous), with periodic evaluation, should be considered. For women not at high fracture risk after 3-5 y of BP treatment, a drug holiday of 2-3 y can be considered.

Bisphosphonate Treatment of Osteonecrosis of the Femoral Head

Yuan HF, Guo CA, Yan ZQ. The use of bisphosphonate in the treatment of osteonecrosis of the femoral head: A meta-analysis of randomized control trials. Osteoporos Int 2015; doi:10.1007/s00198-015-3317-5.

Yuan et al reported a meta-analysis of studies of treatment of osteonecrosis of the femoral head (ONFH). They examined only randomized control trials, progression to collapse, total hip arthroplasty (THA) incidence, and improvement of Harris hip score (HHS). Five eligible trials were identified involving 329 subjects with 920.9 patient-years of follow-up. The clinical outcomes were not improved by BP therapy (progression to collapse: risk ratio=0.71 (0.41, 1.24), p=0.23; THA incidence: risk ratio=0.61 (0.33, 1.15), p=0.13; HHS improvement: mean difference = 3.26 (-5.12, 11.64), p=0.45). The current analysis does not support the use of BPs for ONFH.

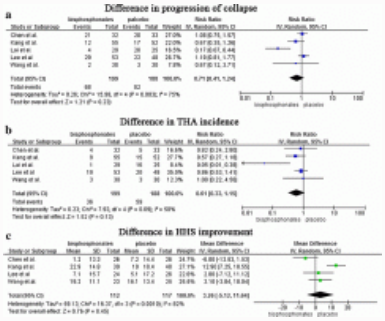


Figure 4. Clinical outcomes of progression to collapse (a), THA incidence (b), and HHS improvement (c) with bisphosphonate therapy when compared with placebo. Reproduced from Osteoporos Int 2015;doi:10.1007/s00198-015-3317-5 with permission from Springer.

Vitamin D and BMD

Jemielita TO, Leonard MB, Baker J, Sayed S, Zemel BS, Shults J, Herskovitz R, Denburg MR. Association of 25-hydroxyvitamin D with areal and volumetric measures of bone mineral density and parathyroid hormone: Impact of vitamin D-binding protein and its assays. Osteoporos Int 2015; doi:10.1007/s00198-015-3296-6.

Jemielita et al compared measures of vitamin D-binding protein (DBP) using a monoclonal vs. polyclonal ELISA in 304 adults (158 blacks, 146 whites), ages 21-80 y. Measures of DBP obtained using a monoclonal vs. polyclonal ELISA were not correlated (r_S=0.02, p=0.76). Free and bioavailable 25(OH)D based on the polyclonal assay were lower in black than white participants (p<0.0001); this race difference was not evident using the monoclonal assay. Adjusted for age, sex, calcium intake, and race, all forms of 25(OH)D were negatively associated with PTH, but the absolute coefficient was greatest for total 25(OH)D (-0.34, p<0.001) versus free/bioavailable 25(OH)D (-0.18/-0.24 depending on DBP assay, p≤0.003). None of the measures of 25(OH)D were associated with BMD across DXA and pQCT sites.

Vitamin D and Muscle Strength

Cangussu LM, Nahas-Neto J, Orsatti CL, Bueloni-Dias FN, Nahas EA. Effect of vitamin D supplementation alone on muscle function in postmenopausal women: A randomized, double-blind, placebo-controlled clinical trial. Osteoporos Int 2015;26:2413-21.

Cangussu et al reported a double-blind, placebo-controlled clinical trial involving 160 Brazilian postmenopausal women randomized to vitamin D3 1000 IU/d orally (n=80) or placebo group (n=80). After 9 months, 25(OH)D from 15.0±7.5 to 27.5±10.4 ng/ml (+45.4 %) in the VITD group and decreased from 16.9±6.7 to 13.8±6.0 ng/ml (-18.5 %) in the placebo group (p<0.001). In the vitamn D group, there was an increase in muscle strength (+25.3 %) of the lower limbs (p=0.036). In women in the placebo group, there was loss (-6.8 %) in the lean mass (p=0.030).

Osteonecrosis of the Jaw

Zhang X, Hamadeh IS, Song S, Lesko LJ, Gong Y. Osteonecrosis of the jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS). J Bone Miner Res 2015; doi:10.1002/jbmr.2693

Zhang et al identified 17,119 cases of ONJ. ORs by therapy were: pamidronate (OR=498.9), zoledronate (OR=171.7), alendronate (OR=63.6). Denosumab had lower ORs than all BPs except for etidronate. In patients with cancer, the ORs for zoledronate and denosumab were 125.2 and 4.9, respectively. In patients with osteoporosis, the OR were 1.1 (1.0-1.18) for zoledronate and 0.63 (0.56-0.70) for denosumab. The intravenous BPs were associated with the highest risk for ONJ, RANKL inhibitor was associated with risk comparable to BPs used for osteoporosis such as etidronate, while the anti-angiogenic agents and m-TOR inhibitors were associated with the lowest risk for ONJ. The high risk for ONJ in zoledronate and denosumab was mainly observed in those treated for prevention of skeletal

events. There was limited evidence risk in those treated for osteoporosis.

de Molon RS, Shimamoto H, Bezouglaia O, Pirih FQ, Dry SM, Kostenuik P, Boyce RW, Dwyer D, Aghaloo TL, Tetradis S. OPG-Fc but not zoledronic acid discontinuation reverses osteonecrosis of the jaws (ONJ) in mice. J Bone Miner Res 2015;30:1627-40.

de Molon et al treated mice with vehicle, zoledronic acid (ZA), or OPG-Fc for 11 weeks to induce ONJ. Antiresorptives were then discontinued for 6 or 10 weeks. ONJ features in ZA and OPG-Fc groups included periosteal bone deposition, empty osteocyte lacunae, osteonecrotic areas, and bone exposure; each resolved 10 weeks after discontinuing OPG-Fc, not ZA. Recovery of tartrate-resistant acid phosphatase-positive osteoclast numbers occurred after discontinuing OPG-Fc, not ZA.

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