OVERVIEW, VOL 12, ISSUE 1

Ego Seeman
Editor

By Ego Seeman Tue, 05/22/2012 - 10:55

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* 19 years ago. 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 still to provoke critical evaluation of the important literature for members of the International Osteoporosis Foundation family and by them. 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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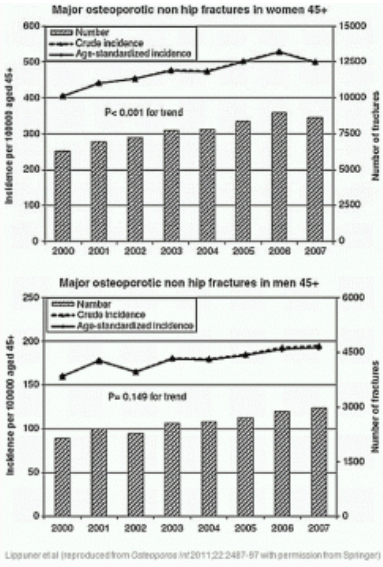
Fractures and Death are Not Going Away
Nonvertebral Fractures are Here to Stay

The burden of fractures and mortality associated with them is not diminishing. The fractures are not only vertebral or hip, most are nonvertebral and nonhip. **Morin et al** report 21,067 incident fractures in men were associated with 10,724 (50.1%) deaths while 49,197 incident fractures in women were associated with 22,018 deaths (44.8%). 76% of the fractures were at sites other than the hip and vertebrae. Postfracture mortality was higher in men than women. **Osteoporos Int 2011;22:2439**

In Switzerland, **Lippuner et al** report that major osteoporotic fractures (hip, clinical spine, distal radius, and proximal humerus) in increased by 15.9% (women) and 20.0% (men) due to an increased nonhip fractures (+37.7% in women and +39.7% in men). The number of individuals aged ≥45 years grew by 11.1% (women) and 14.6% (men) over the study period of 7 years. **Osteoporos Int 2011;22:2487**



Lippuner et al (reproduced from Osteoporos Int 2011;22:2487-97 with permission from Springer)

Hello Cortical, Goodbye Trabecular, Bone

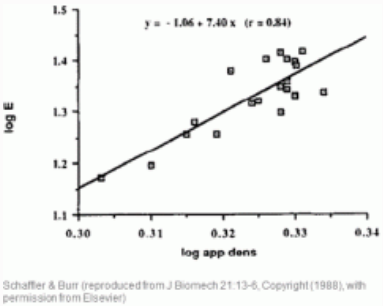
The skeleton is 80% cortical, only 20% is trabecular. 70% of all age-related bone loss is cortical. 50% is lost by remodeling upon the Haversian canals of the inner third of the cortex – the cortex thins from within, not from the marrow outwards – Jepsen suggested this years ago, Zebaze proved it. Porosity is *the* single morphological 'footprint' of structure decay. Trabecular bone loss has ruled for decades, a humbling error as our children teach us.

Trabecular bone had its 15 minutes of fame bestowed by Albright, then Riggs, who noted forearm densitometry wasn't a big hit because it did not distinguish patients with and without spine fractures. Dual photon absorptiometry topped the charts in the second half of the 20th century as spine densitometry seemed to discriminate fracture and nonfracture cases better than single photon absorptiometry. Densitometry stays in the top 40 in this dark side of the 21st century even though half of all fractures arising from above the nominal threshold of -2.5 SD; are all these 'non-osteoporotic' fractures? They are still called 'osteoporotic' fractures but what it meant is they are fragility fractures. Well, if they are fragility fractures, what is the structural basis of this half of the burden of fractures?

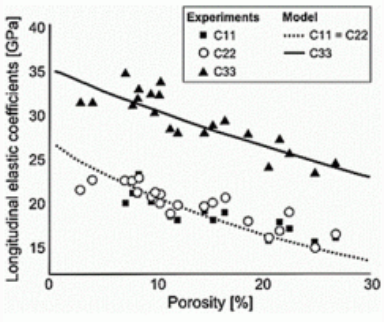
Parfitt made the point that the slow loss of a larger volume of cortical bone is equally if not more important than the rapid loss of a small volume of trabecular bone. Let's not waist youth on the young. Zebaze, examining scanning electron microscopic images of bone, found large pores distant from the endocortical surface and reasoned that these could not arise by endocortical resorption dissolving the cortex 'outwards' producing cortical thinning from the marrow outwards. He recognized that the mechanism was intracortical remodeling thinning the cortex from its inside, especially the intracortical remodeling upon Haversian canals traversing in the inner part of the cortex.

Returning to the same place and knowing it for the first time: porous bone

Porosity is a quantifiable 'fingerprint' of bone loss and bone fragility. Take a look at Schaffler & Burr (J Biomech 1988;21:13). This inverse power function showed that the apparent density predicted the elastic modulus log E = 1.06 +7.4 log apparent density. A unit decrease in apparent density (produced by increasing porosity), reduced stiffness seven fold. For trabecular bone, stiffness is proportional to apparent density cubed, so increasing the void volume in cortical bone is much more deleterious than increasing the void volume of an already porous material. The current report by **Granke et al** is similar. Middiaphyseal cortical bone was scanned using acoustic microscope (SAM) and synchrotron radiation μCT. Stiffness correlated inversely with cortical porosity (R^2=0.72-0.84). **Bone 2011;49:1020**



Schaffler & Burr (reproduced from J Biomech 21:13-8, Copyright (1988), with permission from Elsevier)

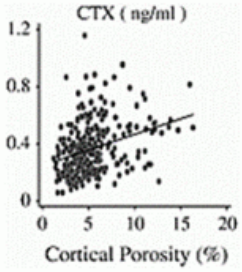


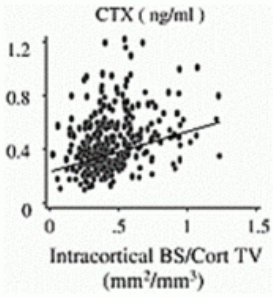
Granke et al (reproduced from *Bone* 49:1020-6, Copyright (2011), with permission from Elsevier)

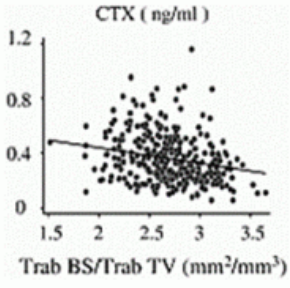
Remodeling is signaled within bone matrix, probably by osteocytes by their sacrificial death. The signals go to a point upon the internal surface of bone, the endosteal envelope.

Remodeling is initiated at a point and the cells recruited orchestrate the tunneling back to the place of origination to remove that damage. So, surface area is important. **Bjornerem et al** report that postmenopausal women that a 1 SD higher tibia intracortical bone surface area was associated with 0.22-0.29 SD higher remodeling markers. A 1 SD lower trabecular bone surface area was associated with 0.15-0.18 SD higher remodeling markers. Intracortical remodeling is self perpetuating by creating porosity and so more surface for remodeling. Remodeling upon the trabecular surfaces is self-limiting because it removes trabeculae with their surface so no more remodeling can occur. **Bone 2011;49:1125**

Cortical remodeling is self perpetuation
Trabecular remodeling is self-limiting







Bjornerem et al (reproduced from *Bone* 49:1125-30, Copyright (2011), with permission from Elsevier)

Advances in Therapeutics

Location, location

Whether patients are treated seems to have more to do with good or bad luck than science. **Diez-Perez et al** report that among 58,009 women, medication use was lowest in Northern Europe (16%) and highest in USA and Australia (32%). Between 48% (USA, Southern Europe) and 68% (Northern Europe) of women aged ≥65 years with previous spine or hip fractures were untreated. Among women with osteoporosis, the percentage treated was lowest in Europe (45-52% vs. 62-65% elsewhere). Women with osteopenia were treated most frequently in USA (31%) and Canada (31%), least in Southern Europe (12%), Northern Europe (13%), and Australia (16%). USA women were 3-fold more likely to be treated as Northern European women. **Bone 2011;49:493**

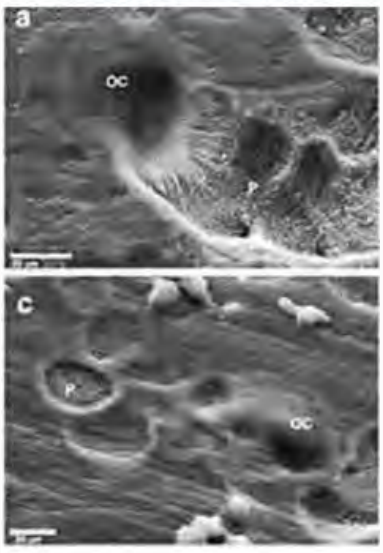
Whaatz new pussycat?

Cathepsin K inhibitors

Cathepsin K (CatK) inhibitors are a fascinating family of drugs. **Leung et al** report that odanacatib (ODN), a selective, potent and reversible inhibitor of CatK, inhibits bone loss. Osteoclastogenesis and survival are unaffected but resorption is decreased as measured by CTX release or resorption area which becomes a series of shallow pits rather than a deep trail-like resorption trench. **Bone 2011;49:623**

What is fascinating is that remodeling intensity is either not inhibited, or less inhibited than observed with classic antiresorptive agents. That is, the number of resorption cavities upon the surfaces of bone remains either unchanged or decreases to some extent but these sites are more shallow. What is bad about this is that if resorption pits are more shallow, then osteons that come to be formed when these refill may be smaller. If they are smaller, then this may reduce the resistance to crack propagation which occurs mainly in interstitial bone (between osteons) and which now increases in absolute and relative terms. However, if remodeling intensity continues, then there may be more of the

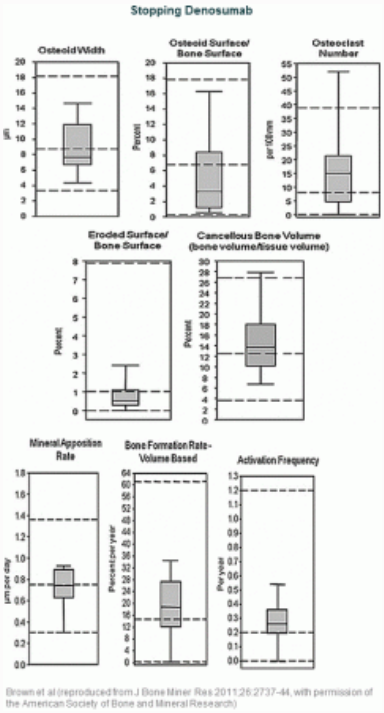
Odanacatib and shallow resorption pits



Leung et al (reproduced from Bone 49:623-35, Copyright (2011), with permission from Elsevier)

smaller osteons offsetting the potentially deleterious effect of smaller size. Another potential benefit is the material composition of bone. Classic antiresorptive agents reduce the intensity of remodeling so osteons that would have been removed are not; they continue to undergo secondary mineralization which increases material stiffness predisposing to the occurrence and lengthening of microcracks. This may be avoided if remodeling intensity is not reduced or less reduced. Is there any evidence for the above? Not yet.

Stopping antiresoptive therapy



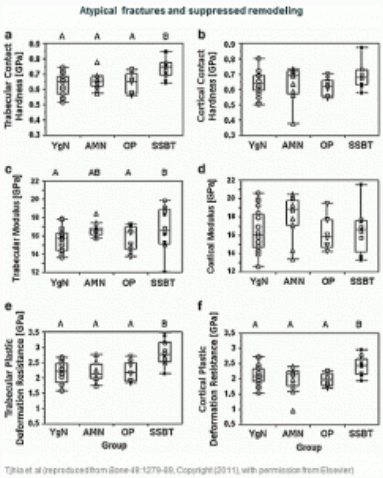
Brown et al (reproduced from J Bone Miner Res 2011;26:2737-44, with permission of the American Society of Bone and Mineral Research)

Denosumab is a power inhibitor of bone remodeling. While this is important in reducing bone loss (as remodeling intensity drives bone loss when basic multicellular unit (BMU) balance is negative, protracted suppression of remodeling may allow secondary mineralization to go to completion in osteons that are no longer removed by high remodeling and this may increase brittleness of bone. **Brown et al** report that 15 subjects enrolled in a cohort study to evaluate the effects of denosumab discontinuation after ~25 months showed normal histology and bone remodeling; similar to those observed in untreated postmenopausal women. With treatment cessation, 100% of biopsy specimens had evidence of tetracycline labels. Biochemical markers were comparable to and highly correlated with pretreatment levels. **J Bone Miner Res 2011;26:2737**

While denosumab does not bind to bone mineral and its suppressive effects appear to reverse quickly, the bisphosphonates are bound to bone and are released and perhaps readsorbed onto bone as remodeling is restored. **Eastell et al** report that postmenopausal women with osteoporosis who completed the risedronate multinational trial plus a 2-year extension, one year after discontinuation, NTX/Cr levels increased toward baseline, total hip and femoral trochanter BMD values decreased, whereas lumbar spine and femoral neck BMD were maintained or slightly increased. **J Clin Endocrinol Metab 2011;96:3367**

Reversibility of treatment may be good or bad. Irreversibility is not a good from the point of view of the material composition of bone. The prolonged suppression of the very mechanism, remodeling, that functions to remove damage and replace old bone with new bone, may contribute to both the accumulation of micro-damage and the occurrence of more damage as the bone becomes more brittle due to homogeneity and complete secondary mineralization as well as increased collagen crosslinking which further reduces elasticity of bone. The alternative is also not good. If treatment is reversible, remodeling reemerges and results in bone loss and probably an increase in bone fragility as structural decay recurs. The answer to this dilemma is to measure the baseline material and composition of bone, measure the changes during therapy and modulate therapy in individuals accordingly. Can it be done? Yes. Must it be done? Yes.

Atypical fractures and suppressed bone remodeling

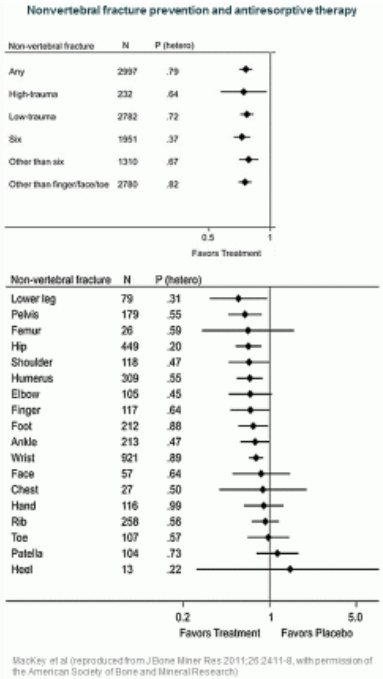


Tjhia et al (reproduced from Bone 49:1279-89, Copyright (2011), with permission from Elsevier)

Tjhia et al report that patients with atypical fractures and severely suppressed bone turnover (SSBT) associated with long-term bisphosphonate therapy had evidence on bone biopsy of increased brittleness assessed using nanoindentation and quantitative backscattered electron microscopy. For cortical and trabecular bone greater resistance to plastic deformation was observed. **Bone 2011;49:1279**

Nonvertebral fracture risk reduction

These are the most common and most challenging fractures to prevent. Few studies have demonstrated fracture risk reduction in this class. When observed, the risk reduction is usually 20-25%; half that reported for hip or spine fractures. **Mackey et al** combined five trials of alendronate, clodronate, denosumab, lasofoxifene, and zoledronic acid involving 30,118 women. The hazards ratio were: all fractures HR=0.76 (95% CI 0.70-0.81), high-



trauma fractures HR=0.74 (95% CI 0.57-0.96), low-trauma fractures HR=0.77 (95% CI 0.71-0.83), nonvertebral six fractures HR=0.73 (95% CI 0.66-0.80), other than nonvertebral six fractures HR=0.78 (95% CI 0.70-0.87), and all fractures other than finger, face and toe HR=0.75 (95% CI 0.70-0.81). The question is whether this reduction can be improved through a better understanding of the pathogenesis and so detection of those at risk. I suspect the answer to this is yes. **J Bone Miner Res 2011;26:2411**

The enigma of the antifracture efficacy of strontium ranelate

Clinical trials provide consistent evidence for rapid and sustained vertebral and nonvertebral fracture risk reduction using strontium ranelate (Meunier et al, N Engl J Med 2004;350:4591; Reginster et al, J Clin Endocrinol Metab 2005;90:2816). The challenge is how? Bone becomes fragile during advancing age because remodeling becomes unbalanced at the level of the BMU; each time bone matrix is remodeled, a smaller volume of bone matrix is deposited than was removed. The rate and extent of the structural decay depends on the size of the negative BMU balance and the intensity of remodeling at the tissue level (activation frequency). The BMU imbalance at the cellular level and the remodeling intensity at the tissue level are two therapeutic targets.

Antiresorptive agents such as the bisphosphonate, alendronate, mainly target tissue level remodeling. By reducing the intensity of remodeling, fewer remodeling sites upon the trabecular, endocortical and intracortical components of the inner (endosteal) envelope remove a volume of bone matrix and replace it with less bone matrix. Structural decay continues, but more slowly, and at a rate determined by the potency of the drug in suppressing tissue level remodeling. If the antiresorptive also corrects the negative BMU balance by reducing the volume of bone matrix resorbed, by increasing the volume of bone matrix deposited, or both, then remodeling would no longer produce structural decay.

Strontium ranelate does not appear to reduce the intensity of bone remodeling. For example, in the study by Arlot et al (J Bone Miner Res 2008;23:215), activation frequency was not reduced. In a more recent study, published only in abstract form at this time, Chavassieux et al (Osteoporos Int 2011;22(Suppl1):S104) reported changes in bone remodeling in 268 postmenopausal women with osteoporosis who received strontium ranelate 2 g/day or alendronate 70 mg/week. The surface extent of remodeling as measured by the mineralizing surface/bone surface (MS/BS) increased from 2.94±3.73% at 6 months to 4.91±4.15% at 12 months with strontium ranelate. Baseline values were not reported. The surface extent of remodeling with alendronate decreased as expected.

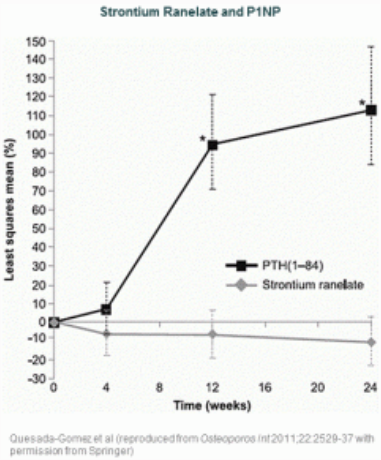
Continued remodeling intensity at the tissue level may be an advantage if a treatment decrease in volume of bone matrix resorbed by the osteoclasts of the many BMUs continuing to remodel bone, increases the volume of bone matrix deposited by the osteoblasts of these many BMUs, or does both. If the number of resorption sites remain unchanged (as reflected in the unchanged activation frequency and MS/BS) and the volume of bone deposited is unchanged or increases sufficiently to produce a net positive BMU balance, then it is plausible that each remodeling event will deposit a net positive volume of bone upon the endocortical surface thickening the cortex focally and upon trabeculae thickening these structures. In the cortex, it is not possible to put back more bone than was removed by a BMU, but if remodeling occurs upon the surface of a large cavity, its size may be reduced focally.

The concept of ‘dual action’ applies to BMU based remodeling – a reduction in the volume of bone resorbed and an increase in the volume of bone formed. Differences in the surface extent of the endosteal envelope undergoing bone resorption at one or more locations and the surface extent of bone formation at other locations is not evidence of ‘dual action’.

There is evidence of reduced resorption of bone in in vitro cell lines and continued or increased proliferation of osteoblast cell lines tissue culture. However, evidence based on histomorphometric analysis in bone biopsy specimens is inconclusive, in part because of methodological constraints. For example, evidence for a reduction in the volume of bone resorbed was not observed in the study by Arlot et al and has not yet been reported in a recently completed study by Chavassieux et al. In the study by Arlot et al, there was evidence of higher mineral apposition rate (MAR), as well as higher osteoblast surface/bone surface (Ob.S/BS) (+38% in cancellous and endocortical bone; p=0.047) compared with controls. (The word ‘higher’ applies, not ‘increased’; few biopsies were paired.) In the study by Chavassieux et al, MAR was higher with strontium ranelate at 6 (0.630±0.127 µm/day, P=0.003) and 12 months (0.624±0.094 µm/day, P=0.009) compared with alendronate (0.553±0.108 µm/day at both time points), but

baseline measurements were not available to establish if MAR actually increased relative to baseline.

While dissociation in remodeling markers, with unchanged or modestly increased markers of bone formation and unchanged or modestly decreased resorption markers (Meunier et al, N Engl J Med 2004;350:4591), are often cited as evidence for a 'dual' action. Remodeling markers reflect tissue level remodeling and to use these as evidence of a dissociation or uncoupling of cell based resorption and formation at the BMU level is flawed.



Quesada-Gomez et al (reproduced from Osteoporos Int 2011;22:2529-37 with permission from Springer)

A recently published study directly assessed the effects of strontium ranelate on markers of bone formation by comparing changes with a known anabolic agent. **Quesada-Gomez et al** report increases in P1NP and BSAP with PTH, PTH(1-84), given during 6 months to 41 subjects but no changes were observed with strontium ranelate given to 40 subjects. **Osteoporos Int 2011;22:2529-37** In another study, Recker et al (J Bone Miner Res 2009;24:1358) reported treatment with teriparatide (n=39, 20 mg/d) increased aminoterminal propeptide of type I collagen (PINP) after 1 month (+57%, p<0.001) while strontium ranelate (n=40, 2 g/d) induced reductions in PINP at 3 and 6 months and in serum β-C-terminal telopeptide of type I collagen (β-CTX) at 1 and 3 months (7). The increase in P1NP was thus not observed with strontium ranelate but whether the increase with reported with PTH 1-84 or 1-34 reflects increases in the number of sites undergoing remodeling or an increase in volume of bone deposited by each or is the result of modeling – the deposition of bone upon quiescent surfaces independent of the remodeling machinery is not known.

Several studies have examined the effect of strontium ranelate on bone architecture in vivo. In the study by Arlot et al, on 2-D histomorphometry, no effects on cortical thickness, porosity, or trabecular bone volume fraction were observed. In 3-D analysis of 3-year unpaired biopsies, 20 in patients who received treatment and 21 in patients who received placebo using μCT the strontium ranelate group had higher cortical thickness (+18%, p=0.008) and trabecular number (+14%, p=0.05), and lower structure model index (−22%, p=0.01) and trabecular separation (−16%, p=0.04); with no change in cortical porosity. In another study, Rizzoli et al (Rheum Int 2010;30:1341) reported that strontium ranelate increased cortical thickness, cortical area and trabecular density after one year as assessed using high resolution computed tomography. The increases in cortical thickness, area, and BV/TV and decrease in trabecular bone area were greater in the strontium ranelate than alendronate group. Trabecular number increased in both groups.

These studies are also difficult to interpret. Strontium ranelate and alendronate are likely to increase photon attenuation because strontium ranelate has twice the atomic number of calcium so the increases photon attenuation may give the impression that structural change due to bone formation has occurred. Alendronate slows remodeling so secondary mineralization of bone matrix that has not been remodeled may increase photon attenuation giving the impression that bone formation has occurred.

The notion that this is a 'dual acting' drug is based on studies in vitro and in animal models in which the bone undergoes modeling during advancing age, not remodeling. Methodological issues in noninvasive imaging limit interpretation of morphological studies in vivo and so information is needed such as publication of full results of the study of Chavassieux et al which may help to define whether there is evidence of new bone using this treatment. Studies are needed to address whether the antifracture efficacy is partly the result of changes in the material composition of bone.

Reviews

Forum on aging and skeletal health: Summary of the proceedings of an ASBMR workshop
Khosla S, Bellido TM, Drezner MK, Gordon CM, Harris TB, Kiel DP, Kream BE, Leboff MS, Lian JB, Peterson CA,Rosen CJ, Williams JP, Winer KK, Sherman SS
J Bone Miner Res 2011;26:2565

Investigation of differences between hip fracture types: A worthy strategy for improved risk assessment and fracture prevention
Pulkkinen P, Gluer CC, Jamsa T
Bone 2011;49:600

Hypoparathyroidism in the adult: Epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research
Bilezikian JP, Khan A, Potts JT, Jr., Brandi ML, Clarke BL, Shoback D, Juppner H, D'Amour P, Fox J, Rejnmark L, Mosekilde L, Rubin MR, Dempster D, Gafni R, Collins MT, Sliney J, Sanders J
J Bone Miner Res 2011;26:2317

Vitamin D supplementation during pregnancy
Abrams SA
J Bone Miner Res 2011;26:2338

Relationship between serum RANKL and RANKL in bone
Findlay DM, Atkins GJ
Osteoporos Int 2011;22:2597

LRP5, serotonin, and bone: Complexity, contradictions, and conundrums
Goltzman D
J Bone Miner Res 2011;26:1997

Unraveling the role of FoxOs in bone: Insights from mouse models
Almeida M
Bone 2011;49:319

Small animal bone healing models: Standards, tips, and pitfalls results of a consensus meeting
Histing T, Garcia P, Holstein JH, Klein M, Matthys R, Nuetzi R, Steck R, Laschke MW, Wehner T, Bindl R, Recknagel S, Stuermer EK, Vollmar B, Wildemann B, Lienau J, Willie B, Peters A, Ignatius A, Pohlemann T, Claes L, Menger MD
Bone 2011;49:591

Genetic mouse models for bone studies: Strengths and limitations
Elefteriou F, Yang X
Bone 2011;49:1242

Geographic trends in incidence of hip fractures: A comprehensive literature review
Cheng SY, Levy AR, Lefaivre KA, Guy P, Kuramoto L, Sobolev B
Osteoporos Int 2011;22:2575

Issues in modern bone histomorphometry
Recker RR, Kimmel DB, Dempster D, Weinstein RS, Wronski TJ, Burr DB
Bone 2011;49:955

Interpretation and use of FRAX in clinical practice
Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, Cauley JA, Compston JE, Dawson-Hughes B, El-Hajj Fuleihan G, Johansson H, Leslie WD, Lewiecki EM, Luckey M, Oden A, Papapoulos SE, Poiana C, Rizzoli R, Wahl DA, McCloskey EV
Osteoporos Int 2011;22:2395

Uncertainties in the prevention and treatment of glucocorticoid-induced osteoporosis
Hansen KE, Wilson HA, Zapalowski C, Fink HA, Minisola S, Adler RA
J Bone Miner Res 2011;26:1989

Pathophysiology of atypical femoral fractures and osteonecrosis of the jaw
Compston J
Osteoporos Int 2011;22:2951

Towards a diagnostic and therapeutic consensus in male osteoporosis
Kanis JA, Bianchi G, Bilezikian JP, Kaufman JM, Khosla S, Orwoll E, Seeman E
Osteoporos Int 2011;22:2789

Emerging therapies to prevent skeletal morbidity in men with prostate cancer
Saylor PJ, Lee RJ, Smith MR
J Clin Oncol 2011;29:3705

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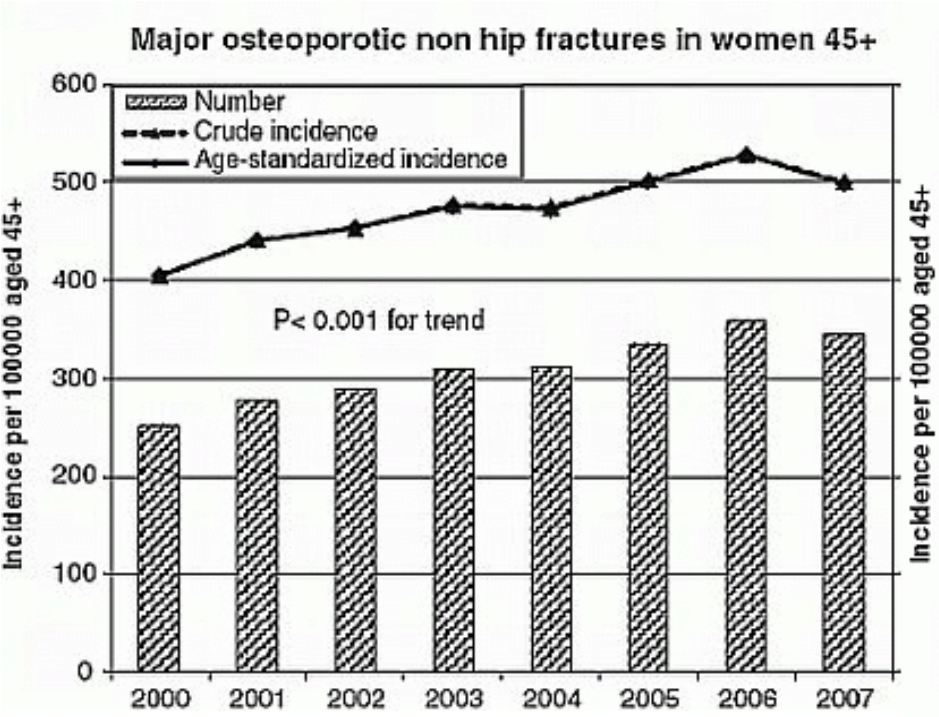
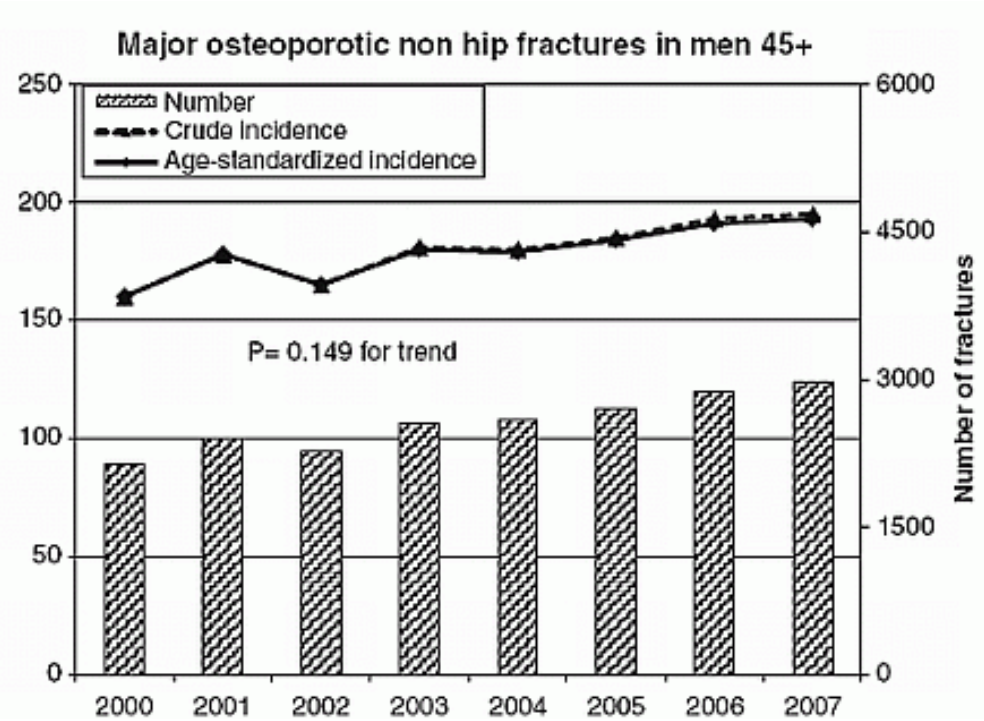
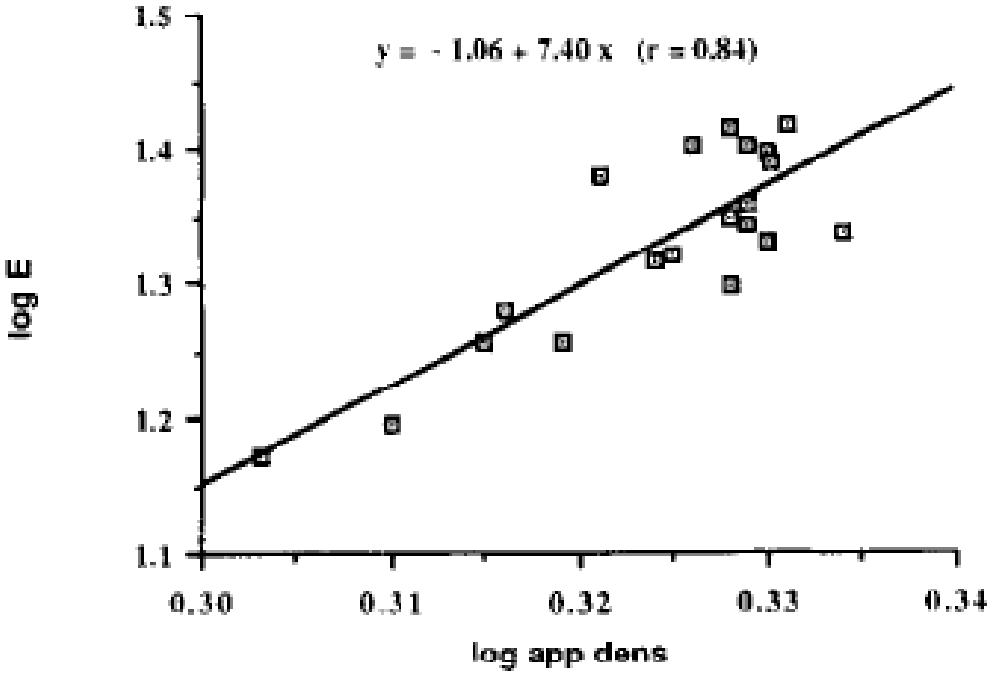
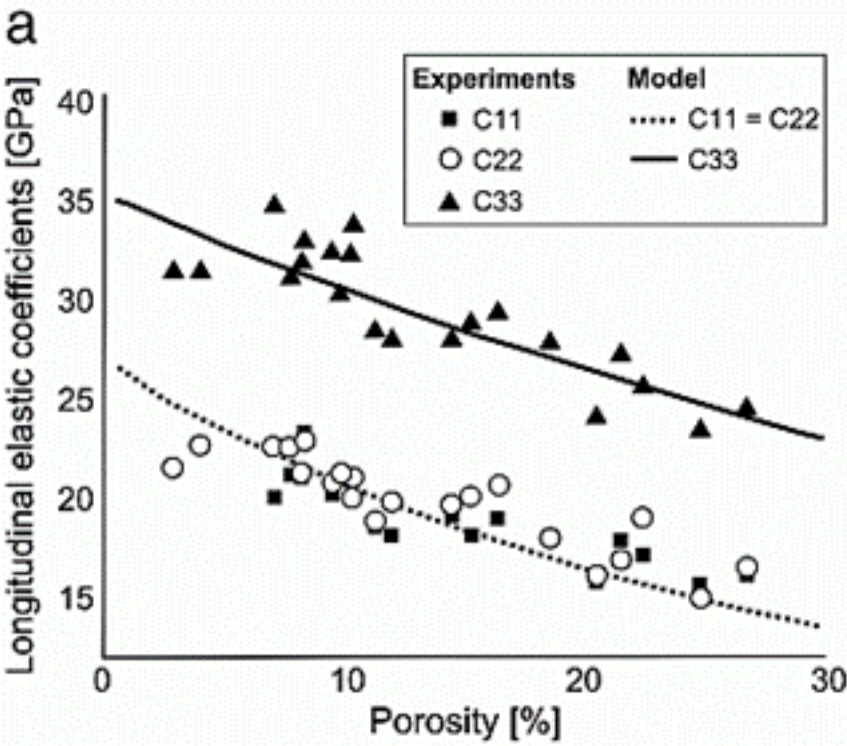




Lippuner et al Osteoporos Int 2011;22:2487

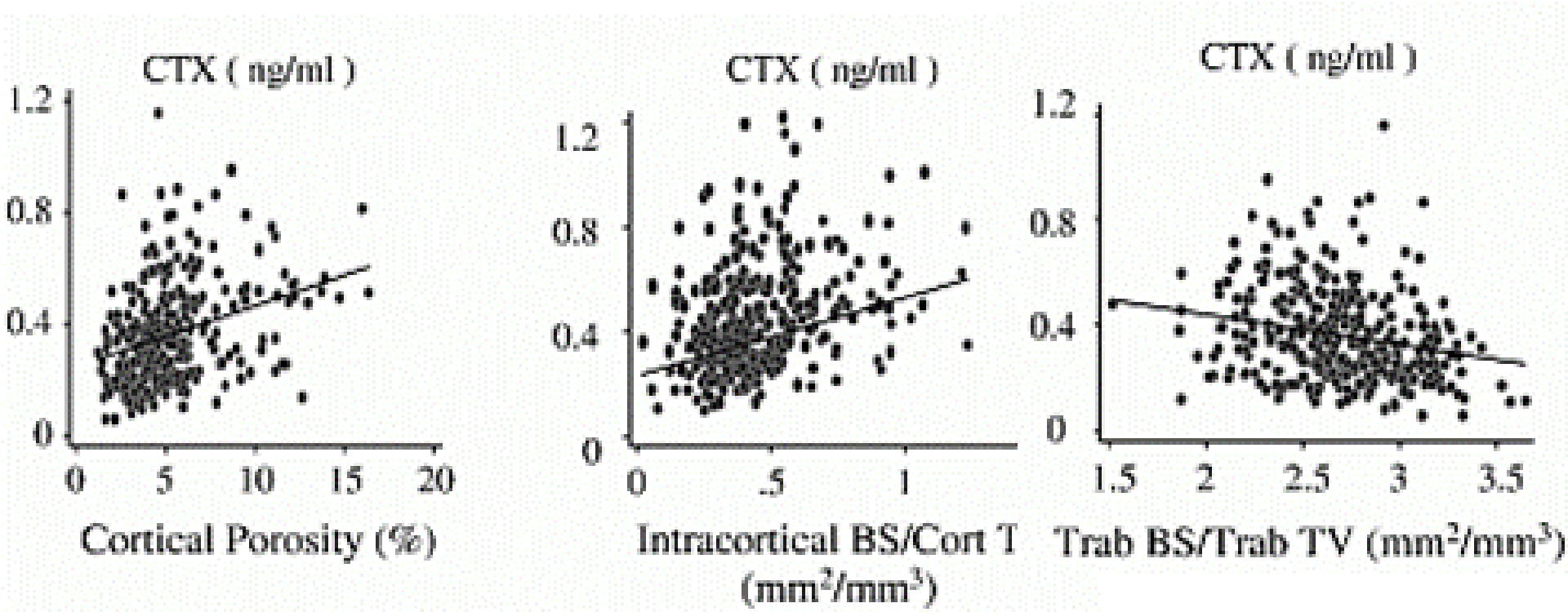


Schaffler & Burr J Biomech 1988;21:13



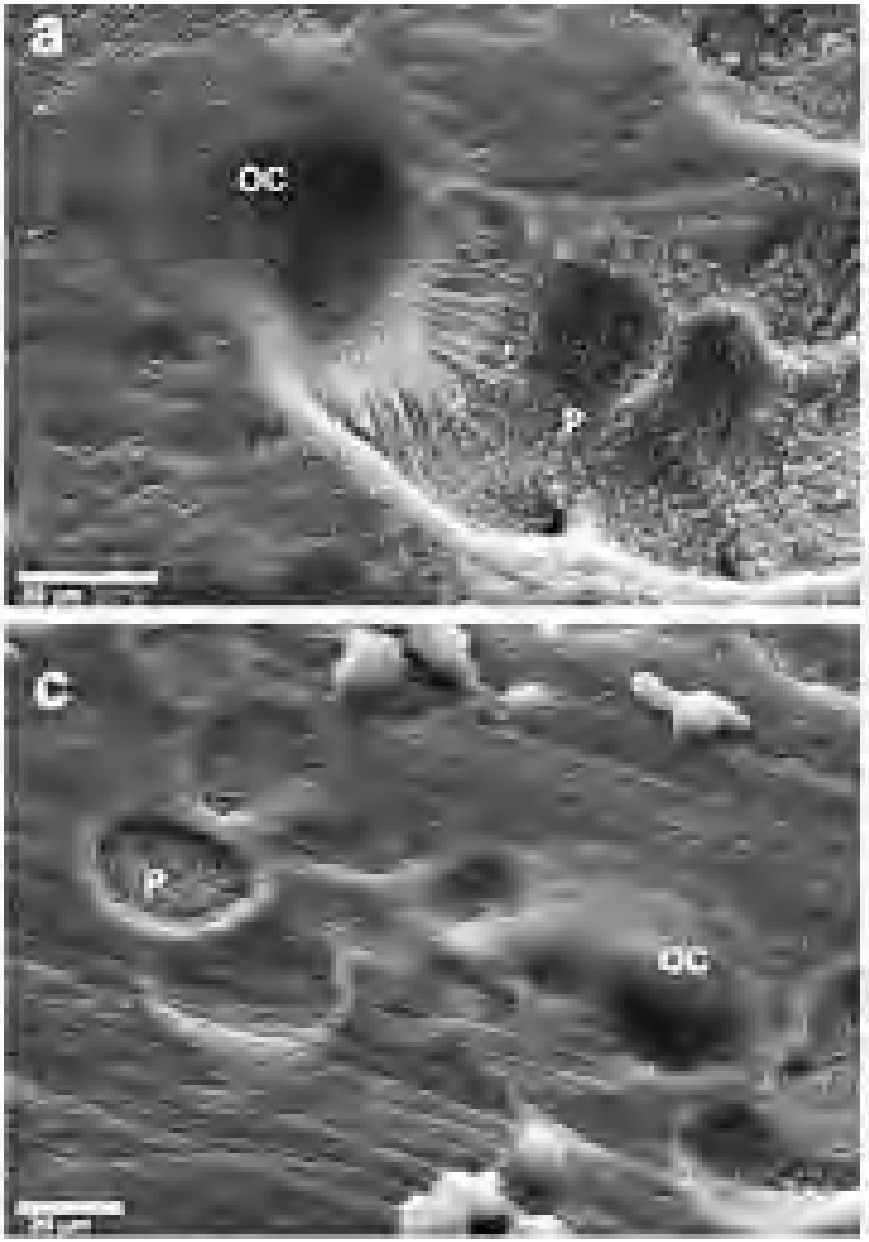
Granke et al Bone 2011;49:1020

Cortical Remodeling is self perpetuation, trabecular remodeling is self-limiting



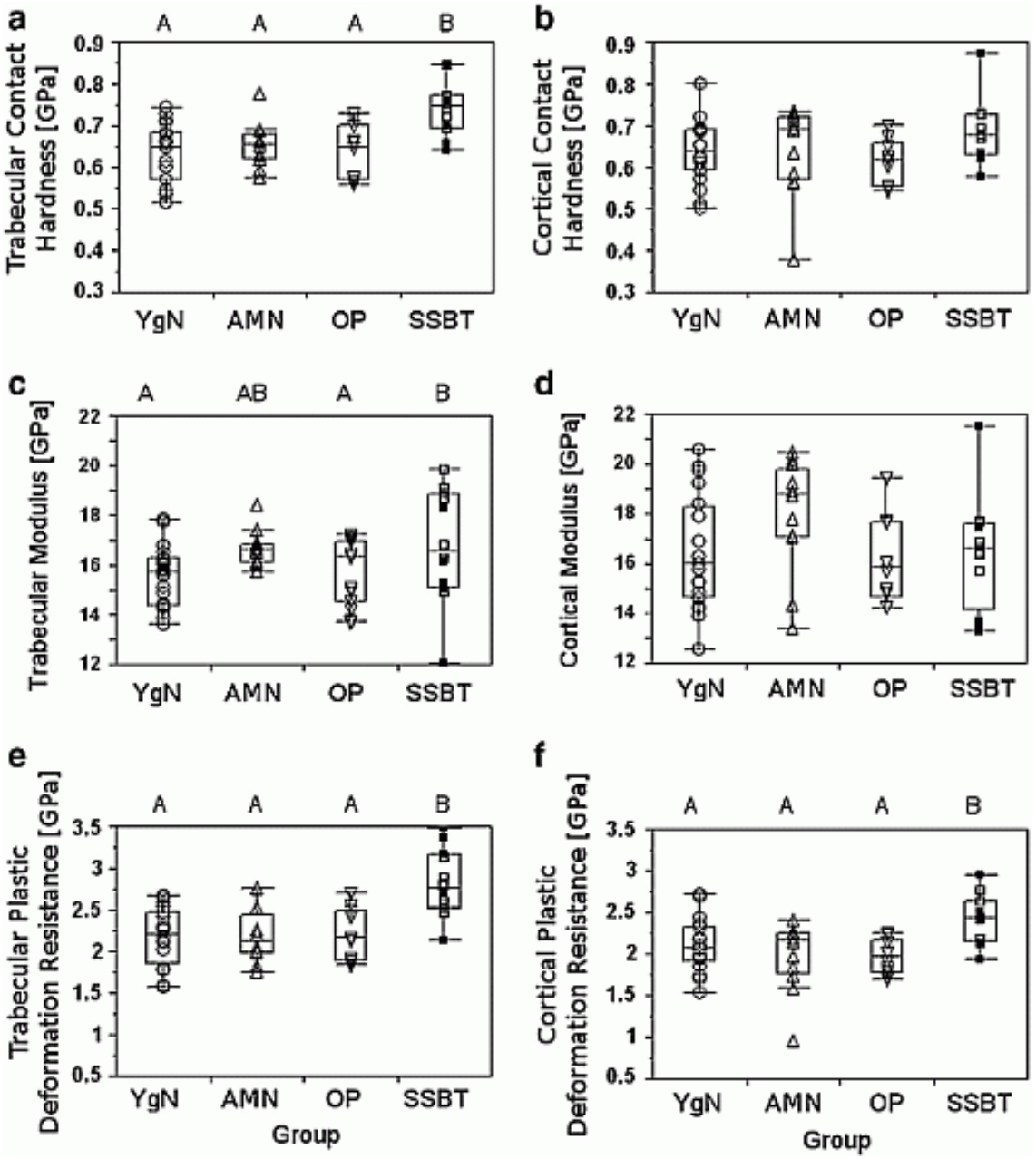
Bjornerem et al Bone 2011;49:1125

Odanacatib and Shallow resorption pits



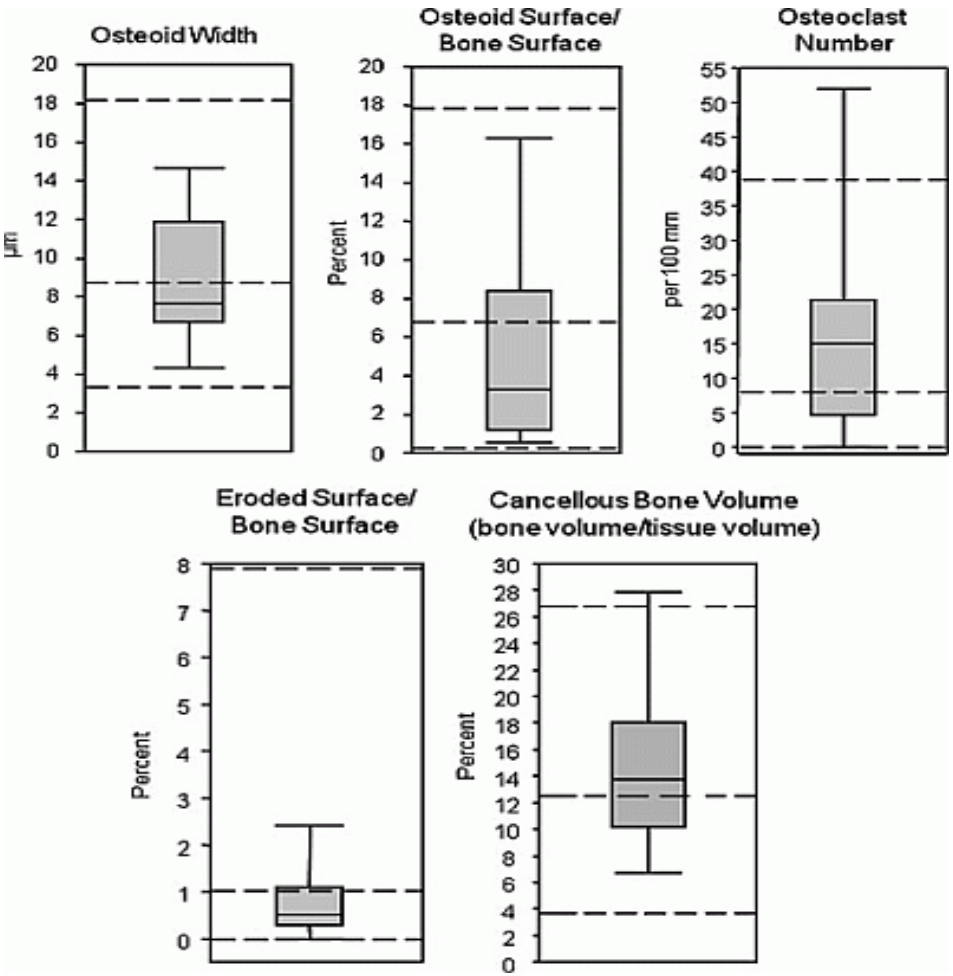
Leung et al Bone 2011;49:623

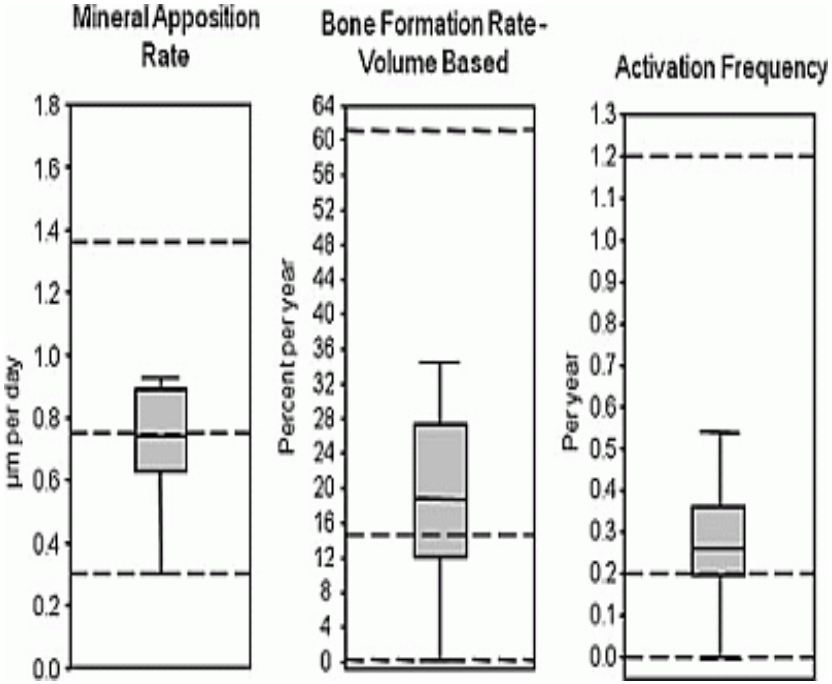
Atypical fractures and suppressed remodeling



Tjhia et al Bone 2011; 49:1279

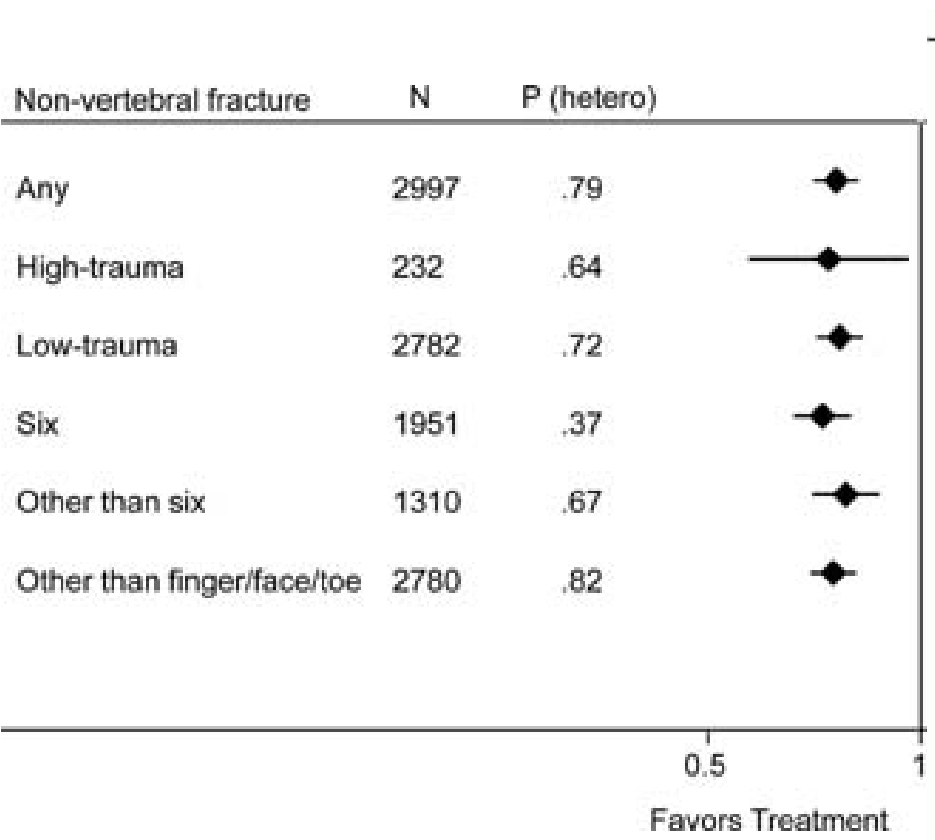
Stopping Denosumab

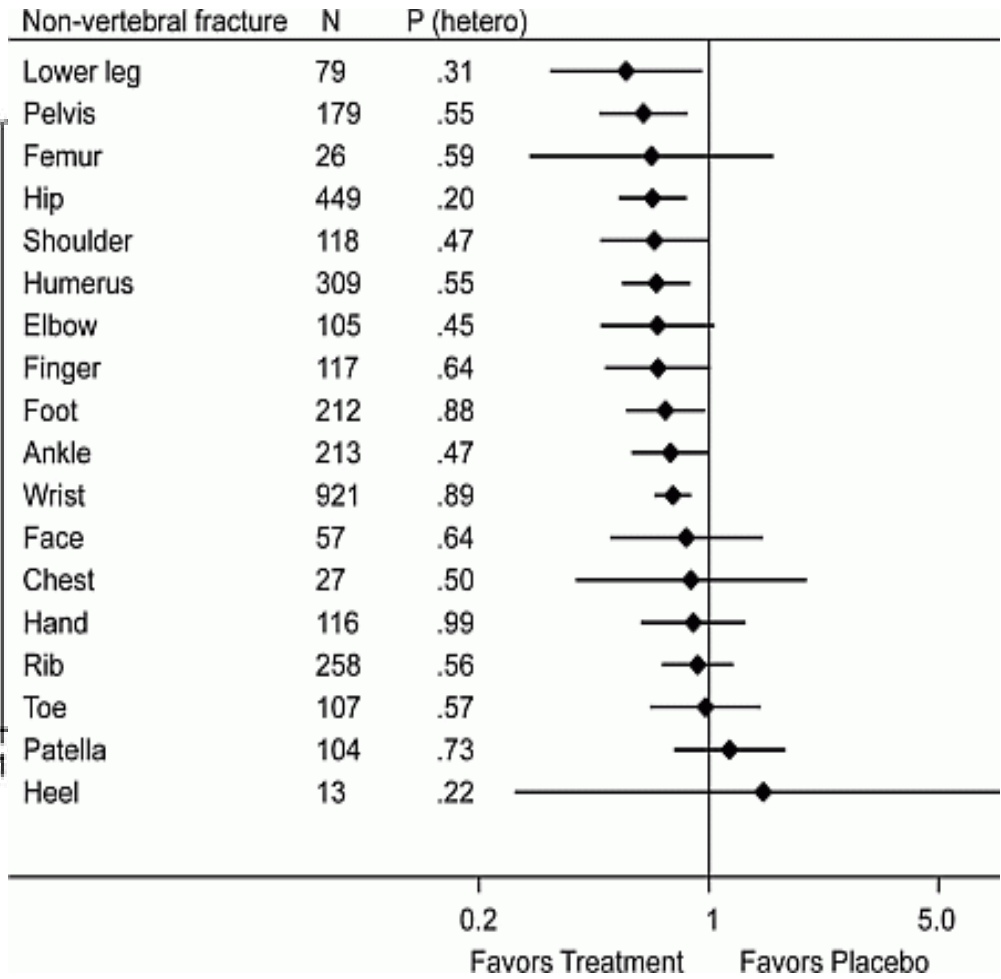




Brown et al J Bone Miner Res 2011;26:2737

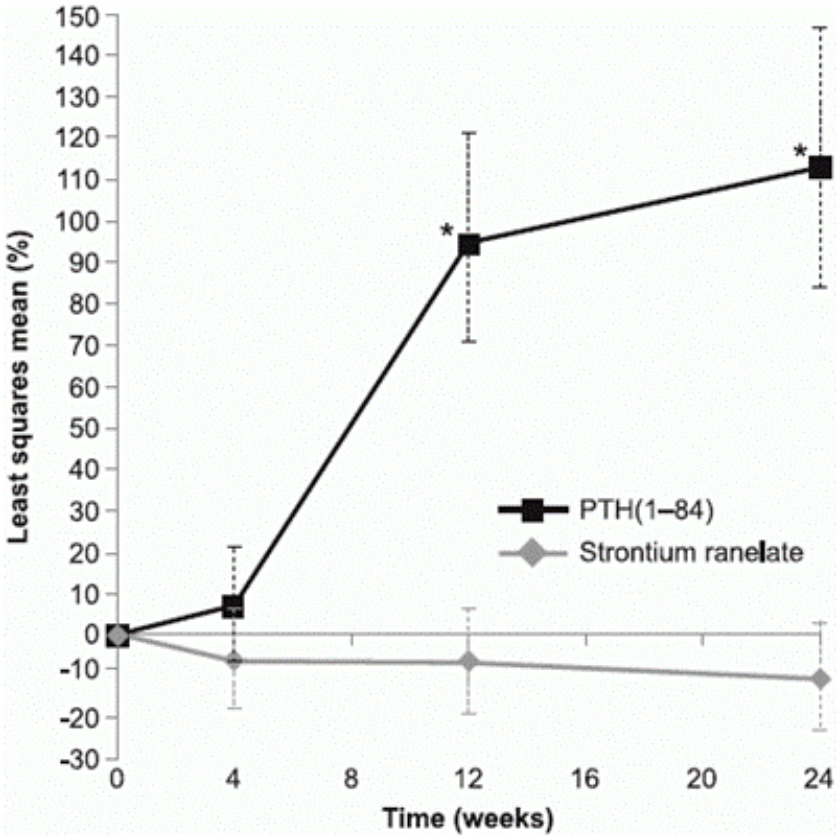
Nonvertebral fracture prevention and antiresorptive therapy





MacKey et al J Bone Miner Res 2011;26:2411

Strontium ranelate and P1NP



Quesada-Gomez et al Osteoporos Int 2011;22:2529

PROGRESS IN OSTEOPOROSIS

Summaries and Critical Analyses of the current literature

OVERVIEW, VOL 12, ISSUE 2

Ego Seeman

Editor

By Ego Seeman Thu, 06/28/2012 - 12:26

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

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

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Volume 12, Issue 2

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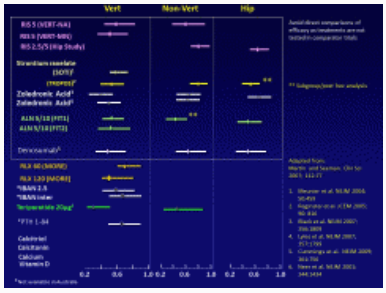
- Progress in Osteoporosis home

Nonvertebral Fractures: As good as it gets?



We now have several therapies convincingly shown to reduce the risk of vertebral fractures, at least during the first 3 years of treatment (1). Most of these treatments reduce this risk by 50-60% relative to a control group given calcium and vitamin D supplementation. Some, like zoledronic acid and denosumab, reduce it by about 70% which is starting to look respectable *(Figure 1 on right)*. I am not suggesting these treatments are 'better' than others. That statement would require evidence based on concurrently conducted comparator trials. None are available or are likely to become available. The sample sizes needed to demonstrate a biologically worthwhile advantage of one treatment over another are prohibitive (2). Nevertheless, treatments should provide a better than 50:50 chance of fracture prevention – is a 50-60% vertebral fracture risk reduction good enough?

This brings us to a real unmet need in this field: nonvertebral antifracture efficacy. While vertebral fractures and trabecular bone loss are 'flagships' of osteoporosis, nonvertebral fractures account for 80% of all fractures, 80% of bone is cortical, not trabecular, most bone lost from the appendicular skeleton is cortical, not trabecular and most of this bone loss occurs by intracortical remodeling with the production of intracortical void spaces (porosity) as enlargement and coalescence of Haversian canals progressively cavitates and thins the cortical shell exponentially reducing its resistance to bending (3-5).

The patient consulting you for advice about fracture risk reduction is four times more likely to sustain a nonvertebral than vertebral fracture. Therefore the choice of treatment should be a drug that has been demonstrated to reduce the risk of non-vertebral fractures, not only vertebral fractures. There are not many alternatives available and the expected benefit to the patients is far

less than the benefit against vertebral fractures.

A reduction in hip fracture risk is reported for alendronate, risedronate, zoledronic acid, denosumab, and strontium ranelate. In the few studies available examining the benefits of these treatments, the risk reduction is about 40-50%; again, there is only a 50:50 chance that the fracture the patient will have will actually be prevented despite compliance with therapy.

How credible are the data? Well, you judge. There is only limited evidence for anti-hip fracture efficacy in the very group having hip fractures: persons over 70 years of age. Briefly, for alendronate, the reduction in hip fracture risk was based on FIT-1 and this data was based on 22 hip fractures in controls and 11 fractures in the treated group, no patients, or only a few, were older than 80 years of age and most were under 75 years of age. For risedronate, the data were more plentiful; event rates were higher and so the result is more robust. The risk reduction was based on the HIP trial by McClung et al (6) but no reduction in hip fracture risk was detected in persons over 80 years of age selected on risk factors. For zoledronic acid there was a reduction in the HORIZON trial overall but not in those over 75 years of age. For denosumab there was evidence of a reduction in risk in the trial overall, but whether there is evidence in the over 70 year old age group is not known. For strontium ranelate there was a reduction in women over 80 years of age, but this was of borderline statistical significance (7).

If we turn to nonvertebral fractures, the evidence becomes painfully sparse as shown in the above figure: risedronate, zoledronic acid, denosumab and strontium ranelate (1,8). Not only is there little data, the veracity of the data is easily challenged. First, in most, if not all studies, hip fractures are included in these analyses. This is usually unstated, but are the results if hip fractures are excluded from the analyses?

Of the few studies demonstrating any nonvertebral fracture risk reduction, this reduction is about 20%. So, say you have a busy day and you see 100 women over 70 years of age. Of these, 5 will sustain a fracture in that year; quite a high incidence of fractures. The problem is you don't know which of the 100 those 5 will be. Therefore, you have to treatment them all. The problem is, of the 5 sustain nonvertebral fractures, when you treatment all 100, only one will have the fracture averted during treatment, the other four will sustain the fracture despite compliance with therapy. I wonder if informed consent requires giving that sort of information and whether this will be acceptable to patients.

Looking at the quality of the evidence is instructive. There was no evidence for nonvertebral fracture risk reduction with alendronate in the FIT-1 and FIT-2 trials; to achieve statistical significance required a post hoc analysis of the pooled of FIT-1 patients and the patients with osteoporosis in FIT-2 (1). Nonvertebral fracture risk was observed with risedronate in one, but not both multicenter trials. For zoledronic acid, it was reassuring to see a nonvertebral fracture risk reduction in the HORIZON trial and in the post-hip fracture trial, a very difficult trial to execute but a most informative one (1,9). Nonvertebral fracture risk has also been reported in the FREEDOM trial with denosumab.

For the other treatments at the bottom of Figure 1, I am unable to put any data at all. The problems in the design and execution of the trials prevent any real confidence in the data. For example, in the studies of calcium and vitamin D subjects recruited were not deficient in these nutrients, so how can the effect of deficiency on fracture rates be assessed and any potential benefit of intervention be detected? In those studies, almost without exception, compliance was 50% with the intervention. Subanalyses looking at the effects of intervention persons deficient in calcium or vitamin D, or in those who comply with therapy, results in violation of randomization – the single design feature that controls for known *and* unknown influential covariates. These subanalyses and meta-analyses of subanalyses sometimes manage to squeeze a $p<0.05$ out of the data, provides enough uncertainty to allow debates at international meetings with a lot of sound and fury signifying nothing.

We are not there yet and the question is why. The answers to this complex question are not available for many reasons but this is a topic for the next issue of *Progress in Osteoporosis*. Now to a summary of the highlights in therapeutics from the recent IOF–ECCEO12 Congress in Bordeaux, more than a nice place to visit.

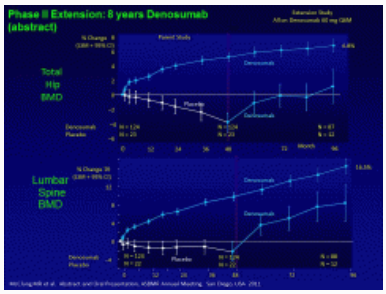
Advances in the Therapeutics of Osteoporosis Presented at IOF–ECCEO12

Treatments With a Predominantly Antiresorptive Action

Denosumab

Does denosumab increase bone density during 8 years?

McClung et al reported the 8 years follow-up in postmenopausal women with osteopenia or osteoporosis randomized to placebo, alendronate or denosumab (10). In the extension study, all subjects received open-label denosumab 60 mg Q6M for 4 years. For the 88 subjects who received denosumab for 8 years, BMD at the lumbar spine and total hip increased from baseline by 16.5% and 6.8%, respectively. Reductions in CTX and BSAP were sustained over 8 years of therapy *(Figure 2 on right)*.



This is an important study. The questions are what is the morphological basis underlying the continued increase in BMD and is this beneficial to bone strength or detrimental. The rise in BMD at spine in the second 4 years is ~8%, similar to the rise in the first 4 years. There are three possible explanations for this.

First, this is partly the result of secondary mineralization; the completion of the formation phase of remodeling cycles by secondary mineralization of osteons not removed because remodeling is suppressed. Secondary mineralization is the enlargement of crystals within collagen fibrils with the displacement of the water within them, so the fibril doesn't enlarge but more and more of its volume is occupied by mineral. Secondary mineralization is part of the remodeling 'transient'; the reversible deficit in matrix and its mineral content that results from the normal delay between completion of excavation of a resorption cavity and its refilling with osteoid which undergoes primary mineralization within a week then slower secondary mineralization (11). Secondary mineralization may take a year but some studies suggest much longer. The duration of completion of secondary mineralization is an area of controversy. Opponents of this explanation hold the view that this cannot be the explanation for the continued rise in BMD because the rise should become asymptotic; as more and more of the bone is fully mineralized there should be flattening of the rise in BMD which should cease to occur after 1-2 years.

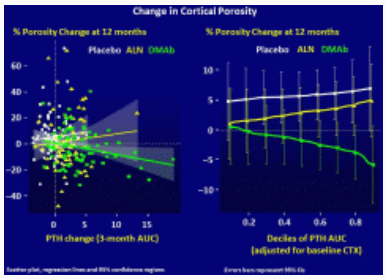
This is indeed what appears to be the case with the rise in BMD at the proximal femur. In this graph, the rise in BMD in the second 4 years is ~1%, i.e., approximately asymptotic. This explanation appears most reasonable in my opinion. Why then is there a continued rise in BMD at the spine? An obvious explanation is that this is an artifact resulting from arthritic changes in the intervertebral disc region and facet joints. The third explanation is that there is new bone formation. This is discussed below.

Does denosumab have effects mediated by endogenous PTH?

Denosumab rapidly and markedly reduces bone resorption at the tissue and cellular levels – i.e., the number of remodeling sites initiated upon the internal surfaces of bone decreases because osteoclastogenesis is inhibited and the resorptive activity of osteoclasts present in excavating resoption pits at the time of starting treatment is also prevented. This rapid suppression of resorption is accompanied by a small transitory fall in serum calcium within the normal range and a rise in endogenous PTH secretion (12).

Seeman et al tested the hypothesis that, in the face of suppressed remodeling, the transitory increase in endogenous PTH will stimulate the activity and lifespan of osteoblasts in existing remodeling cavities, and so will increase the volume of bone deposited in these resorption cavities more than otherwise would be produced, and that the cavity created will be smaller (because osteoclasts have been inhibited from completing resorption) (13). Together, the smaller resorption cavities and the larger volume of bone deposited within them may reduce or abolish the negative bone balance, and perhaps even induce a positive balance resulting in a reduction in porosity or even some bone building effect.

Postmenopausal women with a mean age of 61 years were randomly assigned in a double-blind, double-dummy trial to denosumab 60 mg Q6M (N=83), alendronate 70 mg QW (N=82), or placebo (N=82). PTH was measured and an area under the curve (AUC) for PTH was derived. With placebo and alendronate, porosity increased with increasing PTH. With denosumab, porosity decreased as PTH increased. (*Figure 3 on right*)

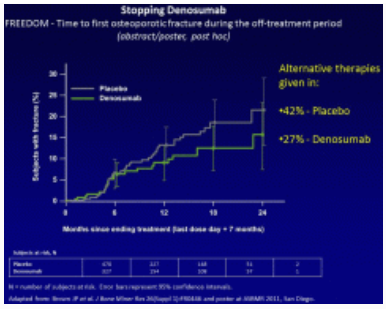


The authors infer that denosumab partially reversed microarchitectural deterioration (i) directly by reducing remodeling intensity and perhaps (ii) indirectly, by a PTH-dependent effect on BMU level bone formation in the setting of full suppression of osteoclast activity. This work is hypothesis generating. The data are consistent with a possible independent effect of endogenous PTH but histomorphometric studies will be needed to determine whether mean wall thickness is increased and mineral appositional rate is increased.

If there is a small anabolic effect of endogenous PTH, could this explain the rise in BMD seen during prolonged therapy? We don't know. Whatever incremental increase in bone formation there may be, this benefit should be the greatest following the first dose of denosumab when remodeling sites present prior the start of treatment are most plentiful providing a bountiful garden of remodeling sites packed with osteoblasts ready to be stimulated by endogenous PTH. Subsequently, although remodeling begins again in the month prior the need for the next treatment, the numbers of BMUs generated for the next rise in endogenous PTH following the second and subsequent injections is likely to be about half the number of BMUs prior treatment because remodeling does not return to its pretreatment level.

Is there a residual fracture risk reduction after stopping denosumab?

Roux et al reported that fracture risk during 2 years after stopping denosumab remained below that of the controls (14). In 470 placebo and 327 denosumab treated subjects from the FREEDOM trial who discontinued treatment after 2-5 doses, the authors report that fracture rates were below the previously placebo treated subjects. After treatment discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab; fracture rate/100



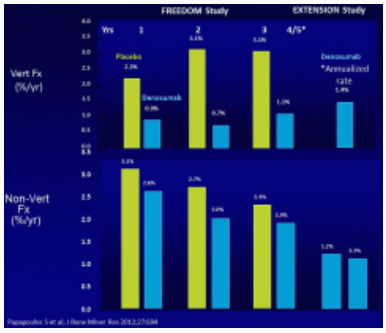
subject-years 13.5 and 9.7, respectively; HR 0.82; 95% CI 0.49, 1.38). (*Figure 4 on right*)

The question being addressed is important because denosumab has a rapid offset of action. Remodeling markers rise rapidly and may over shoot, so the question is whether this recurrence of remodeling creates stress concentrators – resorption cavities that concentrate stress, like cutting a test tube to make it easier to snap.

The data is difficult to interpret because initiation of therapy, usually bisphosphonates, occurred in both groups after stopping denosumab; in 42% placebo vs. 28% denosumab treated subjects. As there were more placebo treated subjects receiving a new therapy, the nonsignificant lower risk of fracture in the denosumab group may be underestimated; had the control group not been treated, their fracture rate would have been higher. There is no easy solution to this dilemma; analysis excluding patients treated with an alternative agent should be done but this will reduce the sample size, so there will be little power to detect any true residual benefit that remains after stopping denosumab, or, indeed, any increased risk over the control group that might be associated with the overshoot in remodeling after stopping denosumab if one truly exists.

Is long-term denosumab efficacious and safe?

Papapoulos et al reported the results of 6 years of denosumab exposure (15). Women from the FREEDOM placebo group received 3 years of denosumab and women from the denosumab group received 3 more years of denosumab. 4550 (77%) enrolled (N=2207 crossover; N=2343 long-term). In the long-term group, further increases in BMD occurred producing 6-year gains of 15.2% at the lumbar spine and 7.5% at the total hip. In the crossover group, yearly incidences of nonvertebral, new vertebral, clinical vertebral, and clinical fractures were lower than those in the FREEDOM placebo group. Fracture incidence remained low in the long-term group. Incidences of adverse events did not increase. (*Figure 5 on right*)

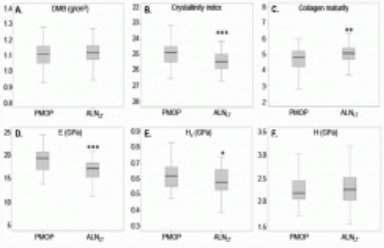


The incidence of fractures was low in the latter years, but the question is whether this is attributable to the treatment. There was no control group. It therefore remains possible that there was loss of high risk individuals and the remaining cohort were healthier individuals who would not have had a fracture without treatment. Note, in the first three years of treatment, the incidence in controls decreased year by year, so this potential bias introduced by sampling cannot be ignored. It is unethical to withhold treatment from individuals at high risk for fracture in clinical trials and so continuing a placebo arm cannot be justified. Thus, the challenge of whether antifracture efficacy is maintained after 3 years is not easily addressed.

Alendronate

Does alendronate modify primary mineralization?

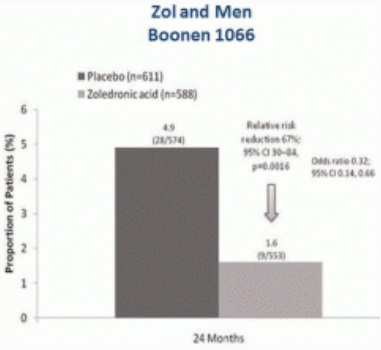
Prolonged suppression of bone remodeling may modify the material composition of bone because osteons that normally would be remodeled and replaced with younger bone are not. They undergo more complete secondary mineralization to become homogeneously mineralized and this reduces the resistance to crack propagation (16). Other changes in material properties may occur and to examine these, **Bala et al** evaluated 150 osteons from iliac cortical bone structural units (BSU) in 6 postmenopausal osteoporotic women treated for ~8 years with alendronate and 5 age-matched controls (17). Cases had a 12% lower elasticity (E) and 6% lower contact hardness (Hc) and higher collagen maturity. Crystallinity index, which is inversely proportional to crystal size/perfection, was higher in alendronate than in controls (25.29±0.76 vs. 24.78±0.70), and inversely correlated with E and Hc (r=–0.43 and r=–0.54, respectively). Collagen maturity correlated with E and Hc in the two groups (r ranged from 0.40-0.70, all p<0.001). Treated bone was also less able to plastically resist deformation at constant strain. Alendronate may alter the mineral crystallinity and impair the mechanical behavior at the BSU level. These are small changes, how they affect whole bone strength remains to be determined; but bilateral or unilateral spontaneous proximal femur fractures occurring in association with prolonged antiresorptive therapy is well documented and cannot be ignored as a potentially causal relationship. (*Figure 6 on right*)



Zoledronic Acid

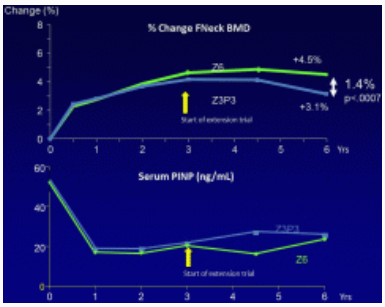
Does zoledronic acid reduce fracture risk in men?

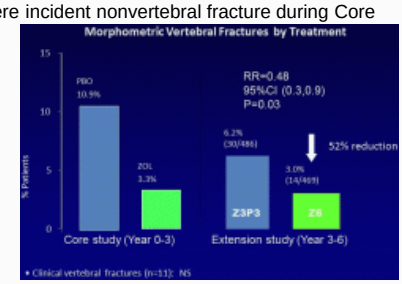
This is a nicely designed and executed study. It is one of the few, if not the only study convincingly showing a fracture benefit of treatment in men. **Boonen et al** report a randomized, controlled study in men with osteoporosis. Zoledronic acid reduced vertebral fracture risk by 67% over 24 months (*Figure 7 on right*). In the 1199-patient double-blind trial, men with osteoporosis aged 50-85 years were randomly assigned to 5 mg (n=588) or placebo (PBO; n=611) infusion at baseline and 12 months (18). Serum testosterone was available in 96% of men. Of these, 146 (26%) zoledronic acid treated and 181 (31%) placebo treated men had total testosterone ≤350 ng/dL. Zoledronic acid reduced the risk of morphometric vertebral fracture by 62% in men with TT >350 ng/dL (p<0.03), and by 72% in those with TT ≤350 ng/dL (p<0.08). The effects on nonvertebral fractures was not reported, presumably this was not significant.



Evidence for sustained fracture risk reduction

Eastell et al report that in the extension of the HORIZON trial, 1233 women who received 3 infusions had 3 additional infusions of zoledronic acid (Z6, n=616) or 3 placebo infusions (Z3P3, n=617) (19). Predictors of new morphometric fracture were a femoral neck and total hip T-score of ≤–2.5 SD and an incident morphometric vertebral fracture during the core trial which were each variously associated with an OR of 3-5 for subsequent morphometric vertebral fracture. For new nonvertebral fracture occurrence, predictors were incident nonvertebral fracture during Core



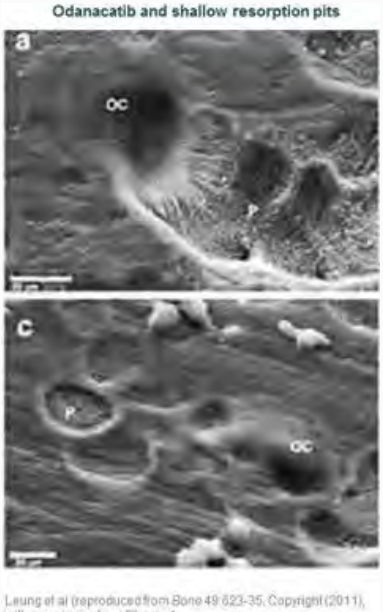


[HR=2.5(1.2,5.3)] and prevalent vertebral fracture [HR=3.0(1.4,6.3)] (*Figures 8, 9 on right*). The authors suggest that in women with hip BMD ≥–2.5 SD, the risk for fracture is low and treatment discontinuation can be considered. In women with hip BMD T-score<–2.5 SD, continued treatment was interpreted to confer benefit against vertebral fracture.

Cathepsin K Inhibitors

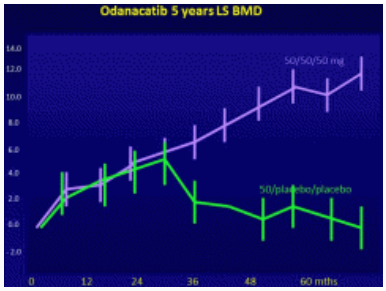
Does odanacatib continue to increase bone density during 5 years therapy?

Odanacatib is a cathepsin K inhibitor that is being assessed in an antifracture efficacy trial at this time and the results are awaited with great anticipation; new treatments are needed in the field as implied in the introduction to this issue of *Progress in Osteoporosis*. The drug reduces bone resorption by osteoclasts producing more shallow resorption cavities (20). This is an interesting observation for many reasons. If the depth of resorption of each pit is smaller and the resorption pit is refilled with the same or more osteoid, then treatment may reduce the negative bone balance. This is important. The negative bone balance is the necessary and sufficient morphological basis of bone loss in osteoporosis; it is the cause of structural decay and a critical target for its prevention (*Figure 10 on right*). If the balance is shifted to be positive, i.e., more bone is deposited in a smaller cavity reconstruction of bone may follow – in this case, it is desirable for bone remodeling intensity to continue to be high, as each remodeling event will deposit a small moiety of bone.



Leung et al (reproduced from Bone 49 823-35, Copyright (2011), with permission from Elsevier)

Resch et al report that women entering the year 4-5 extension, after 5 years, mean BMD changes for women who received odanacatib 50 mg continuously were: spine 11.9%, femoral neck 9.8%, trochanter 10.9%, total hip 8.5%, and 1/3 radius -1.0% (21). For women who switched from 50 mg to placebo after 2 years, changes were: lumbar spine -0.4%, femoral neck -1.6%, trochanter -1.0%, total hip -1.8%, and 1/3 radius



-4.7%. After 5 years, for women continuously receiving 50 mg, mean changes from baseline in remodeling markers were: -67.4% for urine NTX/creatinine and -15.3% for serum BSAP. For women who switched from 50 mg to placebo after 2 years these changes were 6.0% and -11.9%, respectively. (*Figure 11 on right*)

The question is what is the morphological basis for the continued rise in BMD? Could this be an anabolic effect – i.e., deposition of new bone (not just refilling of the remodeling space transient). Does this treatment result in deposition of osteoid, producing by a positive balance by each BMU? Another possibility is periosteal apposition. Studies in monkeys suggest periosteal apposition occurs with this agent (22). If so, is it sufficient to alter bone morphology – i.e., increase total bone CSA, and so increase resistance to bending?

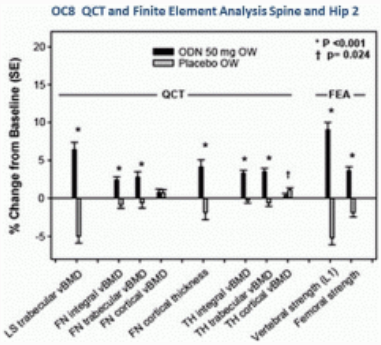
Yet another possibility that must not be dismissed is that this is a rise in BMD, not an increase in bone mass at all. Noninvasive imaging methods such as DXA and CT scanning do not measure mass, they measure the attenuation of photons produced by mineral. If the same bone mass or bone volume becomes more fully mineralized due to progression of secondary mineralization, the photon attenuation will increase and this is often spoken of as an increase in bone 'mass'. Neither the mass nor volume of bone has increased – this is a trap for young investigators unaware of the vagaries in language and the abuse of these vagaries that result.

Secondary mineralization is likely to contribute to the rise in BMD because remodeling is suppressed by this agent. A contribution by new bone formation has not been excluded and the studies in monkeys reporting periosteal apposition are of great interest. If remodeling intensity is not reduced as much as it is with the bisphosphonates, then each remodeling event will remove older more mineralized bone, so the extent of secondary mineralization should be less with this class of drug than with bisphosphonates. On the other hand, if remodeling continues and the negative bone balance persists, then each remodeling event will remove bone, even though more slowly than before treatment, and so structural decay will continue but slowly.

If resorption depth is reduced, then the size of the hemiosteon upon a trabecular surface or endocortical surface or the diameter of an osteon within cortical bone will be less; i.e., there will be more interstitial bone between the osteons – unless the continued remodeling at a lower rate maintains osteonal numbers. The osteons will be smaller but there will be more of them if remodeling intensity is not slowed so the net effect is the proportion of the cortical bone that is osteonal remains unchanged. The relevance of this is in microdamage accumulation which occurs more commonly in interstitial bone (bone between osteons). If remodeling is slowed and the osteons are small, then the interstitial bone increases in absolute and relative terms. This may have adverse effects on the material composition of bone.

Does odanacatib modify bone structure?

Odanacatib has been reported to increase periosteal bone formation and cortical thickness in nonhuman primates (22). **Brixen et al** used QCT to examine the effects of odanacatib on trabecular and cortical bone in a randomized, double-blind, 2-year trial of 214 postmenopausal women with low aBMD who received odanacatib 50 mg or placebo weekly (23). Compared with the placebo-treated women, odanacatib treated women had greater increases in integral and trabecular spine vBMD and compressive strength (estimated using FEA), and integral and hip trabecular vBMD and sideways-fall strength at the hip. Femoral neck cortical thickness increased with odanacatib but declined with placebo. Serum CTX was lower in the odanacatib group than placebo (-43% vs. 3%) but serum P1NP did not differ (ODN -11%, placebo -2%). (*Figure 12 on right*)



The authors suggest cortical thickness increased, but for this to occur, periosteal apposition and/or endocortical apposition must be documented. There was no evidence provided for either in this study. The way cortical thickness is calculated should be considered. This is a derived value obtained by dividing cortical area by perimeter. There is no such thing as a single cortical 'thickness', the thicknesses of the cortex vary at each point around a perimeter of a tubular bone and at each cross-section along its length. The information needed here is what were the periosteal and endocortical circumferences, and cortical area. In addition, what does an increase in cortical 'density' mean in morphological terms – did cortical porosity decrease, and/or did tissue mineralization density increase? The increase in cortical density by either mechanism may alter edge detection producing a seeming increase in cortical thickness.

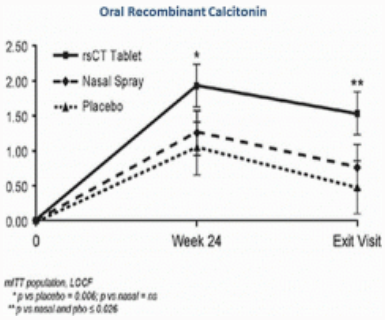
Does ONO-5334 modify bone structure?

This is another well investigated cathepsin K inhibitor that shows promise. **Engelke et al** randomized postmenopausal women with osteoporosis or osteopenia (with a vertebral fracture) to ONO-5334 (50 mg b.d, 100 or 300 mg qd), placebo or alendronate 70 mg qw double-blind study using QCT (24). Of about 120 women with follow-up scans at 2 years, in the spine, all ONO-5334 doses showed similar changes in trabecular BMD but cortical changes favored 300 mg qd. In the femur, ONO-5334 300 mg qd produced higher BMD increase than other doses, particularly for trabecular BMD. Compared to alendronate, ONO-5334 50 mg bd and 300 mg qd appeared to

show equivalent increases in integral and cortical BMD and superior increases in trabecular BMD.

Calcitonin

Does oral recombinant calcitonin warrant a revisit?



Binkley et al reported a randomized, double-blind, double-dummy, active- and placebo-controlled, multiple-dose, phase III study to assess the efficacy and safety of oral recombinant calcitonin in 565 postmenopausal women (25). Patients were randomized (4:3:2) to oral recombinant salmon calcitonin (rsCT) (0.2 mg/day), synthetic salmon calcitonin (ssCT) nasal spray (200 IU/day) or placebo for 48 weeks. rsCT increased spine BMD (1.5±3.2%); greater than ssCT nasal spray (0.78±2.9%) or placebo (0.5±3.2%) (*Figure 13 on right*). Changes in spine BMD in those receiving nasal calcitonin did not differ from placebo. Oral rsCT also resulted in greater improvements in trochanteric and total proximal femur BMD than ssCT nasal spray. Reductions in resorption markers with oral rsCT were greater than those observed in ssCT nasal spray or placebo. Gastrointestinal adverse events were reported by nearly half of women and were the principle reason for premature withdrawals. Oral rsCT was superior to nasal ssCT and placebo for increasing BMD and reducing bone turnover. Oral rsCT was safe and as well tolerated as ssCT nasal spray or placebo. These modest changes are hard to interpret and given the null results of the PROOF trial (except for one of the arms), without evidence of benefits in structure and strength, what is the lesson?

Agents With Other Modes of Action

Strontium Ranelate

Does strontium ranelate increase bone mass in women and in men?

The operative word is 'mass'. **Felsenberg et al** report that in 189 women randomized to strontium ranelate (SR) (2 g/day) or alendronate (70 mg/week) during 2 years (26), ultradistal tibia total bone mineral content (BMC) increased by 3.3% and trabecular BMC increased by 2.3% in SR group and by 1.7% and 1.3%, respectively, in ALN group. The moment of inertia (MI) and density-weighted MI increased by 1.2±1.6% and 1.7±2.1%, respectively, in the SR group and by 0.5±1.8% and 0.9±2.4%, respectively, in the ALN group. Mean increases of 0.7±1.8% for the section modulus and 1.3±2.4% for strength strain index (SSI) were found in the SR group, no change was observed in the ALN group. Between-group difference favored SR for each trait. The authors infer greater effects on bone mass and strength parameters at the tibia compared to ALN in women with postmenopausal osteoporosis after 2-year treatment.

These data need to be interpreted cautiously. The word bone 'mass' is abused in this field. Osteoid is deposited by osteoblasts and when it is mineralized it is 'bone' or 'bone mass'. When strontium is deposited in bone by substitution for a calcium atom, the attenuation of photons is increased, so there is an increase in what we refer to as the apparent BMD. The same occurs with antiresorptive agents. When these are administered, remodeling intensity decreases and osteons that would have been removed are not. They undergo more complete secondary mineralization – the bone mass or volume do not increase, the mass or volume is more fully mineralized so the apparent density increases. Neither agent makes new bone – there is no evidence that these agents are anabolic. The estimates of bone strength are not direct measurements of bone strength – peak tolerated loads, resistance to bending or torsion, they are mathematically derived estimates that use the apparent density in the formulae.

Does strontium ranelate increase bone mineral density in men?

Yes. *Kaufman et al* reported the results of a 2-year randomized double-blind placebo-controlled trial (SR 2 g/day/placebo 2:1) in 261 men (27). The ITT population consisted of 243 men, age 72.7±5.7 years with lumbar and femoral neck BMD T-Score of -2.7±1.0 and -2.3±0.7, respectively; 29% of patients had prevalent vertebral fractures. BMD increased in the SR group: lumbar (L2-L4) by 9.8±1.1%; femoral neck by 3.3±0.9% and total hip by 3.7±0.8% (all $p<0.001$). An improvement in the quality of life was observed (-0.34±0.7 in the SR group vs. -0.07±0.5 in the placebo group ($p=0.009$). Vertebral fracture incidence was lower in the SR than in the placebo group but not significantly so (5.8% vs. 7.8%). The same was observed for clinical nonvertebral fractures recorded as adverse events (3.5% vs. 4.6%).

Does strontium ranelate protect against fatigue damage?

Strontium ranelate has been demonstrated to reduce the risk of vertebral and non-vertebral fractures in well designed and executed trials. The question is how. **Ammann and Rizzoli** report SR influences bone microarchitecture and intrinsic bone tissue properties which independently improve estimates of bone strength. The authors suggest that the changes may prevent the formation of microcracks and/or their propagation (28). Vertebrae of intact female rats treated over 8 weeks with SR at 625 mg/kg or with a vehicle were cyclically loaded in axial compression for 100 cycles. The selected peak load corresponded to 5% of the adjacent vertebra maximal load (domain of elastic deformation). The vertebrae were then loaded to failure. Maximal load was 267±19 and 233±20 N in unloaded SR and control groups, respectively. Cyclic loading induced a deterioration of post yield load in control rats (19.81±3.38 vs. 11.80±2.03 N in unloaded vs. fatigue control groups, respectively, $p<0.05$). This was prevented in SR treated rats (18.42±4.00 vs. 18.78±3.71 N in unloaded vs. fatigue SR groups, respectively). The post yield

deflection was unaffected in either group. This suggests less damage accumulation under fatigue loading.

Is strontium ranelate safe?

Clinical trials are designed to assess efficacy, not safety and so post marketing data is needed to evaluate safety. **Jakob et al** report the results of an observational cohort study to assess safety and treatment persistence with SR during 3 years follow-up in 12,702 postmenopausal women from 7 countries (29). Mean age was 69.0 years with 16.5% of patients being over 80 years. Mean follow-up duration was 32 months and mean treatment duration was 25.2 months (24,956 patient-years of treatment). VTE was reported in 55 patients, an incidence of 2.1/1000 patient-years (95% CI 1.6, 2.8), lower than that observed in patients treated with SR in the phase III studies (7.9/1000 patient-years; 95% CI 6.3, 9.7). No DRESS syndrome or Stevens-Johnson syndrome was reported. Persistence of SR treatment was 80%, 68% and 64% after 12, 24 and 32 months treatment, respectively.

Anabolic Agents

Does antisclerostin antibody reduce fractures in rodent models of osteogenesis imperfecta (OI)?

Yes. **Devogelaer et al** report that Scl-Ab improved biomechanical properties and reduced fracture rates in OI mice. Seven-week-old OI and control (WT) mice received PBS or Scl-Ab (25 mg/kg twice weekly for 10 weeks (30). Scl-Ab reduced the number of fractures by 56% (2.8±0.6 vs. 6.3±1.5 in controls; $p<0.001$). In the tibia, ultimate strength increased (midshaft: +30%, proximal: +98% vs. controls), stiffness increased (midshaft: 132%; proximal: 88% vs. controls) and plastic energy increased (midshaft: 125%, proximal: 260% vs. controls). These strength increases were associated with increases in tibia BMD (midshaft: +30%, proximal: +50% vs. PBS) and cortical thickness (midshaft: +40%, proximal: +75% vs. PBS). Scl-Ab therapy also increased BMD and cortical thickness in the humerus and lumbar vertebra so that at the end of therapy, the strength, BMD and cortical thickness of bones of the OI skeleton were similar to WT. Scl-Ab therapy also enhanced the strength, BMD and cortical thickness in tibia, humerus and vertebra of WT normal mice.

Devogelaer et al also assessed the effects of Scl-Ab on fracture rates in axial skeleton of 5-7-week-old OI and WT mice (31). Scl-Ab reduced pelvic fractures by 65% (0.4±0.5 per mouse vs. 1.1±0.8 in PBS; $p<0.02$) and improved LVB trabecular bone parameters including: BMD (55%), BV/TV (111%), TbTh (40%), TbN (48%) and TbPf (-43%). In WT, Scl-Ab was also associated with improvements in BV/TV (160%), TbTh (33%), TbN (96%) and TbPf (-94%). Scl-Ab therapy decreased SMI in WT mice, but not in OI mice.

Does PTH(1-84) accelerate pelvic fracture healing?

Holzer et al report that in 65 patients with pelvic fractures, 21 received once daily 100 µg PTH(1-84) within two days of admission, 44 patients without PTH treatment served as a control group (32). Functional outcome was assessed using a pain Visual Analogue Scale (VAS) and a Timed Up and Go (TUG) test. In all 21 patients treated with PTH(1-84) pelvic fractures healed at a mean of 7.8 weeks, whereas in patients with no PTH treatment fractures healed after 12.6 weeks. At week 8 all fractures in the treatment group were healed and four fractures in the control group (healing rate 100% vs. 9.1%; ($p<0.001$). Both the VAS and TUG improved ($p<0.001$) compared to control. PTH(1-84) accelerates fracture healing in pelvic fractures and improves functional outcome.

Is an analog of human PTHrP anabolic?

Hattersley et al report that BA058, a synthetic analog of hPTHrP(1-34), was assessed in randomized, double-blind, placebo-controlled phase II study of postmenopausal women with osteoporosis randomized to placebo, BA058 20, 40, 80 µg or teriparatide 20 µg for 24 weeks (33). 184 patients completed 6 months treatment. The spine BMD was 1.6% with placebo, 2.9%, 5.2%, and 6.7% with BA058 20, 40 and 80 µg, respectively, and 5.5% with teriparatide. The difference from placebo was significant for BA058 40 and 80 µg and for teriparatide. Further increases in spine BMD were seen during the extension phase (n=55), with a mean percent change at 48 weeks of 0.7% with placebo, 5.1%, 9.8%, 12.9% with BA058 20, 40 and 80 µg, respectively, and 8.6% with teriparatide. A dose dependent increase in total hip BMD was seen at 24 weeks; the mean change was 0.4% with placebo, 1.4%, 2.0%, and 2.6% with BA058 20, 40, and 80 µg, respectively, and 0.5% with teriparatide. At 24 weeks the change in serum and urine markers was significant from baseline for BA058 40 and 80 µg and for teriparatide for P1NP, BSAP, osteocalcin and CTX, and with teriparatide for NTX. BA058 was well tolerated. The proportion of patients with elevated calcium levels was lower with BA058 than with teriparatide. BA058 80 µg resulted in significant BMD gains.

References

1. Delmas PD. Treatment of postmenopausal Osteoporosis. Lancet 2002;3589:2018.

2. Kanis JA, Alexandre JM, Bone HG, et al. Study design in osteoporosis: a European perspective. J Bone Miner Res 2003;18:1133.

3. Kanis JA, Borgstrom F, Zethraeus N, et al. Intervention thresholds for osteoporosis in the UK. Bone 2005;36:22.

4. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet 2010;375:1729.

5. Schaffler MB and Burr DB. Stiffness of compact bone: effects of porosity and density. Biomechanics 1988;21:13.

6. McClung MR, Geusens P, Miller PD, et al. Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001;344:333.

7. Seeman E, Vellas B, Benhamou C, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res 2006;21:1113.

8. Chen JS, Sambrook PN. Antiresorptive therapies for osteoporosis: a clinical overview. Nat Rev Endocrinol 2012;8:81.

9. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799.

10. McClung MR, Lewiecki EM, Bolognese MA, et al. Denosumab continues to affect bone mineral density and biochemical markers of bone turnover for up to 8 years : results of a phase 2 extension trial. Osteoporos Int 2012;23(Suppl 2):S74.

11. Parfitt AM. Morphologic basis of bone mineral measurements: transient and steady-state effects of treatment in osteoporosis. Miner Electrolyte Metab 1980;4:273.

12. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821.

13. Seeman S, Libanati C, Austin M, et al. The transitory PTH increase following denosumab administration is associated with reduced intracortical porosity: a distinctive characteristic of denosumab therapy. Osteoporos Int 2012;23(Suppl 2):S76.

14. Roux C, Brown JP, Beck-Jensen JE, et al. Denosumab discontinuation and associated fracture risk : a FREEDOM trial analysis. Osteoporos Int 2012;23(Suppl 2):S105.

15. Papapoulos SE, Brown JP, Chapurlat R, et al. Denosumab treatment of postmenopausal women with osteoporosis for 6 years: results from the first 3 yearas of the FREEDOM extension. Osteoporos Int 2012;23(Suppl 2):S76.

16. Tai K, Dao M, Suresh S, Palazoglu A, Ortiz C. Nanoscale heterogeneity promotes energy dissipation in bone. Nat Mater 2007;6:454.

17. Bala Y, Depalle B, Douillard T, et al. Bone tissue micromechanical properties are altered independently of mineralization in osteoporotic women long-term treated alendronate. Osteoporos Int 2012;23(Suppl 2):S110.

18. Boonen S, Reginster JY, Kaufman JM, et al. Efficacy of one-yearly zoledronic acid 5 mg in men with osteoporosis with different levels of serm total testosterone. Osteoporos Int 2012;23(Suppl 2):S79.

19. Eastell R, Cosman F, Cauley JA, et al. After 3 years of annual zoledronic acid, who should remain on treatment? Results from the HORIZON-PFT extension. Osteoporos Int 2012;23(Suppl 2):S240.

20. Costa AG, Cusano NE, Silva BC, Cremers S, Bilezikian JP. Cathepsin K: its skeletal actions and role as a therapeutic target in osteoporosis. Nat Rev Rheumatol 2011;7:447.

21. Resch H, Binkley N, Bone H, et al. Treatment with the cathepsin K inhibitor odanacatib in postmenopausal women with low BMD: 5 year results of a phase 2 trial. Osteoporos Int 2012;23(Suppl 2):S61.

22. Cusick T, Chen CM, Pennypacker BL, et al. Odanacatib treatment increases hip bone mass and cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation in the ovariectomized adult rhesus monkey. J Bone Miner Res 2012;27:524.

23. Brixen K, Chapurlat R, Cheung AM, et al. Imaging and finite element analysis of the spine and hip following 2 years of treatment with odanacatib in postmenopausal women. Osteoporos Int 2012;23(Suppl 2):S62.

24. Engelke K, Nagasse S, Fuerst T, et al. Effects of the cathepsin K inhibitor, ONO-5334, on BMD as measured by 3D QCT in the hip and the spine after 2 years of treatment. Osteoporos Int 2012;23(Suppl 2):S62.

25. Binkley N, Bolognese M, Sidrowicz-Bialynicka A, et al. A phase 3 trial of the efficacy and safety of oral recombinant calcitonin: the ORALCAL trial. Osteoporos Int 2012;23(Suppl 2):S78.

26. Felsenberg D, Beller G, Fiore C, et al. Beneficial effects of strontium ranelate compared to alendronate on bone mass and strength parameters at the tibia in postmenopausal osteoporotic women: a 2-year study. Osteoporos Int 2012;23(Suppl 2):S113.

27. Kaufman JM, Audran M, Bianchi G, et al. Efficacy and safety of strontium ranelate in the treatment of male osteoporosis. Osteoporos Int 2012;23(Suppl 2):S260.

28. Ammann P, Rizzoli R. Strontium ranelate fully prevents alteration of bone mechanical properties in response to cyclical loading. Osteoporos Int 2012;23(Suppl 2):S73.

29. Jakob FJ, Palacios S, Audran M, et al. Final results of a 3 years prospective observational cohort study of patients treated with strontium ranelate. Osteoporos Int 2012;23(Suppl 2):S73.

30. Devogelaer JP, Behets C, Ammann P, et al. Sclerostin antibody increased bone mass and reduced fractures in osteogenesis imperfecta mice. Osteoporos Int 2012;23(Suppl 2):S74.

31. Devogelaer JP, Chappard D, Behets C, et al. Sclerostin neutralizing monoclonal antibody decreases significantly the number of pelvic fractures and improves markedly the size and interconnectivity of lumbar trabecular bone in oim/oim mice. Osteoporos Int 2012;23(Suppl 2):S209.

32. Holzer G, Peichl P, Holzer LA, Maier R. Parathyroid hormone 1-84 accelerates fracture healing in public bones of elderly osteoporotic women. Osteoporos Int 2012;23(Suppl 2):S77.

33. Hattersley G, Bilezikian JP, Guerriero J, et al. BA0258, a novel analog of human parathyroid hormone-related protein, exerts significant effects on BMD in postmenopausal women with osteoporosis. Osteoporos Int 2012;23(Suppl 2):S77.

Comments

n v osteoporosis

Submitted by dr.ranjan on Tue, 07/03/2012 - 06:15

dear sir, it article is immense informative to the health professionals.

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Subject

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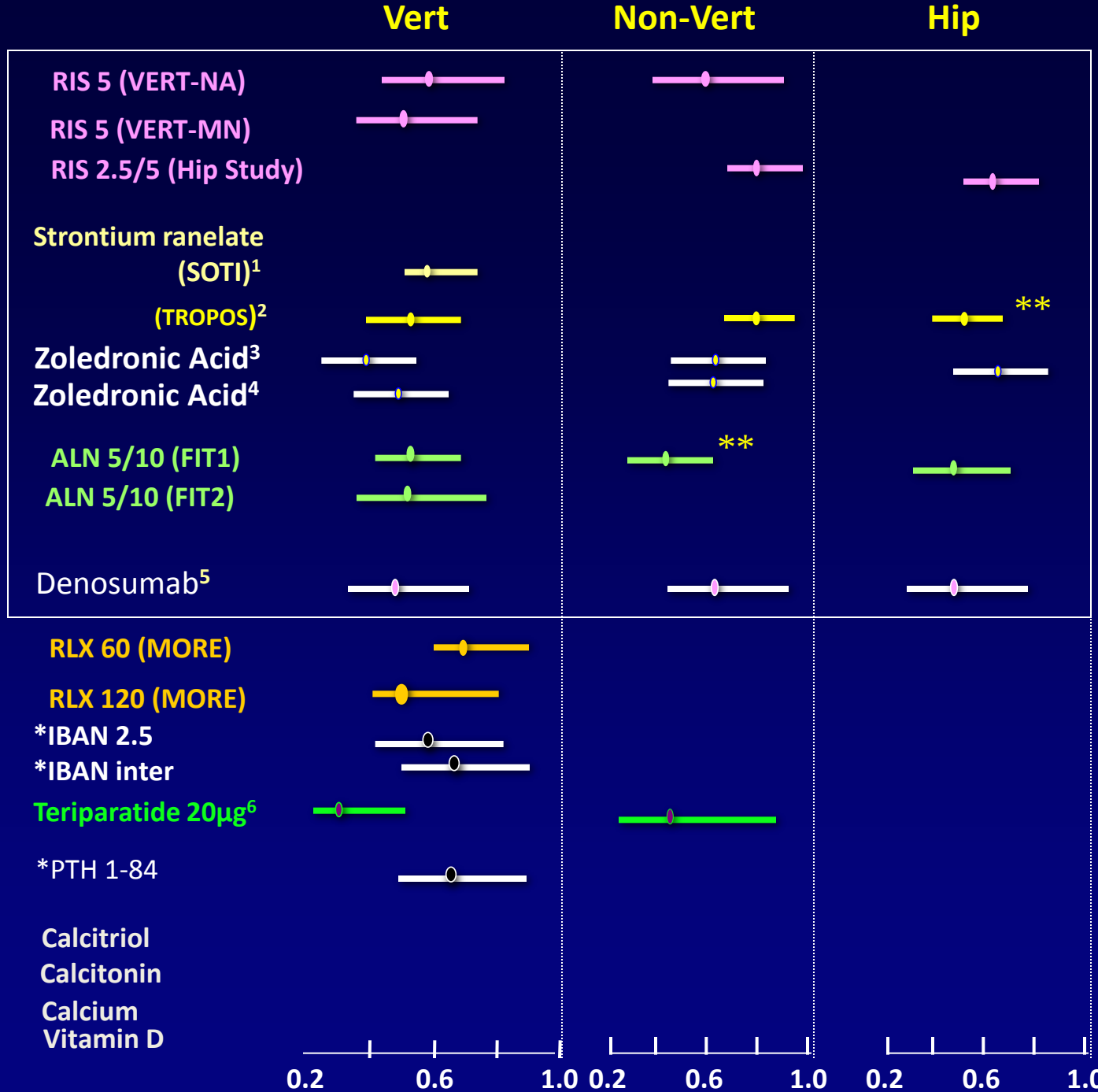


Avoid direct comparisons of efficacy as treatments are not tested in comparator trials

** Subgroup/*post hoc* analysis

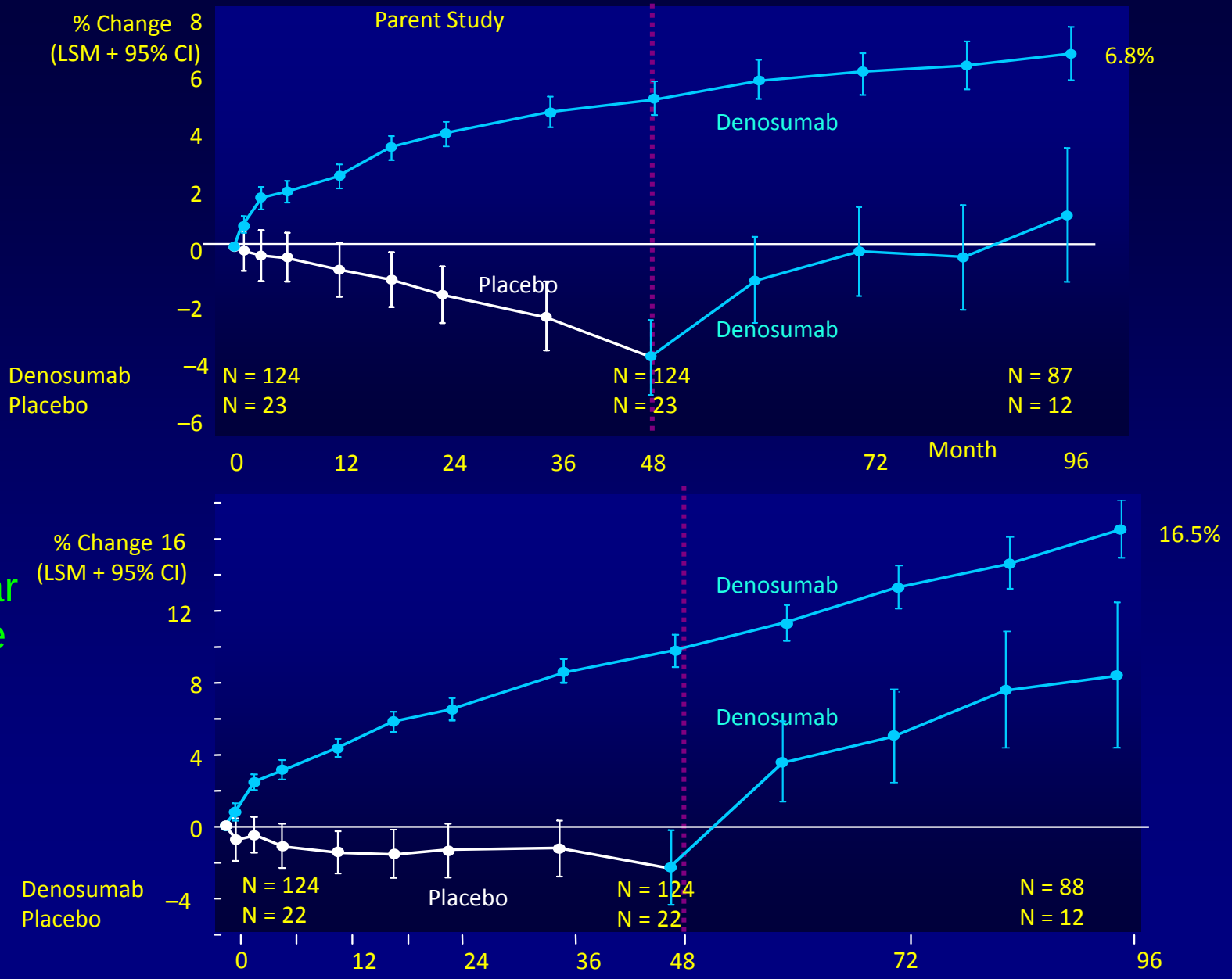
Adapted from:
Martin and Seeman. Clin Sci 2007; 112:77

1. Meunier et al. NEJM 2004; 50:459
2. Reginster et al. JCEM 2005; 90: 816
3. Black et al. NEJM 2007; 356:1809
4. Lyles et al. NEJM 2007; 357:1799
5. Cummings et al. NEJM 2009; 361:756
6. Neer et al. NEJM 2001; 344:1434

*Not available in Australia

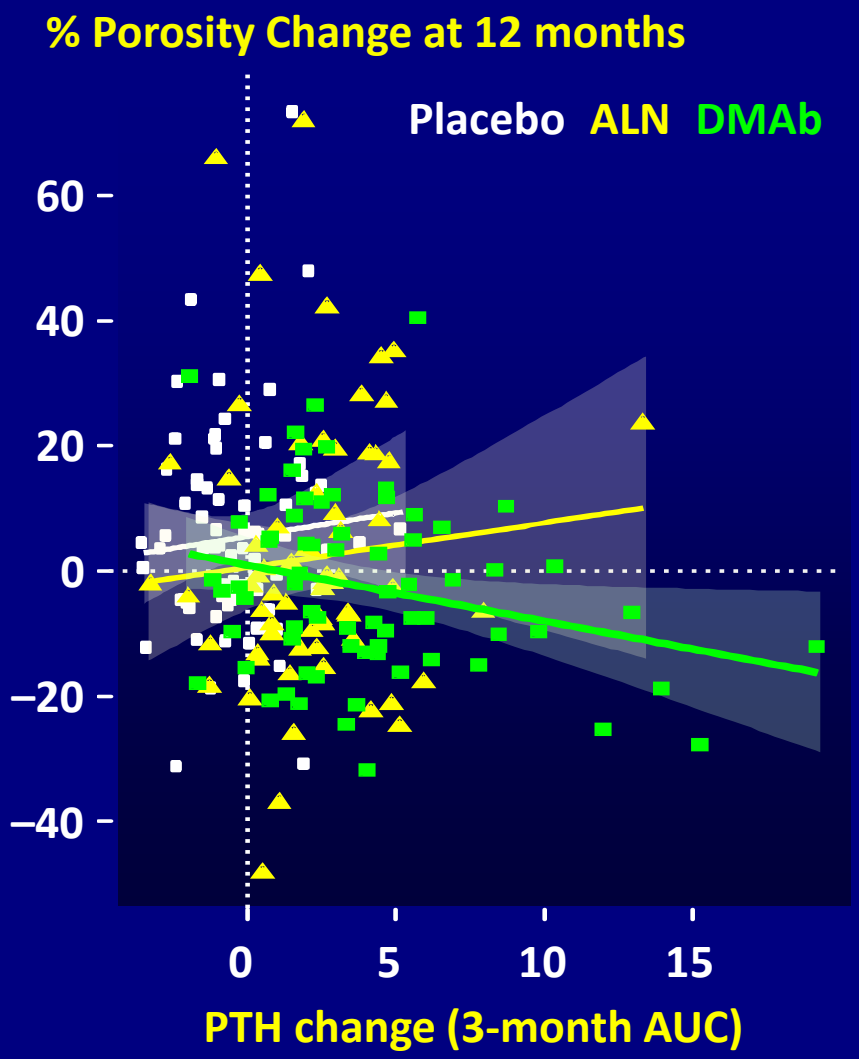
Phase II Extension: 8 years Denosumab (abstract)

Extension Study
All on Denosumab 60 mg Q6M

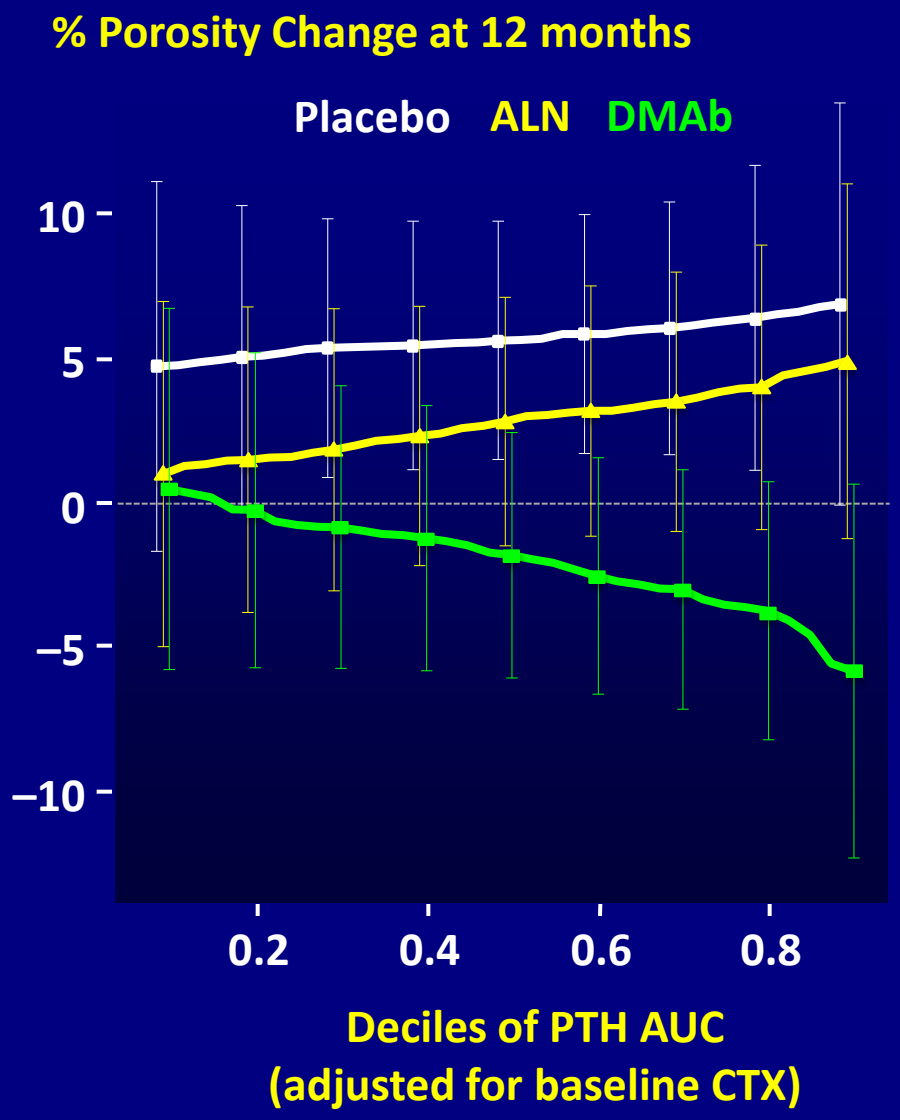


McClung MR et al. Abstract and Oral Presentation, ASBMR Annual Meeting. San Diego, USA 2011

Change in Cortical Porosity



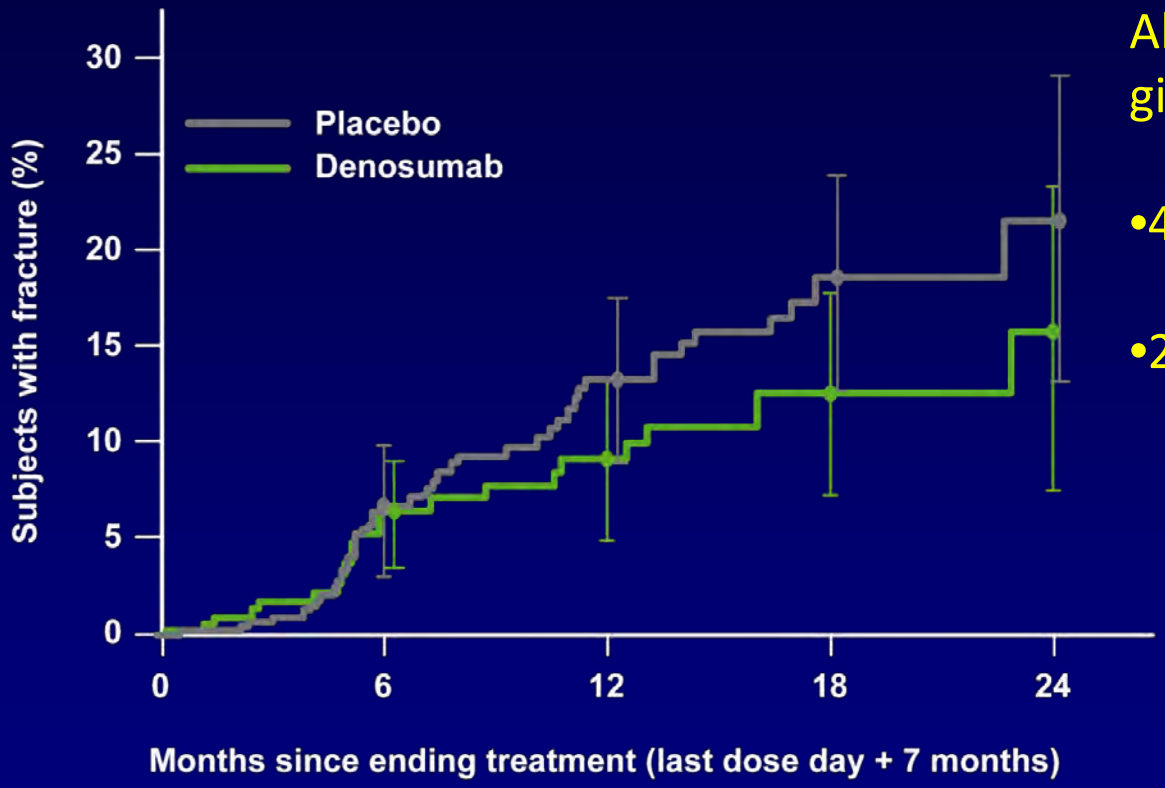
Scatter plot, regression lines and 95% confidence regions



Errors bars represent 95% CIs

Stopping Denosumab

FREEDOM - Time to first osteoporotic fracture during the off-treatment period *(abstract/poster, post hoc)*



Alternative therapies given in:

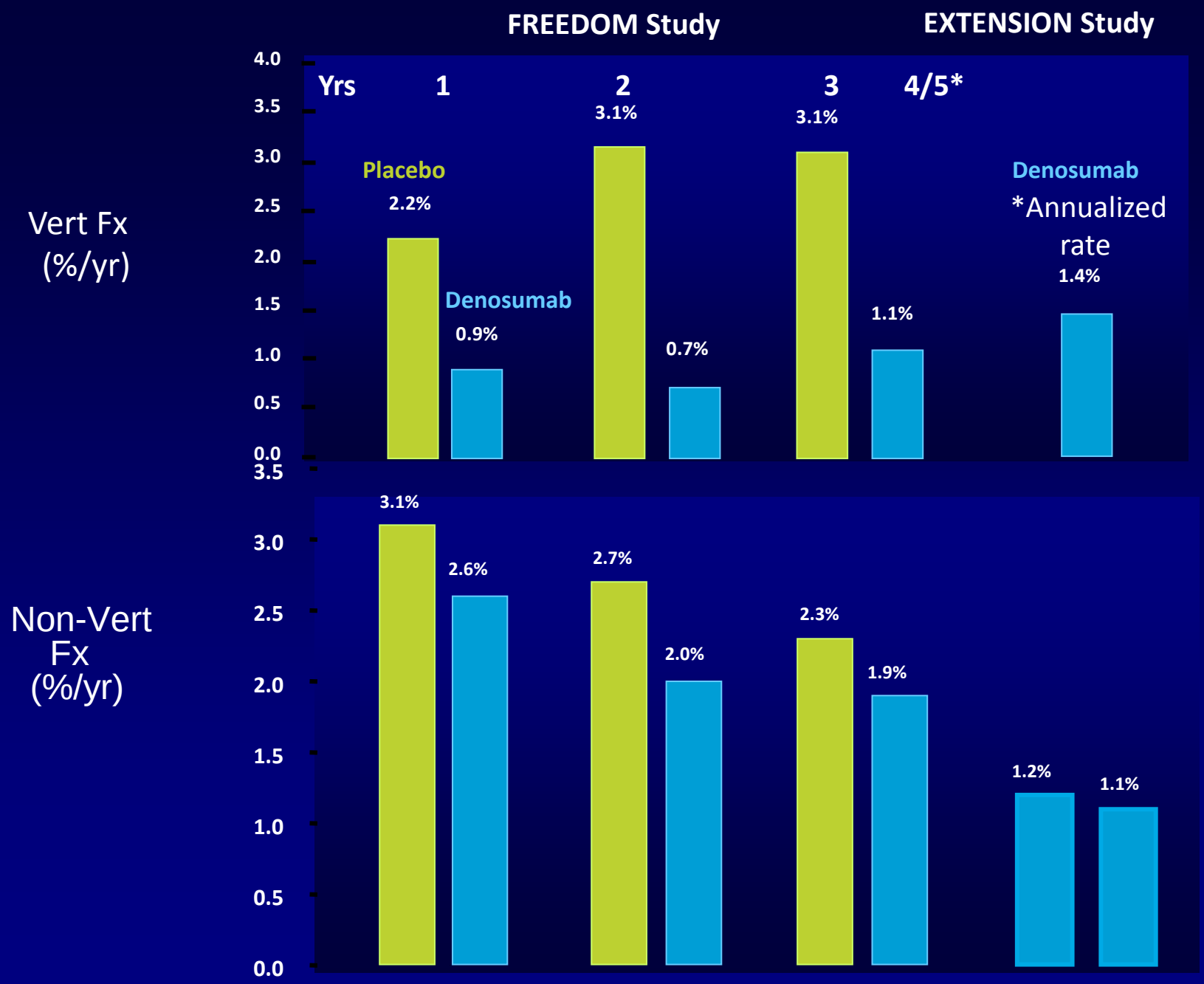
- 42% - Placebo
- 27% - Denosumab

Subjects at risk, N

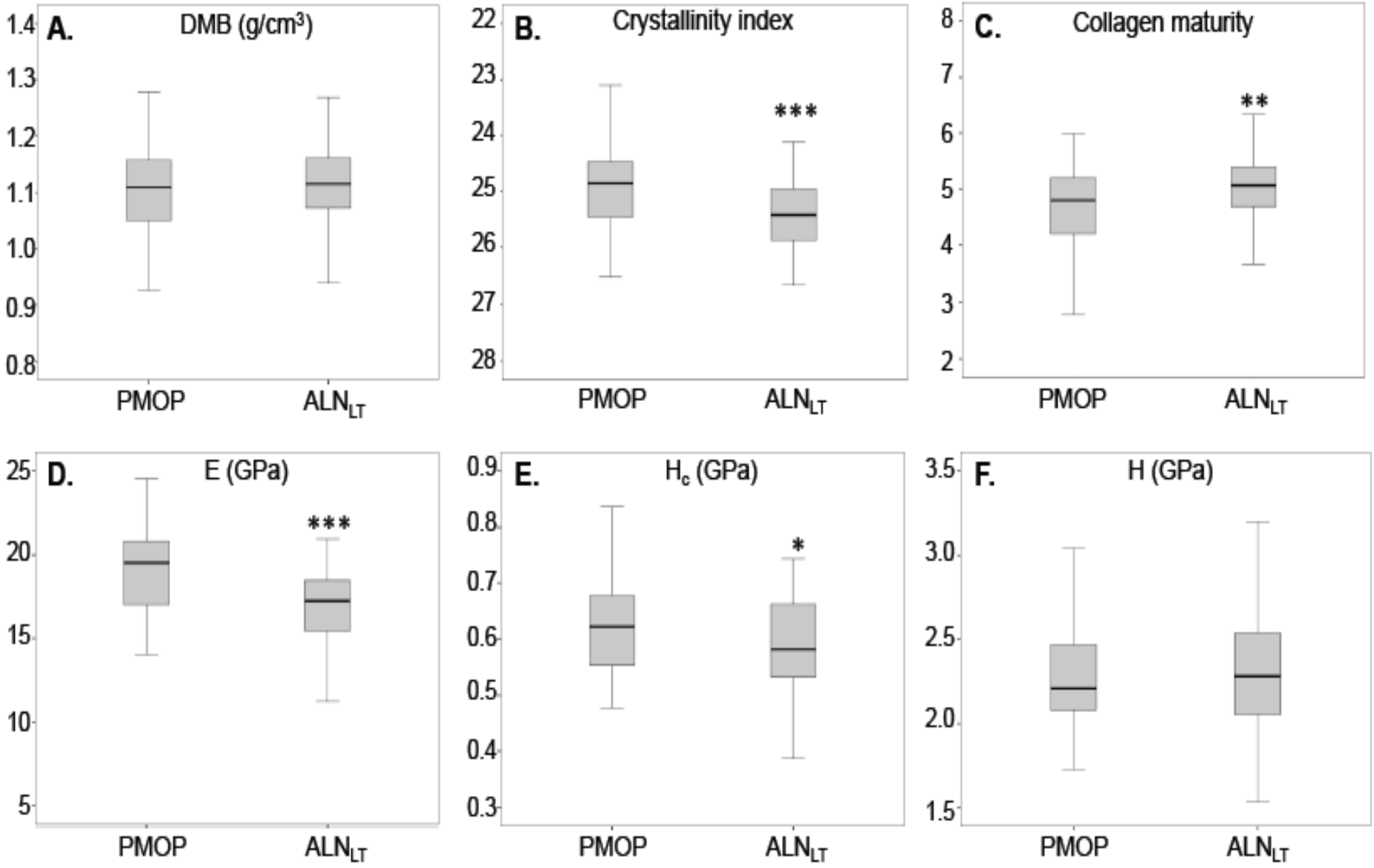
Placebo	470	227	148	51	2
Denosumab	327	154	108	57	1

N = number of subjects at risk. Error bars represent 95% confidence intervals.

Adapted from: Brown JP *et al. J Bone Miner Res* 26(Suppl 1):FR0446 and poster at ASBMR 2011, San Diego.



Papapoulos S et al, J Bone Miner Res 2012;27:694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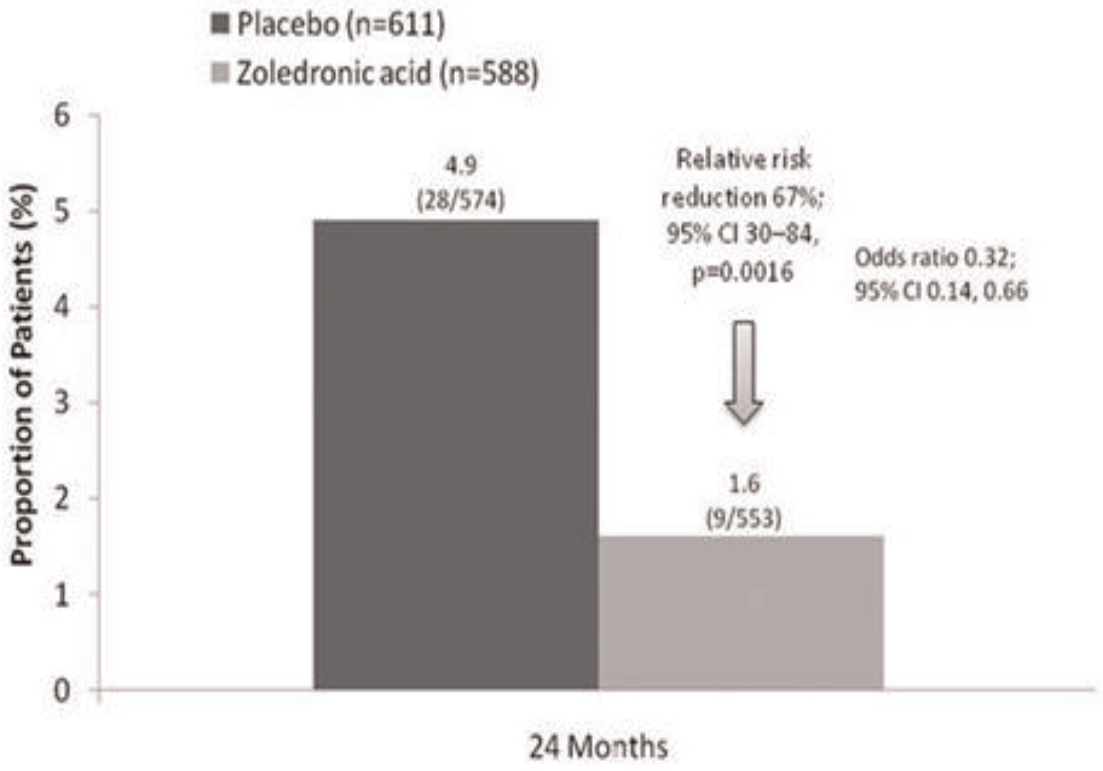

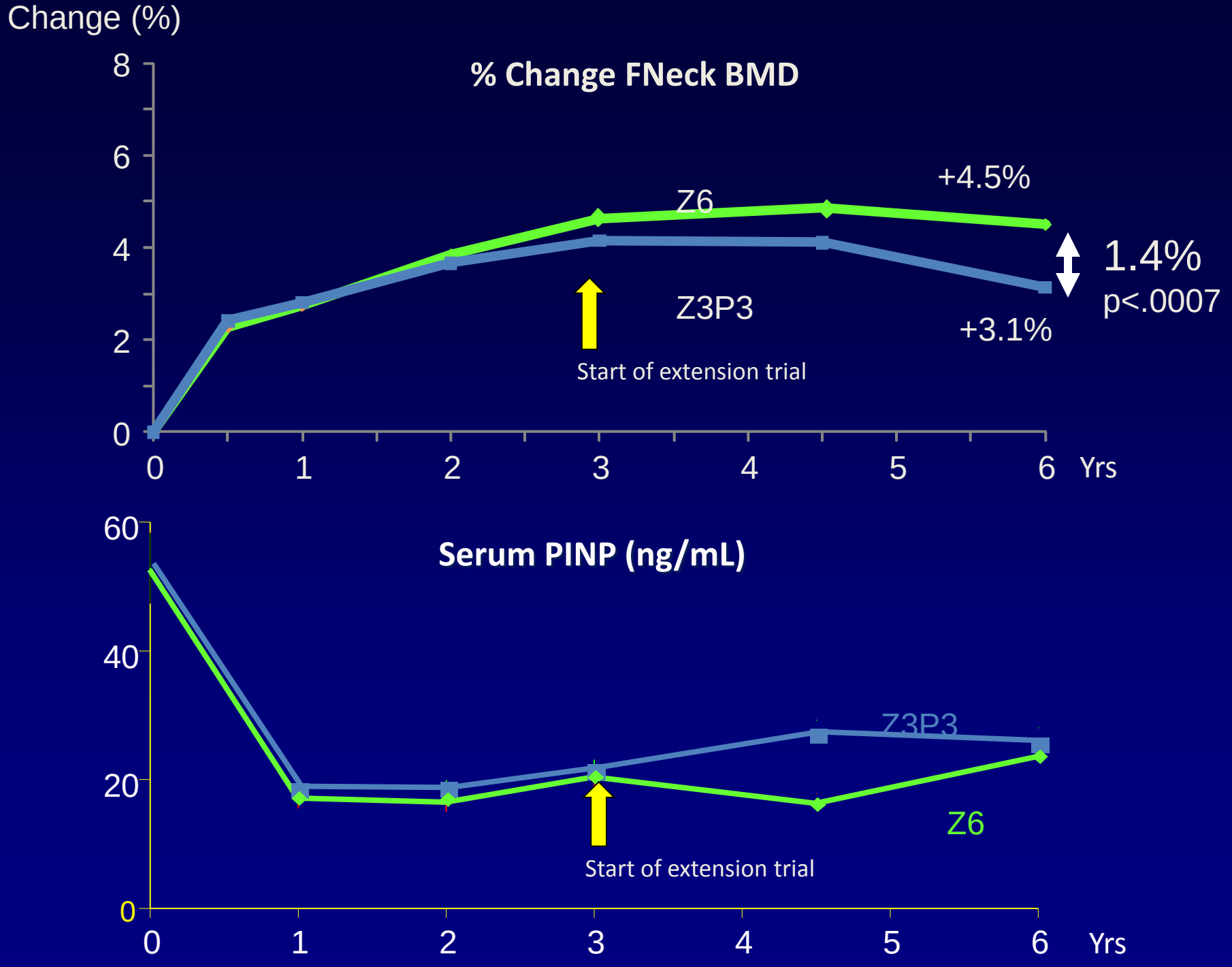
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Serum PINP (ng/mL)
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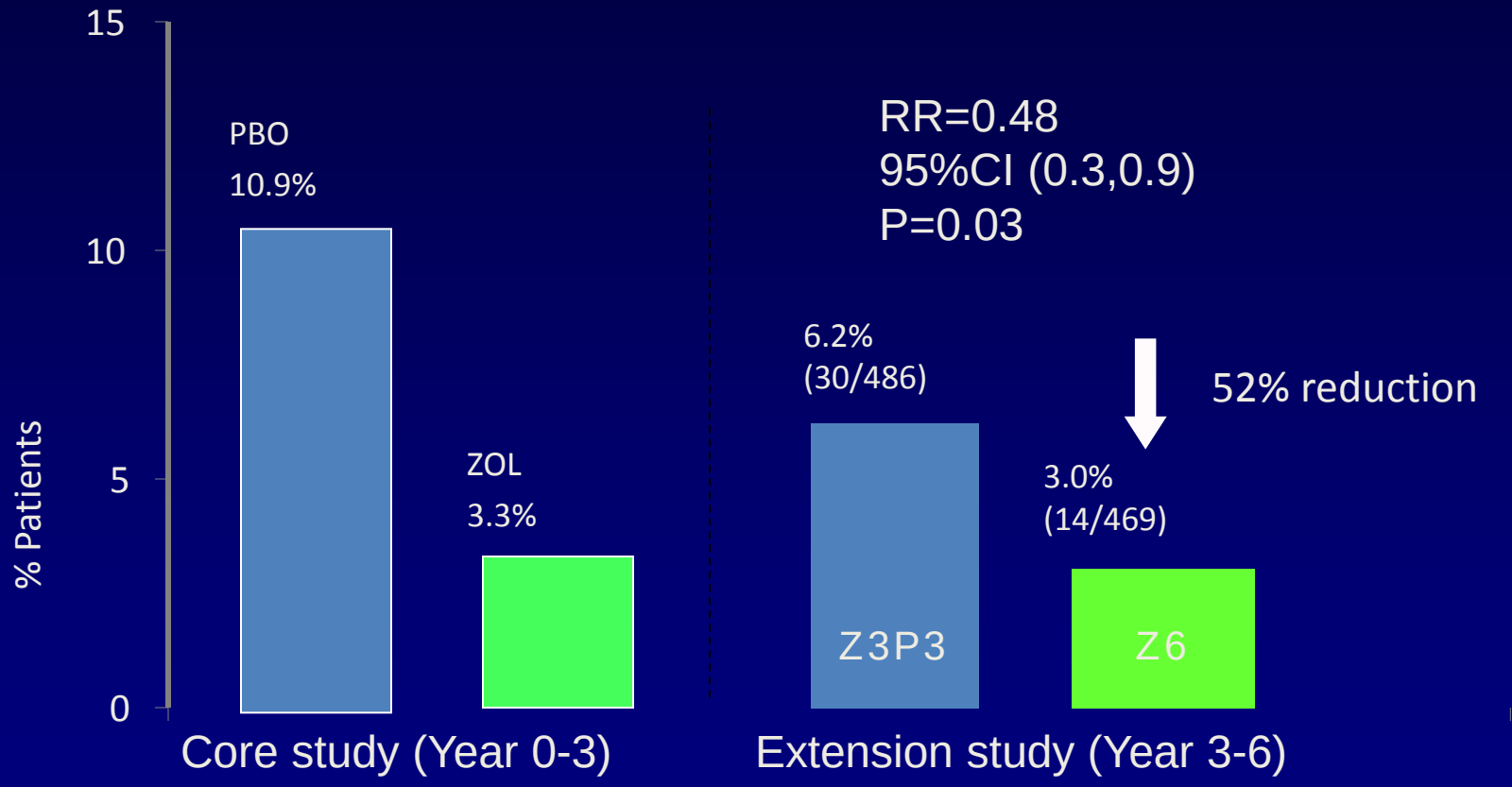
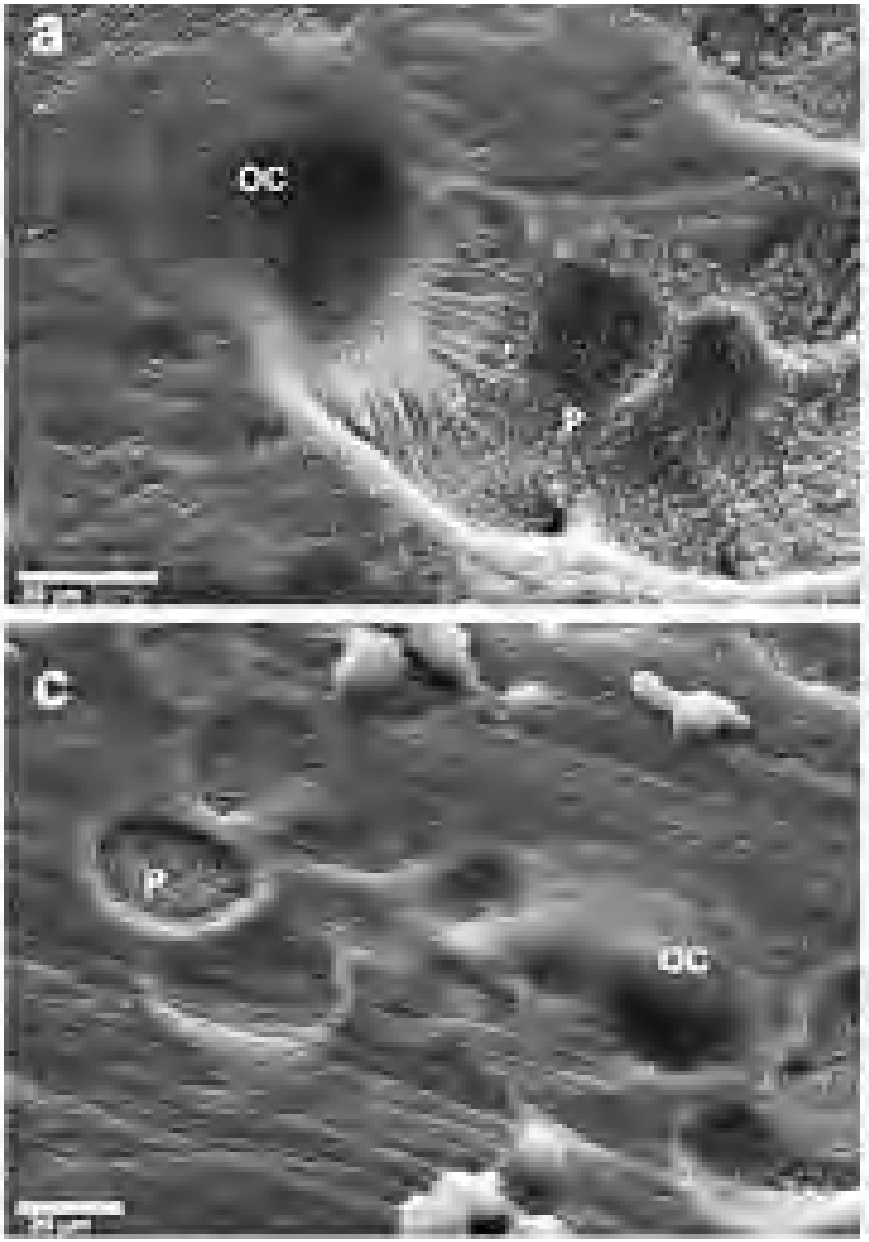
Morphometric Vertebral Fractures by Treatment



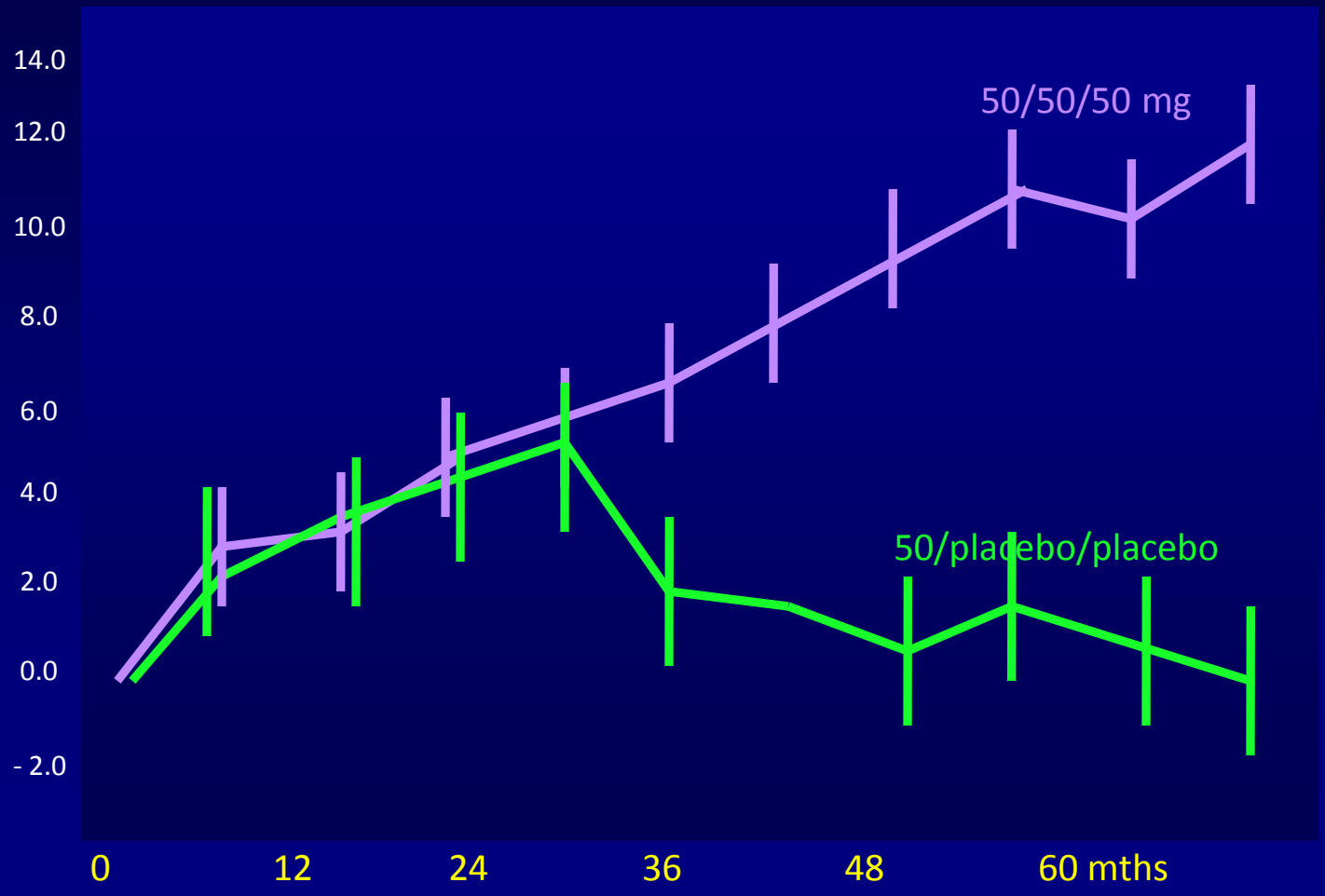
- Clinical vertebral fractures (n=11): NS

Odanacatib and shallow resorption pits

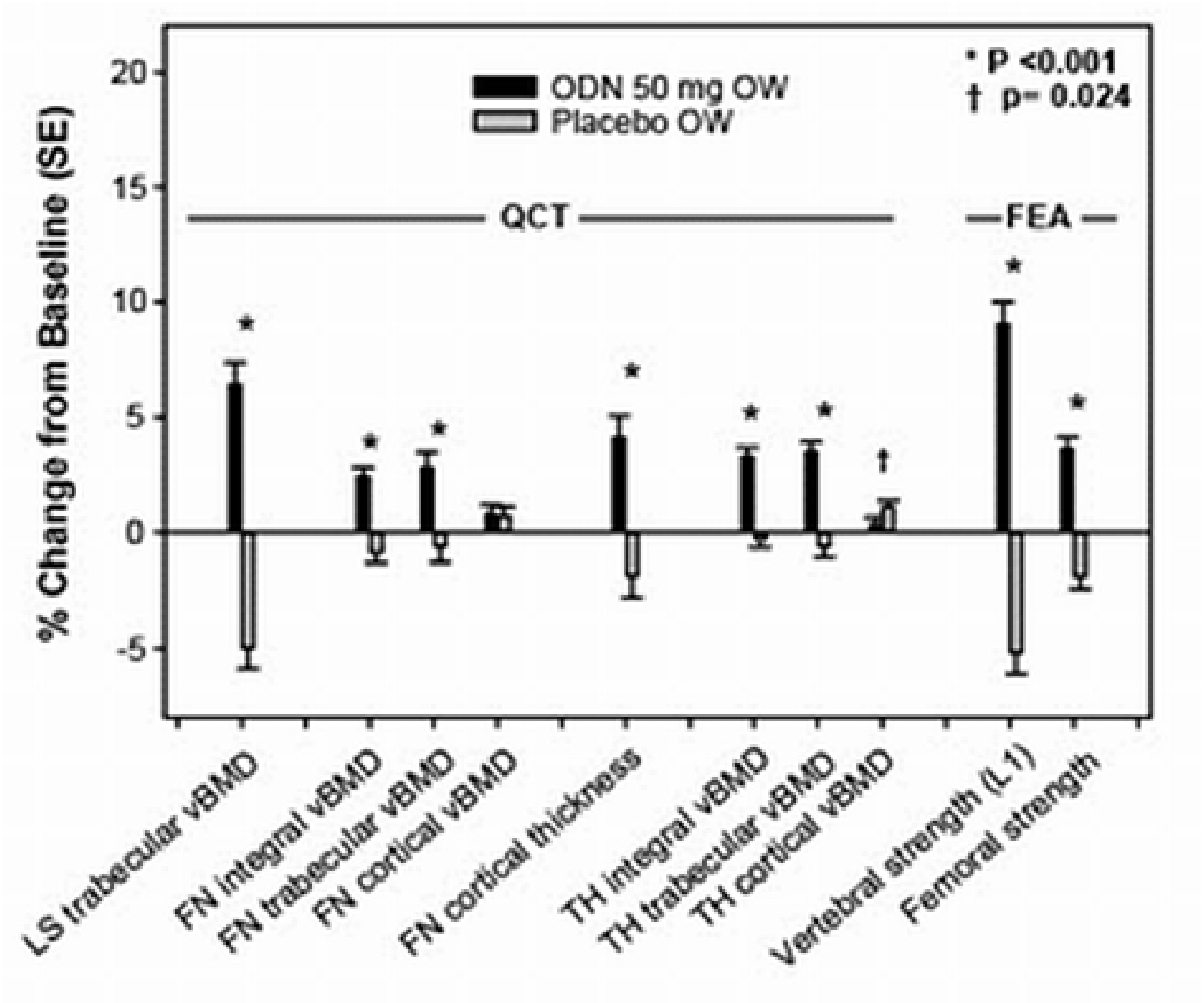


Leung et al Bone 2011;49:623

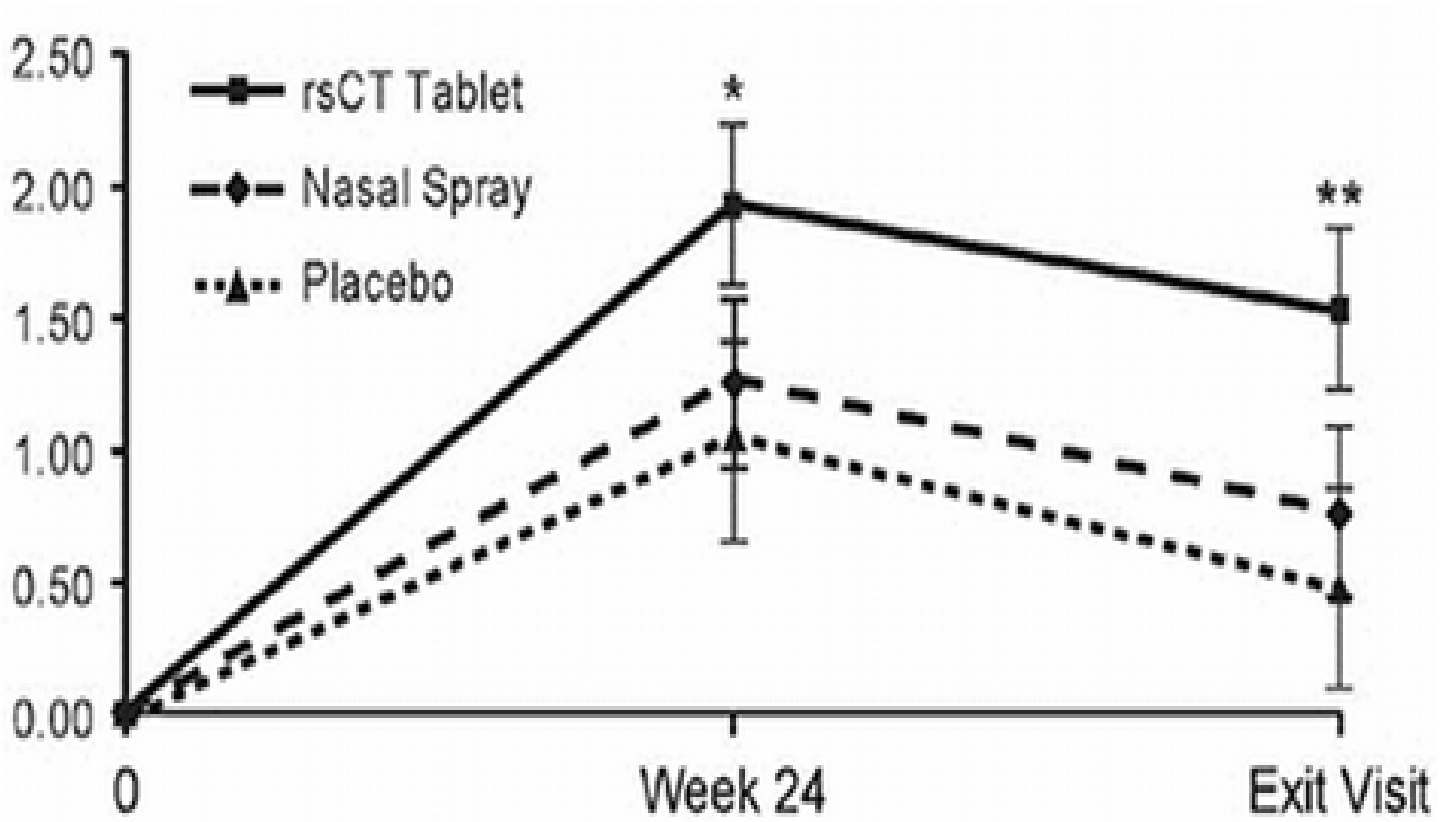
Odanacatib 5 years LS BMD



OC8 QCT and Finite Element Analysis Spine and Hip 2



Oral Recombinant Calcitonin



mITT population, LOCF
** p vs placebo = 0.006; p vs nasal = ns*
*** p vs nasal and pbo ≤ 0.026*

OVERVIEW, VOL 12, ISSUE 3

Ego Seeman

Editor

By Ego Seeman Thu, 11/22/2012 - 12:49

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

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

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The Negative Bone Remodeling Balance The Cause of Structural Decay

In young adulthood, remodeling is balanced, the volumes of bone removed and replaced during each remodeling cycle are equal so no permanent bone loss occurs (1). The first abnormality in remodeling is likely to be a reduction in the volume of bone formed by each basic multicellular unit (BMU), which is seen as a reduction in mean wall thickness (MWT) in bone biopsy specimens (2). This reduction in the volume of bone formed probably occurs around midlife, but this is not well documented. The work of Lips et al suggests there is a decline in MWT before menopause, but the data appear to be nonlinear with little diminution in MWT before menopause (2). The work of Vedi et al suggests that negative BMU balance precedes menopause, but the sample sizes were small and the reduction in MWT was modest, so that the amount of bone lost and the structural decay produced before menopause is likely to be modest given that remodeling intensity does not increase before menopause (3).

Once established, this negative balance is the necessary and sufficient cause of bone loss. Each time bone is remodeled, less bone is deposited than was removed, producing structural decay (4). Trabeculae thin and perforate, cortices become more porous and thin focally (5,6). This negative BMU balance is the 'cause' of structural deterioration and bone fragility, it is the target for therapeutic intervention (Figure 1).

Figure 1. The negative bone balance is the cause of structural decay and is due to a decline in both the volumes of bone deposited and resorbed by each BMU, but a greater decline in the former. Ac.F: activation frequency. (E Seeman, with permission)

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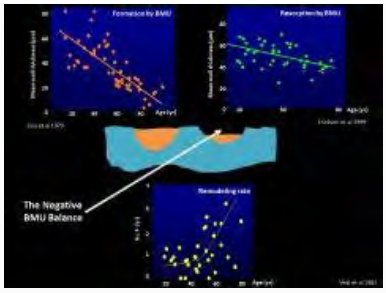


After menopause, remodeling intensity increases and the negative bone balance may also worsen, resulting in accelerated structural decay. With time, trabeculae disappear and remodeling within the trabecular compartment slows down because there are no more trabeculae to remodel. In cortical bone, remodeling upon Haversian canals enlarges them focally, they coalesce, large pores appear (canals are seen as pores in cross-section), the cortices cavitate and thin from the 'inside' (6) (Figure 2).

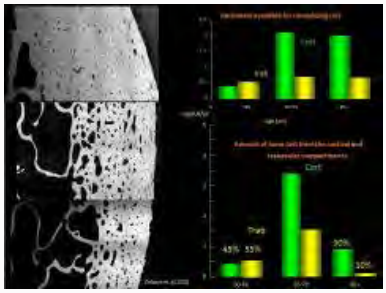


Figure 2. Intracortical remodeling cavitates compact cortex thinning it from the 'inside'. Yellow denotes trabecular bone, green cortical bone. Surface perimeter is the y-axis in the upper figure, amount of bone loss is the y-axis in the lower image. (Adapted from Zebaze et al (6))

The Surfaces of Bone
Where the Action is

Remodeling is surface dependent; for the cells of the BMU to resorb and replace bone, there must be a point upon which remodeling is initiated. This occurs upon one of the three (endocortical, intracortical, trabecular) components of the internal or endosteal surface of bone. These three components are contiguous, they are connected. The mineralized bone matrix volume is enveloped, residing 'inside' the periosteal surface and 'outside' the three components of the endosteal surface (Figure 3).

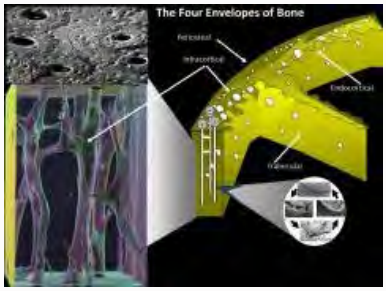


Figure 3. Mineralized bone matrix is enveloped by four 'envelopes'. The periosteal surface is the outer envelope and the external surface of the whole bone volume. The whole bone includes the mineralized bone volume and the void volumes. The void volume comprises the medullary canal, the Haversian and Volkmann canals, and remodeling units in varying stages of excavation and refilling. (E Seeman, with permission)

Bone formation upon the periosteal envelope and upon the endocortical envelope during puberty in females or during anabolic therapy separates these surface, so cortical thickness increases. Resorptive remodeling upon the endocortical envelope during advancing age brings it closer to the periosteal envelope, thinning the cortex; while resorptive remodeling upon the Haversian canals enlarges them focally, they coalesce forming giant pores in cross-section, which fragment the cortex, particularly the inner part of the cortex adjacent to the medullary canal. This region, where the compact cortex merges with trabeculae abutting the endocortical surface, is the corticomedullary or corticotrabecular junctional region. Remodeling here is intense and fragments the cortex – it becomes 'trabecularized' (6,7). The fragments of cortex look like trabeculae, but they are thicker, have a chaotic architecture and are unlikely to serve to buttress the cortex, as do the true trabeculae within the medullary canal.

The right answers require the right questions. The living bone is the cellular activity upon these surfaces. Instead of asking what is the effect of growth, ageing, exercise, disease and drug therapy on bone mineral density (BMD), the right question is what are the effects of each of these factors on the cellular activity upon these surfaces, and so the movement of these surfaces relative to each other and hence the three dimensional architecture of the bone.

Antiresorptives Reduce Remodeling Intensity

For therapeutic agents to stop bone loss, they must correct the negative bone balance by either reducing the volume of bone resorbed by the osteoclasts of the BMU, or by increasing the volume of bone formed by the osteoblasts of the BMU, or both. If the negative bone balance is made less negative, then treatment must reduce the intensity of bone remodeling to slow the loss of bone. Antiresorptive agents reduce the intensity of bone remodelling – the number of sites appearing on a bone surface at any time decreases, but they probably do not correct the negative BMU balance. So each time the fewer number remove bone, they then deposit less producing a net

loss of bone and more structural decay, but this proceeds more slowly.

This is important, if the negative balance remains unchanged and fewer remodeling sites remove more bone than they deposit, structural decay will continue, albeit at a slower rate, *despite* compliance with treatment. This is not detectable using bone densitometry because secondary mineralization of the much larger volume of mineralized bone matrix not being remodeled progresses in completeness of secondary mineralization. The crystals enlarge and more of the bone volume has a higher and higher density, so BMD continues to rise. This is not 'seen' by the BMD machine because the rise in BMD produced by the increasingly complete secondary mineralization is occurring in a much larger volume of bone than the small volume being removed from it. So BMD rises in a progressively smaller and smaller total volume of bone (Figure 4).

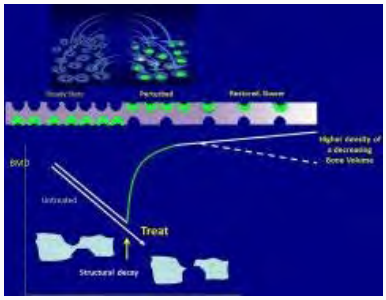


Figure 4. When an antiresorptive is administered, resorption sites excavated before treatment refill (green) while fewer new remodeling sites (blue) are excavated. Areal BMD increases (green and white line) also because secondary mineralization of bone is no longer removed. If remodeling continues albeit more slowly, and the negative BMU balance persists, then total mineralized bone volume will decrease (dashed line), but its density will increase perhaps making bone more brittle. (E Seeman, with permission)

The decision to use a drug partly depends on the remodeling status of the skeleton. If potent remodeling suppressants are used and remodeling is fully suppressed, structural deterioration will be prevented, perhaps at the price of compromising the material composition of bone, particularly in persons with low baseline remodeling. It makes little sense treating someone with low bone remodeling with the most potent remodeling suppressants. Using a less potent remodeling suppressant may result in continued structural deterioration with preservation of the material composition of bone. What is worse – allowing structural deterioration or allowing some compromise in the material composition of bone? The answer to this is not clear, I suspect it is worse to allow structural decay.

If antiresorptive agents abolish the negative BMU balance, remodeling will not produce further permanent structural decay. If treatment makes remodeling balance positive by reducing the volume of bone resorbed and increasing the volume of bone deposited, then it makes sense to increase remodeling intensity because each remodeling event will deposit a small moiety of bone, reconstructing the skeleton focally.

Access to Remodeling Sites
Are all Antiresorptives Equal?

Several recent publications signal the importance of access to remodeling in cortical and trabecular bone as one explanation for differences in efficacy of treatments in suppressing remodeling. Most antiresorptive agents reduce the intensity of bone remodeling by about 50% as measured by circulating remodeling markers. Why 50%? One reason may be that remodeling upon Haversian canals within cortical bone may be less accessible to bisphosphonates than remodeling upon the endocortical and trabecular surfaces. Trabecular bone consists of flattened plates with a low mineralized bone matrix volume and a large surface area – they have a large surface area/bone matrix volume configuration (Figure 5).

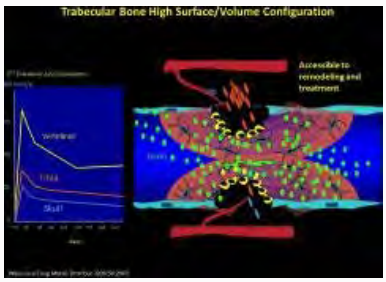
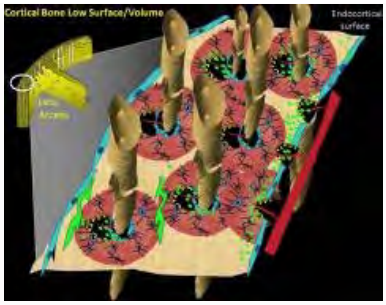


Figure 5. Left panel shows graph adapted from Weiss et al. Note the higher concentration of bisphosphonate in vertebrae than cortical sites. (Right panel) Trabecular plates are thin and have a large surface area. Adsorbed bisphosphonate (green) penetrates the smaller bone matrix volume so osteoclasts will encounter and engulf drug preventing further resorption. (E Seeman with permission)

Bisphosphonates bind to bone mineral and those with higher affinity for mineral cannot penetrate deeply into matrix. This is not a problem in trabecular bone because of its high surface/volume ratio. However, in cortical bone with its low surface to volume ratio, access to the deeper matrix is limited, so that drugs binding with high affinity, like alendronate, may be unable to reach and concentrate within the deeper interstitial bone or at the periphery of osteons; so remodeling initiated at points on Haversian canals may excavate mineralized bone matrix that does not contain bisphosphonate, and so osteoclasts continue to excavate matrix (Figure 6).

Figure 6. Cortical bone has a large volume and is enveloped with a relatively *smaller surface area, so bisphosphonates (green dots) adsorbed upon the surface cannot access remodeling deep within cortical bone around Haversian canals to remove deep cracks in interstitial bone (green). Remodeling may be less inhibited, especially by bisphosphonates avidly bound to*



matrix beneath the endosteal envelope. (E Seeman, with permission)

Weiss et al report that the concentration of labeled zoledronic acid is higher in trabecular sites containing large amounts of trabecular bone like the vertebrae compared with the femur, a predominent cortical site (8). As reported in experiments by Allen et al, risedronate is a drug that has a lower binding affintity to matrix and penetrates more deeply beneath the surface.

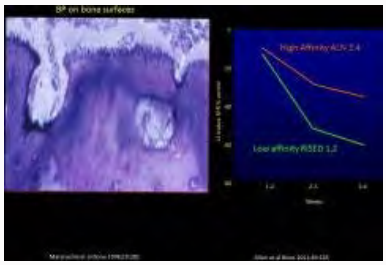


Figure 7. (Left panel) Bisphosphonate is bound beneath the bone surface to matrix and cannot penenetrate deeply. (Right panel) Risedronate binds less avidly to mineral than alendronate. Remodeling is more rapidly and more greatly suppressed by risdronate as reflected in the greater reduction in the surface extent of bone formation. (Adapted from Allen et al (9))

In another experiment by **Turek et al**, mature female rabbits were injected with both low- and high-affinity bisphosphonate analogs bound to different fluorophores (10). Staining intensity ratios between osteocytes within rib osteons or within vertebral trabecular hemiosteons were compared to osteocytes outside the cement line and was greater for the high-affinity than the low-affinity compound which distributes across the cement line, while the high-affinity compound concentrates mostly near surfaces. The affinity of bisphosphonates for the bone determines the reach of the drugs in cortical and cancellous bone (Figure 8).

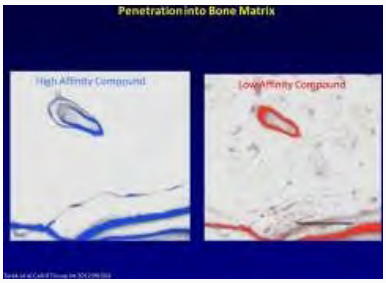


Figure 8. Turek et al. report the high affinity (blue) is concentrated around vessels and does not penetrate matrix. In right panel there is greater penetration of low affinity (red) with matrix staining of osteocytes (10).

Roelofs et al also published a study examining the effects of differing drug affinities for bone mineral and the effect on the distribution on mineral surfaces (11). Fluorescent conjugates of risedronate and its lower-affinity analogues deoxy-risedronate and 3-PEHPC were used (Figure 9). In growing rats, all compounds preferentially bound to forming endocortical surfaces in cortical bone. At forming surfaces, penetration into the mineralizing osteoid inversely correlated with mineral affinity. Lower-affinity compounds also showed a higher degree of labeling of osteocyte lacunar walls and labeled lacunae deeper within cortical bone, indicating increased penetration into the osteocyte canalicular network. These findings indicate that the bone mineral affinity of bisphosphonates is likely to influence their distribution within the skeleton.

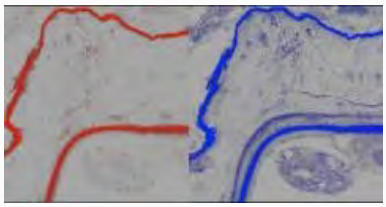
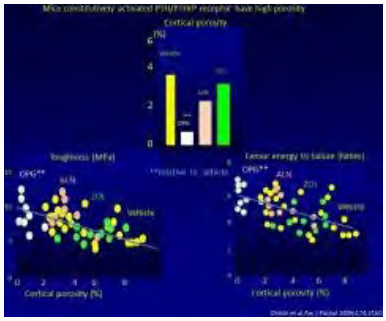


Figure 9. Roelofs et al report penetration into the mineralizing osteoid is inversely correlated with mineral affinity (11). Lower-affinity florescent-psuedocoloured compounds show a higher degree of labeling of osteocyte lacunar walls and labeled lacunae deeper within cortical bone indicating increased penetration into the osteocyte canalicular network.

So, what might this mean in terms of bone morphology and bone strength? In a wonderful paper laiden with many interesting observations, **Ohishi et al** reported that osteoprotegerin (OPG), which does not bind to matrix and has a wide matrix distribution, reduced porosity in the mouse model of high turnover and porosity (12). Zoledronic acid and alendronate reduced porosity but no differently to vehicle treated mice, yet preservation of trabecular bone was similar with all three treatments so that this is not simple a dose effect (Figure 10).

Figure 10. Ohishi et al report that OPG, which does not bind to matrix, reduced porosity in the mouse model (12). Zoledronic acid and alendronate reduced porosity but no differently to vehicle treated mice. Trabecular bone was equally preserved by all treatments so the greater benefit in cortical bone of OPG is not a dose specific effect.



Does a CAT Have 9 Lives?

Remodeling inhibitors capitalise on reducing the size of the remodeling transient. That's how they increase BMD. The Parfittian treatise on this subject is essential reading (13). The remodeling transient is the result of the normal delay between the completion of bone resorption, which takes about 3 weeks, and the completion of bone formation, which takes about 3 months. Because of this time lag, at any time, there will be a reversible and transient deficit in bone volume that is the sum of the volume of the newly excavated cavities, the volume of the newly unmineralized osteoid just deposited by other BMUs, the volume of the osteoid that has undergone primary but not secondary mineralization (now called 'bone'), and the volume of bone that is undergoing secondary mineralization, which does not reach completion for about a year, if not longer; secondary mineralization is also part of the transient remodeling space deficit.

When an antiresorptive is administered, there is inhibition of the appearance of new resorption cavities and so the refilling of cavities (which remains incomplete because of the negative bone balance) excavated prior starting therapy occurs without being offset by the appearance of new resorption cavities. The higher the baseline remodeling, the larger the remodeling transient and so the greater the BMD response to a given inhibitor of remodeling. As discussed above, the rapid rise in BMD is due to the refilling of excavated cavities, the completion of primary and secondary mineralization in tissue that would otherwise have been removed had remodeling intensity not been reduced. BMD then rises more slowly and as a result of secondary mineralization.

The cathepsin K (CAT K) inhibitors do not appear to reduce remodeling intensity, but the evidence for this is not robust and may be species specific. Bone et al reported no reduction in activation frequency, the percent mineralizing surface, bone formation rate or eroded surface; each a measure of the intensity of remodeling upon the bone surface (14). The numbers of biopsies available were limited so the data is not robust, but if remodeling intensity is not slowed so that sites excavated before treatment refill but with the appearance of the same number of new sites, how can BMD increase?

One explanation is a reduction in the depth of resorption sites without a change in their numbers. There is evidence supporting this notion (15). Perturbing steady state by allowing partial refilling of sites present before treatment while the *same* number of resorption sites appear, but each is *half the depth* should increase BMD to about the same degree as partial refilling of sites present before treatment with appearance of *half the number* of new sites of the same depth (Figure 11).

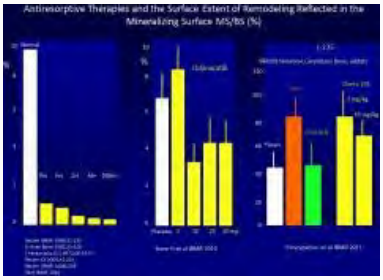


Figure 11. Antiresorptives like the bisphosphonates and densosumab reduce the intensity of remodeling as reflected in histomorphometric measures and bone remodeling markers. This is not the case with CAT K inhibitors.

This might explain the similar rise in BMD in patients treated with alendronate and odanocatib. However, if the volume of bone deposited remains unchanged, then the negative BMU balance will lessen; more shallow resorption pits are likely to refill more completely. So when steady state is restored at the same rate of remodeling but they are more shallow and more fully refilled, bone loss will lessen but will continue unless the negative BMU balance is abolished. If the volume of bone formed increases, as suggested by several authors, then bone loss may stop, but bone mass will not increase unless the negative BMU balance is made positive. BMD will rise in the two scenarios (lessening or stopping bone loss even though the mass or volume of bone does not rise) because the bone not removed (because pits are more shallow) undergoes more complete secondary mineralization. In addition, as remodeling sites are more shallow, interstitial bone (bone between osteons) may increase in relative and absolute terms and undergo more complete mineralization contributing to the rise in BMD. Moreover, if there is relatively more interstitial bone than osteonal bone, this may compromise bone strength as interstitial bone is usually more densely mineralized than osteonal bone, has higher pentosidine content, has fewer osteocytes and is a common site of microdamage (5).

Bone resorption markers decrease following treatment with this class of drugs – a puzzling observation if remodeling intensity does not decrease. But this may be the result of a decrease in the depth of the same number of remodeling sites. Remodeling markers tend to drift back up after initial suppression despite continued treatment. This might reflect the continued remodeling taking place when remodeling returns to its new steady state. Remodeling now continues,

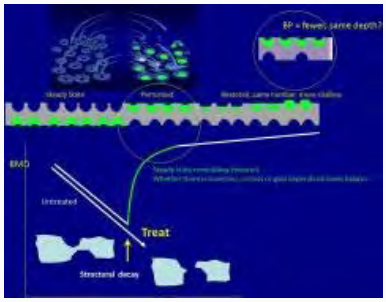
perhaps at the same intensity, but now the remodeling cavities excavated are smaller and appear at the same rate as the smaller cavities being refilled.

Bone ‘formation’ markers appear to decline less than bone ‘resorption’ markers, suggesting that osteoclasts (which remain or increase in numbers) may signal bone formation to continue (16). However, the notion that there is continued or increased bone formation by the BMUs in the presence of reduced resorption by each of them is difficult to demonstrate convincingly for several reasons.

For example, inferring circulating markers of bone remodeling are surrogates of bone resorption and formation at the morphological level is problematic. There are very few studies comparing levels of remodeling markers and volumes of bone formed or resorbed and at best the correlations are ~0.5 or less. Moreover, it remains unclear whether remodeling markers reflect remodeling intensity at the tissue level, at the cellular level, and whether they arise due to remodeling at cortical bone or trabecular bone or indeed differently at different sites of the skeleton.

Comparing markers is frought with difficulty. The variance in resorption and formation markers differ and markers are not normally distributed. Thus, a 50% reduction in a ‘resorption’ marker is not necessarily ‘less’ than a 25% reduction in a ‘formation’ marker. In addition, CAT K inhibitors prevent degradation of some markers, leaving the levels higher giving the impression that remodeling, or worse, that bone ‘formation’ is continuing.

Figure 12. If a drug like a CAT K inhibitor reduces the depth of resorption but not remodeling intensity, then the rise in BMD should be similar to that observed by a bisphosphonate that halves the number of sites without affecting the resorption depth. However, the effects on bone morphology and material properties may differ. (E Seeman, with permission)



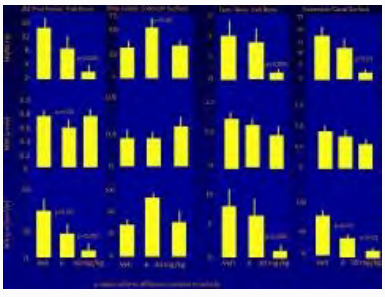
There are three recent papers that lend support for the notion that CAT K inhibitors reduce resorption depth and area excavated by osteoclasts, may reduce remodeling intensity in subhuman primates and increase bone strength.

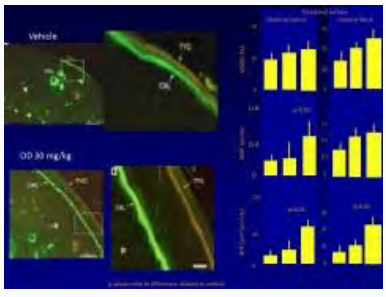
Jayakar et al report that OVX odanacatib (ODN) treated nonhuman primates had increases in integral vBMD and cortical thickness at the upper distal radius and at the distal 1/3 radius compared with and OVX-Veh treated animals. Axial compression showed the OVX-ODN group had 33% greater peak stress than the OVX-Veh group (17).

Masarachia et al report that in estrogen-deficient, skeletally mature rhesus OVX monkeys treated for 21 months with vehicle or ODN, treatment suppressed markers of bone remodeling and maintained osteoclast numbers (18). ODN prevented bone loss in lumbar vertebrae and dose-dependently increased L1 to L4 BMD. Treatment also tended to increase bone strength with a correlation (R=0.838) between peak load and bone mineral content of the lumbar spine.

A most interesting paper was published by **Cusick et al** (19). The authors report that ODN increased femoral neck (FN) BMD and ultimate load relative to vehicle treated nonhuman primates. Histomorphometry of FN and proximal femur (PF) revealed that ODN decreased 'bone formation rate' (BFR) upon the trabecular and intracortical surfaces. This is an ambiguous term. BFR is the product of the surface extent of remodeling which reflects remodeling intensity and mineral appositional rate (MAR). BFR may increase or decrease because of change in one or both of these terms. A change in the surface extent of remodeling reflects remodeling intensity, a change in MAR reflects a change in the number and work of osteoblasts, amount of bone deposited depends on the MAR. When authors report BFR is 'increased', this does not necessarily mean there is an anabolic effect.

The authors report ODN stimulated periosteal BFR 6-fold at the FN and 3.5-fold at the PF with the 30 mg/kg dose vs. vehicle. However, examination of the figures reveals MAR increased in one location only (Figures 13-14); the “increased” BFR is therefore a function of the high surface extent of remodeling or modeling on the periosteum. The differing behaviour on each surface, reduction, increase or no change in the surface extent of remodeling, and behavior of MAR is difficult to interpret because it is inconsistent. Moreover, the claim is made that ODN increased cortical thickness at the FN by 21% ($p=0.08$) and PF by 19% ($p<0.05$) vs. vehicle after 21 months of treatment needs to be carefully interpreted as changes in edge detection by the imageing method may occur when bone tissue density increases. More studies of histomorphometry and microstructure are needed in this class of drug.





Figures 13-14. Cusick et al report effects of ODN on BFR is site specific. For PF and FN trabecular bone, BFR was reduced with both doses due to a decrease in MS/BS, MAR was reduced or unchanged. The result was the same for the intracortical (Haversian) surface but mainly seen with the larger dose. On the proximal femur endocortical surface, MS/BS increased at the lower dose but there was no effect on MAR or the net derived BFR. On the periosteal surface of the proximal femur, BFR was increased due to a higher MAR with the higher dose and with long term labeling assessment. On the periosteal surface of the femoral neck, BFR increased even though neither small increase in MS/BS and MAR were not significant.

Bisphosphonates
Oldies but Goodies

Zoledronic acid – is once enough?

Boonen et al (20) report a post hoc analysis of persistence of the antifracture effect of zoledronic acid from 9355 women randomized in two placebo-controlled pivotal trials. Zoledronic acid reduced the risk of all clinical fractures at 12 months (HR=0.75, 95% CI 0.61-0.92). Year-by-year analysis showed reduced risk for all clinical fractures in each of the 3 years (year 1: OR=0.74, 95% CI 0.60-0.91; year 2: OR=0.53, 95% CI 0.42-0.66; year 3: OR=0.61, 95% CI 0.48-0.77). Year-by year data during the first 3 years of treatment are not usually shown in clinical trials. What is usually presented is years 0-1, 0-2 and 0-3, so the carry over effect of the first year influences those results.

Grey et al (21) report that a single dose of 5 mg zoledronic acid decreased bone turnover and increased BMD during 3 years in 50 postmenopausal women with osteopenia. After 5 years, β-CTX and P1NP were lower by 48% and 45%, respectively. BMD in the zoledronic acid group was higher by 4.2% at the spine, by 5.3% at the total hip, and by 2.7% at the total body. This is important. Is it necessary to treat patients with suppressed remodeling with further doses of zoledronic acid when remodeling remains suppressed after one injection for 1 to even 5 years? I suspect not, but what is needed are fracture endpoints because if remodeling continues and the BMU balance remains negative, then structural decay may be continuing albeit slowly, and this will remain undetectable using bone densitometry because the rise in tissue mineralization density of the whole mineralized bone volume will overwhelm and obscure the continued loss of bone with its mineral content.

The good and bad of remodeling suppression

Remodeling suppression is good because it reduces the number of new remodeling sites appearing upon bone surfaces and so reduced the structural decay that follows, as less bone is deposited than was removed. However, remodeling suppression is bad because the bone that is no longer removed undergoes more complete secondary mineralization, and so the mineral content from osteon to osteon may become more similar, and this loss of heterogeneity in tissue mineralization density is held to allow crack propagation. Reduced remodeling means reduced damage removal as well.

Donnelly et al (22) compared biopsies from the proximal femur in bisphosphonate-naive (−BIS, n=20) and bisphosphonate-treated (+BIS, n=20, duration 7±5 years) patients with intertrochanteric (IT) and subtrochanteric (ST) fractures using FTIRI. The mean FTIRI parameters were similar, but the widths of the distributions tended to be reduced in the +BIS group, the widths of the cortical collagen maturity and crystallinity were reduced in the +BIS group relative to those of the −BIS group by 28% and 17%, respectively. The cortical mineral:matrix ratio was 8% greater in tissue from patients with atypical ST fractures (n=6) than that of patients with typical fractures (n=14) (atypical 5.6±0.3 vs. typical 5.2±0.5, p=0.03).

Hofstetter et al (23) used Raman and Fourier transform infrared microspectroscopy (FTIRM) analysis to examine material properties at bone forming trabecular surfaces in iliac crest biopsies from women treated with alendronate (ALN) or risedronate (RIS). There were 33 women treated with ALN for 3-5 years [ALN-3], 35 with ALN for >5 years [ALN-5], 26 with RIS for 3-5 years [RIS-3], and 8 with RIS for >5 years [RIS-5]). In RIS-5 there was a decrease in the proteoglycan content (-5.83% compared to ALN-5). RIS-3 and RIS-5 were associated with lower mineral maturity/crystallinity (-6.78% and -13.68% vs. ALN-3 and ALN-5, respectively), and pyridinoline/divalent collagen crosslink ratio (-23.09% and -41.85% vs. ALN-3 and ALN-5, respectively). ALN and RIS exert differential effects on the intrinsic bone material properties at actively bone forming trabecular surfaces.

Abrahamsen et al (24) examined 30,606 ALN users and 122,424 controls. ALN users were more likely to have undergone recent upper endoscopy (4.1 vs. 1.7%, p<0.001). ALN users had a lower risk of incident gastric cancer [OR 0.61; 0.39-0.97) and no increased risk of esophageal cancer (OR 0.71; 0.43-1.19). Risk reductions were greater in users with 10+ prescriptions. The risk of dying of esophageal cancer was reduced in ALN users after 3 years (OR 0.45: 0.22-0.92) but not after 9 years (OR 1.01; 95% CI: 0.52-1.95).

Chiang et al (25) report the relationship between ALN and the risk of all malignancies in women with osteoporosis and age over 55 years. The study included 6906 women with osteoporosis taking ALN, and 20,697 age- and comorbidity-matched women without bisphosphonate treatment. During 4.8 years, 821 patients from the study group and 2646 patients from the control group had new cancers (11.9% vs. 12.8%, p=0.054). The person-year incidence of newly-developed cancer in ALN users and controls was 28.0 and 29.4 per 1000 person-years, respectively (adjusted HR, 1.05; 95% CI, 0.97-1.13; p=0.237).

Boonen et al (26) report a 2-year, randomized, double-blind, placebo-controlled study in men. RIS 35 mg once a week decreased BTMs and increased BMD. In the open-label extension, all patients received RIS 35 mg once a week, and 1000 mg elemental calcium and 400-500 IU

vitamin D daily for up to 2 years. A total of 218 (of 284) patients enrolled in the open-label extension. RIS continued to produce increases in lumbar spine BMD from baseline (7.87%) in the group of patients who took it for 4 years. RIS produced increases in lumbar spine BMD from baseline (6.27%) in the former placebo group who took it for 2 years during the open-label extension.

SERMs
In Search of Place

The problem with SERMs is the lack of evidence of efficacy against nonvertebral fractures. This is a serious limitation because 80% of all fractures are nonvertebral. **Eastell et al** (27) describe the changes in BTMs in response to lasofoxifene in 1126 women aged 59-80 years during 5 years. Lasofoxifene decreased resorption and bone formation markers; 0.5 mg/d was similar to 0.25 mg/d. 0.5mg/d resulted in response rates for CTX (decrease from baseline >60%), P1NP (>50%), and bone ALP (>30%) of 35%, 45%, and 43% of women at month 12, respectively, compared with placebo responses of 4%, 4%, and 7%. In contrast, the increase in BMD took longer (50% responded after 36 months of lasofoxifene 0.5 mg/d) and was not as specific (15% of placebo group responded). This is difficult to explain. The data suggest that more than half of the participants do not respond. The question is why are these agents such weak remodeling suppressants?

Calcitonin: It seemed like a good idea at the time

Binkley et al (28) report results of oral calcitonin in postmenopausal osteoporosis (ORACAL) in a randomized, double-blind phase 3 study in 565 women randomized to oral recombinant salmon calcitonin (rsCT) tablets (0.2 mg/d), synthetic salmon calcitonin (ssCT) nasal spray (200 IU/d), or placebo for 48 weeks. Women randomized to oral rsCT had greater increase in lumbar spine BMD (1.5%) greater than those randomized to ssCT nasal spray (0.78%) or placebo (0.5%). Oral rsCT also resulted in greater improvements in trochanteric and total proximal femur BMD and greater reduction in those observed in ssCT nasal spray. CT is a weak remodeling suppressant, but the evidence for antifracture efficacy has never been demonstrated convincingly; and so it seems inappropriate to consider this agent as a first line treatment for fracture prevention.

Calcium Supplementation Works in Those Deficient

Calcium supplementation is a weak remodeling suppressant. In persons who are calcium replete and have a low rate of bone remodeling, the effects are difficult to demonstrate. However, in persons with a high rate of bone remodeling and a low calcium intake, the benefit of suppressing remodeling and the subsequent rise in BMD should be demonstrable. **Khadilkar et al** (29) report in a double-blind, matched-pair, cluster, randomization study of 1-year supplementation with calcium, multivitamin with zinc and vitamin D in 214 school-going premenarchal girls. The mean increase in TBBMC was higher in the Ca-group (22.3%) and Ca+MZ-group (20.8%) compared to control group (17.6%) ($p<0.05$) with no differences between Ca+MZ and Ca groups.

Lewis et al (30) reviewed randomized controlled trial evidence of adverse events. In seven studies, self-reported gastrointestinal (GI) adverse event rates were more common in participants receiving calcium. These were described as constipation, excessive abdominal cramping, bloating, upper GI events, GI disease, GI symptoms, and severe diarrhea or abdominal pain (calcium 14.1%, placebo 10.0%) (RR 1.43, 95% CI 1.28-1.59, $p<0.001$). Adjudicated functional GI hospitalizations in one study were calcium 6.8%, placebo 3.6% (RR 1.92, 95% CI 1.21-3.05, $p = 0.006$). Self-reported myocardial infarction (MI) rates of 3.6% in the calcium group and 2.1% in the placebo group. After adjudication, the MI rates were 2.4% in the calcium group and 1.6% in the placebo group (RR 1.45, 95% CI 0.88-2.45, $p=0.145$).

These data support the hypothesis that calcium tablets increase the incidence of adverse GI events. Read between the lines. Whether this accounts for an increase in self-reported MI in calcium treated patients but not controls is possible, but it is not the solution to the controversy which requires properly designed and executed trials with adequate sample sizes and preplanned global outcomes including cardiac events. If there is a small increase in cardiac events, it will remain undetected with sample sizes of a few hundred individuals because of lack of power, not because the truth is that calcium is safe. We just don't know.

Little is seen in the large randomized trials because they are flawed in study design and execution. Most subjects are not calcium deficient, so how can an effect of 'deficiency' be detected or the benefit (or risk) of supplementation be documented? In addition, most if not all, have dropout rates of 50%, so how can credible inferences be inferred examining the results in compliers when randomization has been violated? Compliers to placebo have better outcomes than noncompliers to placebo.

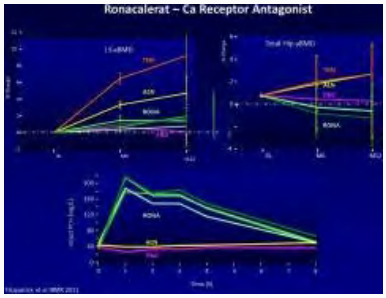
Anabolic Agents

Calcium sensing receptor antagonists and endogenous PTH

Fisher et al (31) report that stimulating endogenous PTH may produce an anabolic effect on the skeleton. This is a nice idea killed by experimentation. The CaSR antagonist JTT-305/MK-5442 increased endogenous PTH. Daily treatment for 12 weeks increased BMD at axial and appendicular skeletal sites, but the changes did not reach significance. Histological analyses

confirmed increases in mineralized surface (MS/BS), reflecting increased remodeling intensity but not necessarily new bone formation. In the presence of existing osteoclasts, endogenous PTH will increase remodeling and produce bone loss. The same observations have been made with several other drugs such as ronacalerat, which was associated with appendicular bone loss (32). With denosumab, acute suppression of remodeling reduces serum calcium within the normal range and increases endogeneous PTH, but reduced synthesis of osteoclasts and reduced activity of existing osteoclasts appears to prevent the resorptive action of the endogenous rise in PTH (33). At this time, endogenous PTH stimulators do not appear to be a viable option in the treatment of osteporosis.

Figure 15. Ronacalerat reduces serum calcium and increases endogenous PTH, but the resorptive action of the drug produces cortical bone loss.



Marsell et al (34) report glycogen synthase kinase 3β (GSK-3β) in the canonical Wnt pathway is a therapeutic target because it inhibits bone formation so that inhibitors of this kinase may produce net bone formation. A GSK-3 inhibitor, AZD2858, dose dependently increased trabecular bone mass in rats after two weeks with a maximum effect at 20 mg/kg daily (total BMC increased by 172%). An effect was also seen at cortical sites (total BMC increased by 111%). Vertebral compression strength increased by 370% and femoral diaphyseal strength increased by 115%.

Ascenzi et al (35) explored the role of orientation of type I collagen in bone strength before and after treatment with PTH. PTH increased the Haversian area by 11.9 to 12.8 mm^2; decreased bright birefringence from 0.45 to 0.40, increased the average percent area of osteons with alternating birefringence from 48.15 to 66.33%, and nonsignificantly decreased the average percent area of semihomogeneous birefringent osteons and of birefringent bright osteons (4.1 vs. 2.1%, p=0.10). Lamellar thickness increased from 3.78 to 4.47 µm for bright lamellae, and from 3.32 to 3.70 µm for extinct lamellae. This increased lamellar thickness altered the distribution of birefringence and the distribution of collagen orientation in the tissue. With PTH, a higher percent area of osteons at the initial degree of calcification was observed, relative to the intermediate-low degree of calcification (57.16 vs. 32.90%), with percentage of alternating osteons at initial stages of calcification increasing from 19.75 to 80.13. PTH increases heterogeneity of collagen orientation.

Other Agents
Mechanisms to be Determined

Strontium ranelate

Strontium ranelate reduces vertebral and nonvertebral fractures, and in post hoc analysis, reduces hip fractures as well. However, like most studies, this evidence is confined to 3-5 years of treatment. Difficulties arise in assessing antifracture effiacy for longer periods of time because of lack of controls and dropouts. **Reginster et al** (36) report that of the original cohort of postmenopausal osteoporotic women participating in SOTI and TROPOS for 5 years, 237 received strontium ranelate 2 g/d during a 5-year open-label extension. As there was no randomized control group, fracture rates were compared with fracture rates observed in the first 5 years in a FRAX®-matched placebo group identified in the TROPOS placebo arm. The incidence of vertebral and nonvertebral fracture in years 6-10 was comparable to the incidence between years 0-5, but was lower than the incidence in the FRAX®-matched placebo group over 5 years ($P<0.05$); relative risk reductions for vertebral and nonvertebral fractures were 35% and 38%, respectively. The authors infer that long-term treatment is associated with the maintenance of antifracture efficacy over 10 years. The veracity of this data is difficult to assess because randomization is violated. The lower fracture rate reported in the treated group may have nothing to do with the treatment. Sampling bias may have resulted in a group less prone to sustaining fractures with or without treatment. Over 10 years, spine BMD increased to 34.5±20.2% above baseline, the morphological basis of this large increase is not known.

References

1. Hattner R, Epker BN, Frost HM. Suggested sequential mode of control of changes in cell behaviour in adult bone remodelling. Nature 1965;206:489.

2. Lips P, Courpron P, Meunier PJ. Mean wall thickness of trabecular bone packets in the human iliac crest: changes with age. Calcif Tissue Res 1978;26:13.

3. Vedi S, Compston JE, Webb A, Tighe JR. Histomorphometric analysis of bone biopsies from the iliac crest of normal British subjects. Metab Bone Dis Relat Res 1982;4:231.

4. Parfitt AM, Mathews CH, Villanueva AR, et al. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. J Clin Invest 1983;72:1396.

5. Seeman E, Delmas PD. Bone quality – the material and structural basis of bone strength and

fragility. N Engl J Med 2006;354:2250.

6. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet 2010;375:1729.

7. Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM. Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. J Bone Miner Res 1997;12:498.

8. Weiss HM, Pfaar U, Schweistzer A, et al. Biodistribution and plasma protein binding of zoledronic acid. Drug Metab Dispos 2008;36:2043.

9. Allen MR, Turek JJ, Phipps RJ, Burr DB. Greater magnitude of turnover suppression occurs earlier after treatment initiation with risedronate than alendronate. Bone 2011;49:128.

10. Turek J, Ebetino FH, Lundy MW, et al. Bisphosphonate binding affinity affects drug distribution in both intracortical and trabecular bone of rabbits. Calcif Tissue Int 2012;90:202.

11. Roelofs AJ, Stewart CA, Sun S, Blazewska KM, et al. Influence of bone affinity on the skeletal distribution of fluorescently labeled bisphosphonates in vivo. J Bone Miner Res 2012;27:835.

12. Ohishi M, Chiusaroli R, Ominsky M, et al. Osteoprotegerin abrogated cortical porosity and bone marrow fibrosis in a mouse model of constitutive activation of the PTH/PTHrP receptor. Am J Pathol 2009;174:2160.

13. Parfitt A. Morphological basis of bone mineral measurements: transient and steady state effects of treatment in osteoporosis. Miner Elecrolyte Metab 1980;4:273.

14. Bone HG, McClung MR, Roux C et al. Odanacatib, a cathepsin K Inhibitor for osteoporosis: A two-year study in postmenopausal women with low bone density. J Bone Miner Res 2010;25:937.

15. Leung P, Pickarski M, Zhuo, MY, Masarachia PJ, Duong LT. The effects of the cathepsin K inhibitor odanacatib on osteoclastic bone resorption and vesicular trafficking. Bone 2011;49;591.

16. Martin TJ, Sims NA. Osteoclast-derived activity in the coupling of bone formation to resorption. Trends Mol Med 2005;11:76.

17. Jayakar RY, Cabal A, Szumiloski J, et al. Evaluation of high-resolution peripheral quantitative computed tomography, finite element analysis and biomechanical testing in a pre-clinical model of osteoporosis: A study with odanacatib treatment in the ovariectomized adult rhesus monkey. Bone 2012;50:1379.

18. Masarachia PJ, Pennypacker BL, Pickarski M, et al. Odanacatib reduces bone turnover and increases mass in the lumbar spine of skeletally mature ovariectomized rhesus monkeys. J Bone Miner Res 2012;27:509.

19. Cusick T, Chen CM, Pennypacker BL, et al. Odanacatib treatment increases hip bone mass and cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation in the ovariectomized adult rhesus monkey. J Bone Miner Res 2012;27:524.

20. Boonen S, Eastell R, Su G, et al. Time to onset of antifracture efficacy and year-by-year persistence of effect of zoledronic acid in women with osteoporosis. J Bone Miner Res 2012;27:1487.

21. Grey A, Bolland MJ, Horne A, et al. Five years of anti-resorptive activity after a single dose of zoledronate – Results from a randomized double-blind placebo-controlled trial. Bone 2012;50:1389.

22. Donnelly E, Meredith DS, Nguyen JT, et al. Reduced cortical bone compositional heterogeneity with bisphosphonate treatment in postmenopausal women with intertrochanteric and subtrochanteric fractures. J Bone Miner Res 2012;27:672.

23. Hofstetter B, Gamsjaeger S, Phipps RJ, et al. Effects of alendronate and risedronate on bone material properties in actively forming trabecular bone surfaces. J Bone Miner Res 2012;27:995.

24. Abrahamsen B, Pazianas M, Eiken P, Russell RGG, Eastell R. Esophageal and gastric cancer incidence and mortality in alendronate users J Bone Miner Res 2012;27:679.

25. Chiang CH, Huang CC, Chan WL, et al. Oral alendronate use and risk of cancer in postmenopausal women with osteoporosis: A nationwide study. J Bone Miner Res 2012;27:1951.

26. Boonen S, Lorenc RS, Wenderoth D, et al. Evidence for safety and efficacy of risedronate in men with osteoporosis over 4years of treatment: Results from the 2-year, open-label, extension study of a 2-year, randomized, double-blind, placebo-controlled study. Bone 2012;51:383.

27. Eastell R, Reid DM, Vukicevic S, et al. Effects of 3years of lasofoxifene treatment on bone turnover markers in women with postmenopausal osteoporosis. Bone 2012;50:1135.

28. Binkley N, Bolognese M, Sidorowicz-Bialynicka A, et al. A phase 3 trial of the efficacy and safety of oral recombinant calcitonin: The oral calcitonin in postmenopausal osteoporosis (ORACAL) trial. J Bone Miner Res 2012;27:1821.

29. Khadilkar A, Kadam N, Chiplonkar S, Fischer PR, Khadilkar V. School-based calcium-vitamin

D with micronutrient supplementation enhances bone mass in underprivileged Indian premenarchal girls. Bone 2012;51:1.

30. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: Relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. J Bone Miner Res 2012;27:719.

31. Fisher JE, Scott K, Wei N, et al. Pharmacodynamic responses to combined treatment regimens with the calcium sensing receptor antagonist JTT-305/MK-5442 and alendronate in osteopenic ovariectomized rats. Bone 2012;50:1332.

32. Fitzpatrick LA, Dabrowski CE, Cicconetti G, et al. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2011;96:2441.

33. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821.

34. Marsell R, Sisask G, Nilsson Y, et al. GSK-3 inhibition by an orally active small molecule increases bone mass in rats. Bone 2012;50:619.

35. Ascenzi MG, Liao VP, Lee BM, et al. Parathyroid hormone treatment improves the cortical bone microstructure by improving the distribution of type I collagen in postmenopausal women with osteoporosis. J Bone Miner Res 2012;27:702.

36. Reginster JY, Kaufman JM, Goemaere S, et al. Maintenance of antifracture efficacy over 10 years with strontium ranelate in postmenopausal osteoporosis. Osteoporos Int 2012;23:1115.

Reviews

What's in a name? What constitutes the clinical diagnosis of osteoporosis?
Siris ES, Boonen S, Mitchell PJ, Bilezikian J, Silverman S
Osteoporos Int 2012;23:2093

A systematic review of hip fracture incidence and probability of fracture worldwide
Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C
Osteoporos Int 2012;23:2239-56

Postmenopausal osteoporosis treatment with antiresorptives: Effects of discontinuation or long-term continuation on bone turnover and fracture risk – a perspective
Boonen S, Ferrari S, Miller PD, Eriksen EF, Sambrook PN, Compston J, Reid IR, Vanderschueren D, Cosman F
J Bone Miner Res 2012;27:963

Frailty and sarcopenia: Definitions and outcome parameters
Cooper C, Dere W, Evans W, Kanis J, Rizzoli R, Sayer A, Sieber C, Kaufman JM, Abellan van Kan G, Boonen S, Adachi J, Mitlak B, Tsouderos Y, Rolland Y, Reginster JY
Osteoporos Int 2012;23:1839

Twenty-five years of PTHrP progress: From cancer hormone to multifunctional cytokine
McCauley LK, Martin TJ
J Bone Miner Res 2012;27:1231

To FRAX or not to FRAX
McClung MR
J Bone Miner Res 2012;27:1240

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J Bone Miner Res 2012;27:743

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J Bone Miner Res 2012;27:747

Osteocyte RANKL: New insights into the control of bone remodeling
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J Bone Miner Res 2012;27:499

Odanacatib: Location and timing are everything
Khosla S
J Bone Miner Res 2012;7:506

Osteoporosis, frailty and fracture: Implications for case finding and therapy
van den Bergh JP, van Geel TA, Geusens PP
Nat Rev Rheumatol 2012;8:163

Regulation of bone-renal mineral and energy metabolism: The PHEX, FGF23, DMP1, MEPE ASARM pathway
Rowe PS
Crit Rev Eukaryot Gene Expr 2012;22:61

Computational modeling of bone density profiles in response to gait: A subject-specific approach
Pang H, Shiwalkar AP, Madormo CM, Taylor RE, Andriacchi TP, Kuhl E
Biomech Model Mechanobiol 2012;11:379

Atypical femur fractures: Refining the clinical picture
Abrahamsen B
J Bone Miner Res 2012;27:975

Autophagy: A new player in skeletal maintenance?
Hocking LJ, Whitehouse C, Helfrich MH
J Bone Miner Res 2012;27:1439

Sclerostin: A new mediator of crosstalk between the skeletal and immune systems
Horowitz MC, Fretz JA
J Bone Miner Res 2012;27:1448

Bone strength and surrogate markers: The first, second, and third fiddle
Miller PD
J Bone Miner Res 2012;27:1623

Recent advances in osteogenesis imperfecta
Cundy T
Calcif Tissue Int 2012;90:439

Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: A review of preclinical and clinical data
Dempster DW, Lambing CL, Kostenuik PJ, Grauer A
Clin Ther 2012;34:521

Osteocyte regulation of bone mineral: A little give and take
Atkins GJ, Findlay DM
Osteoporos Int 2012;23:2067

Osteocyte regulation of bone mineral: A little give and take
Atkins GJ, Findlay DM
Osteoporos Int 2012;23:2067

Integration of cellular adhesion and Wnt signaling: Interactions between N-cadherin and LRP5 and their role in regulating bone mass
Zhong Z, Williams BO
J Bone Miner Res 2012;27:1849

A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis
Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgstrom F, Cooper C, Diez Perez A, Eastell R, Hofbauer LC, Kanis JA, Langdahl BL, Lesnyak O, Lorenc R, McCloskey E, Messina OD, Napoli N, Obermayer-Pietsch B, Ralston SH, Sambrook PN, Silverman S, Sosa M, Stepan J, Suppan G, Wahl DA, Compston JE
Osteoporos Int 2012;23:2257

What's in a name? What constitutes the clinical diagnosis of osteoporosis?
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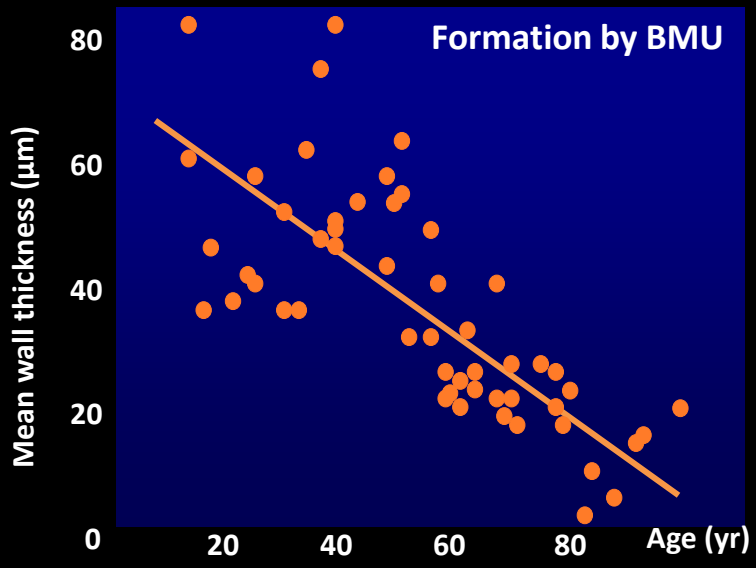
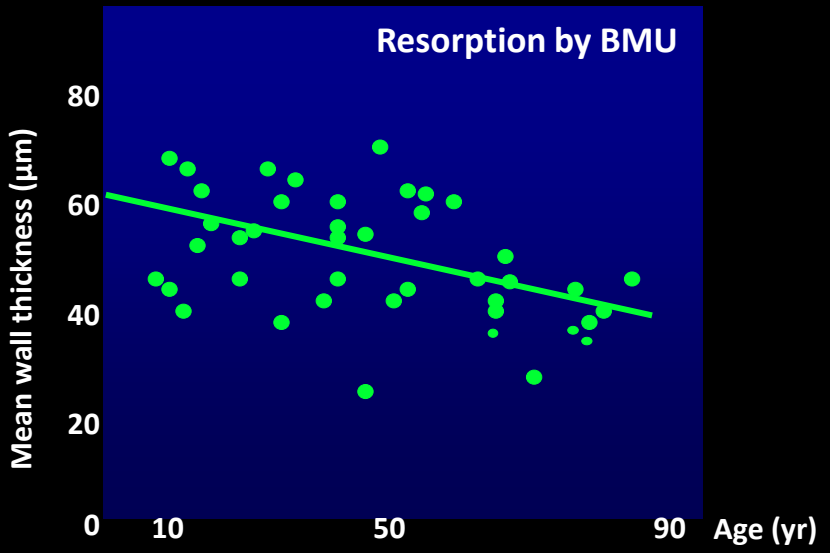
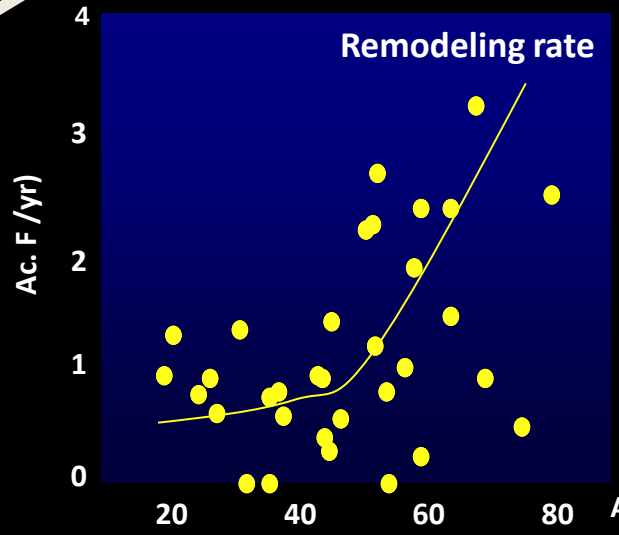


Lips et al 1979

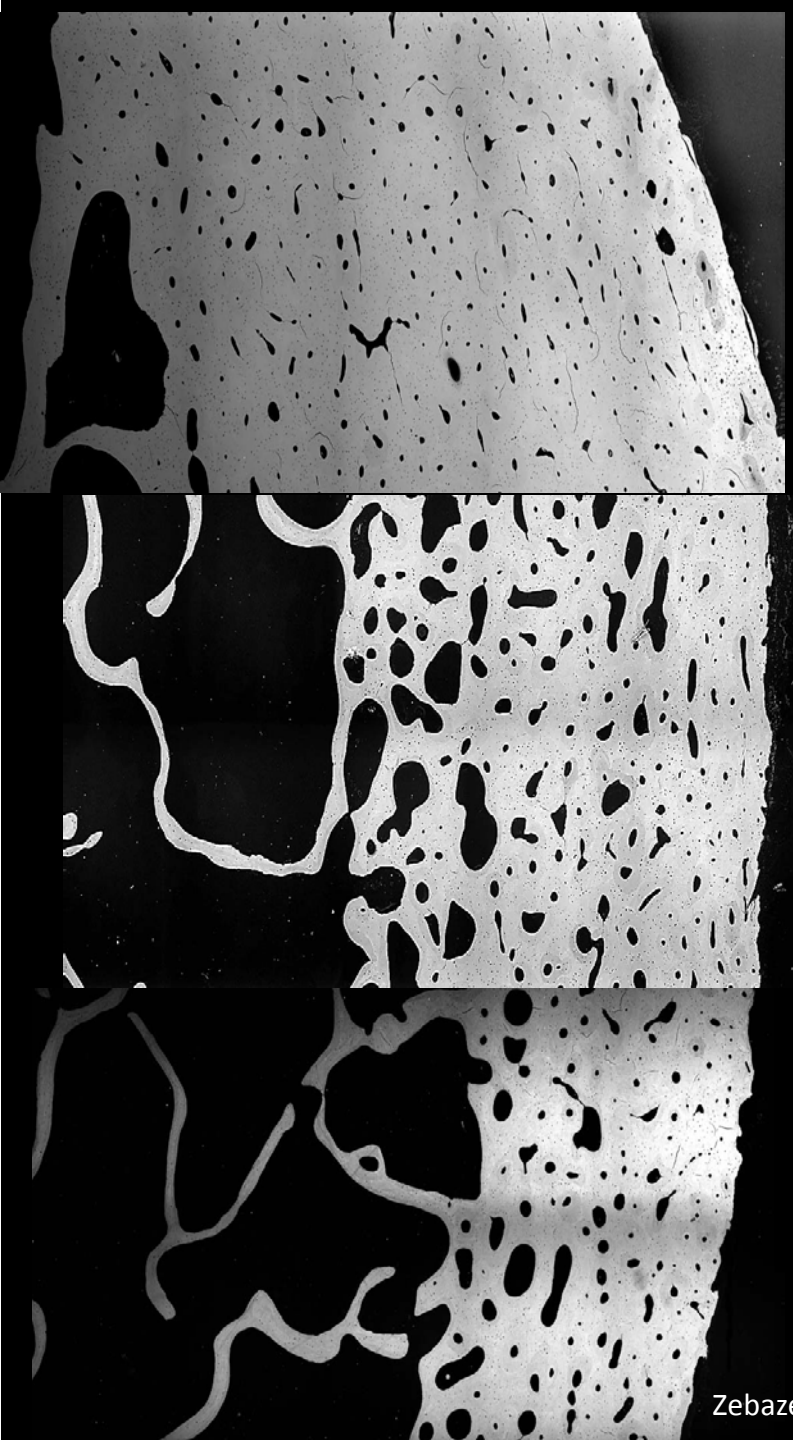


Erickson et al 1999

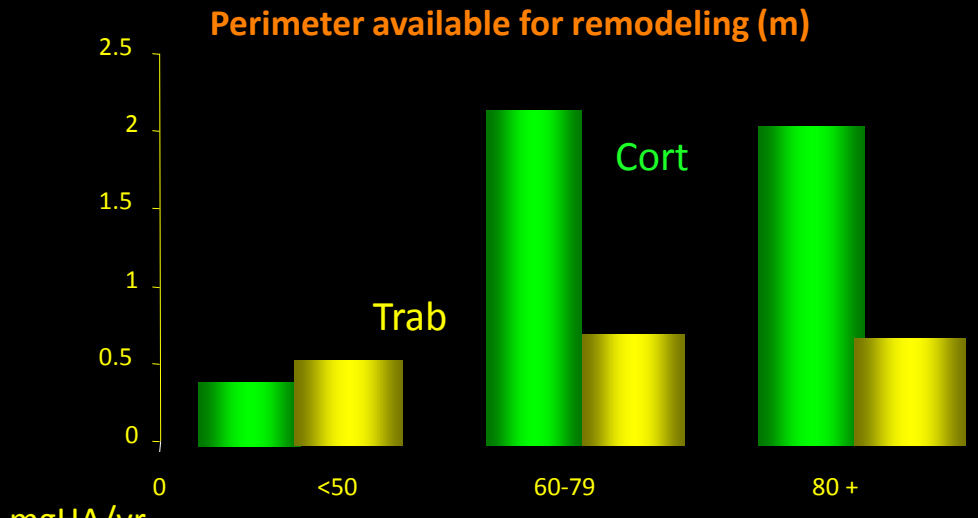
The Negative BMU Balance

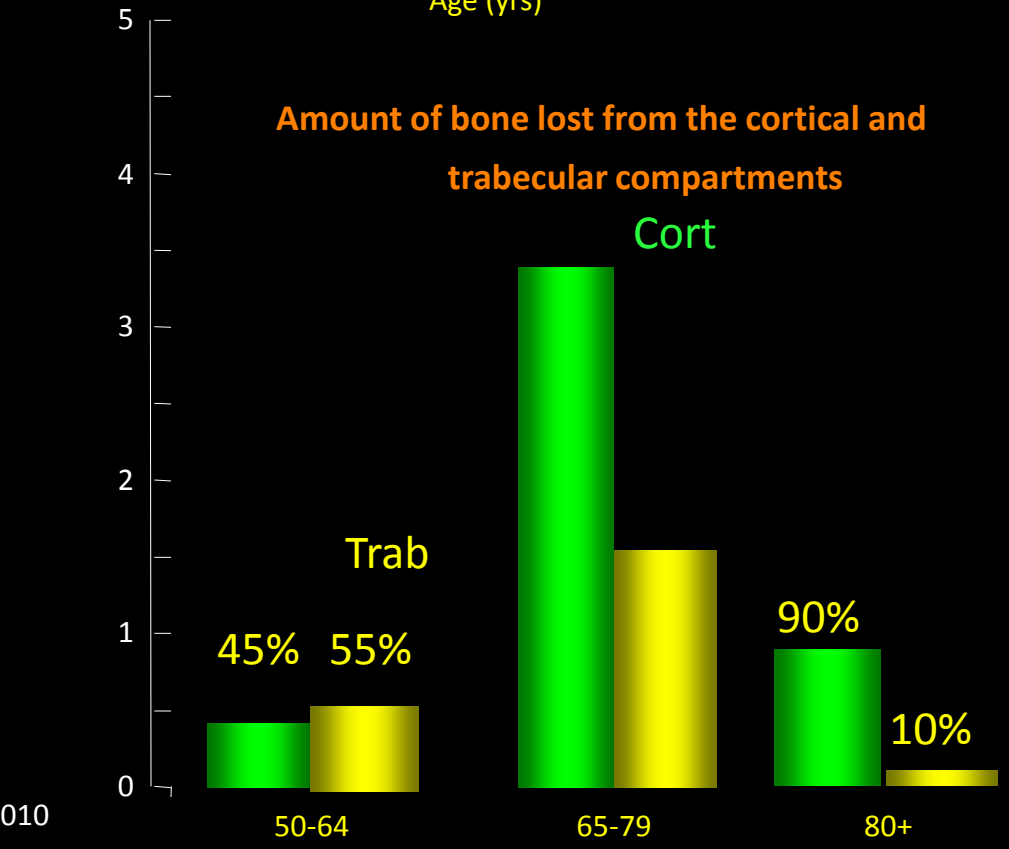


Vedi et al 1982

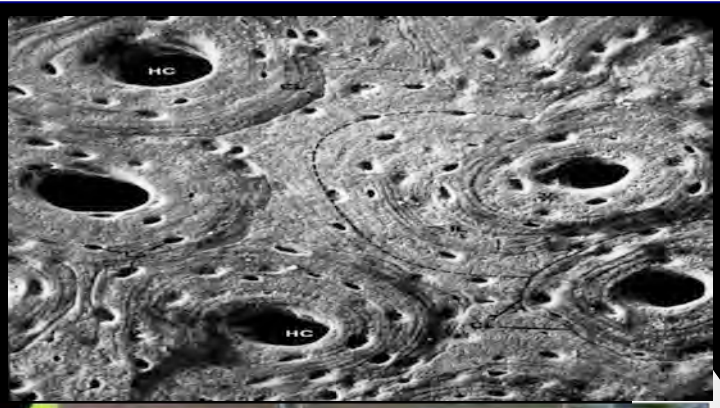


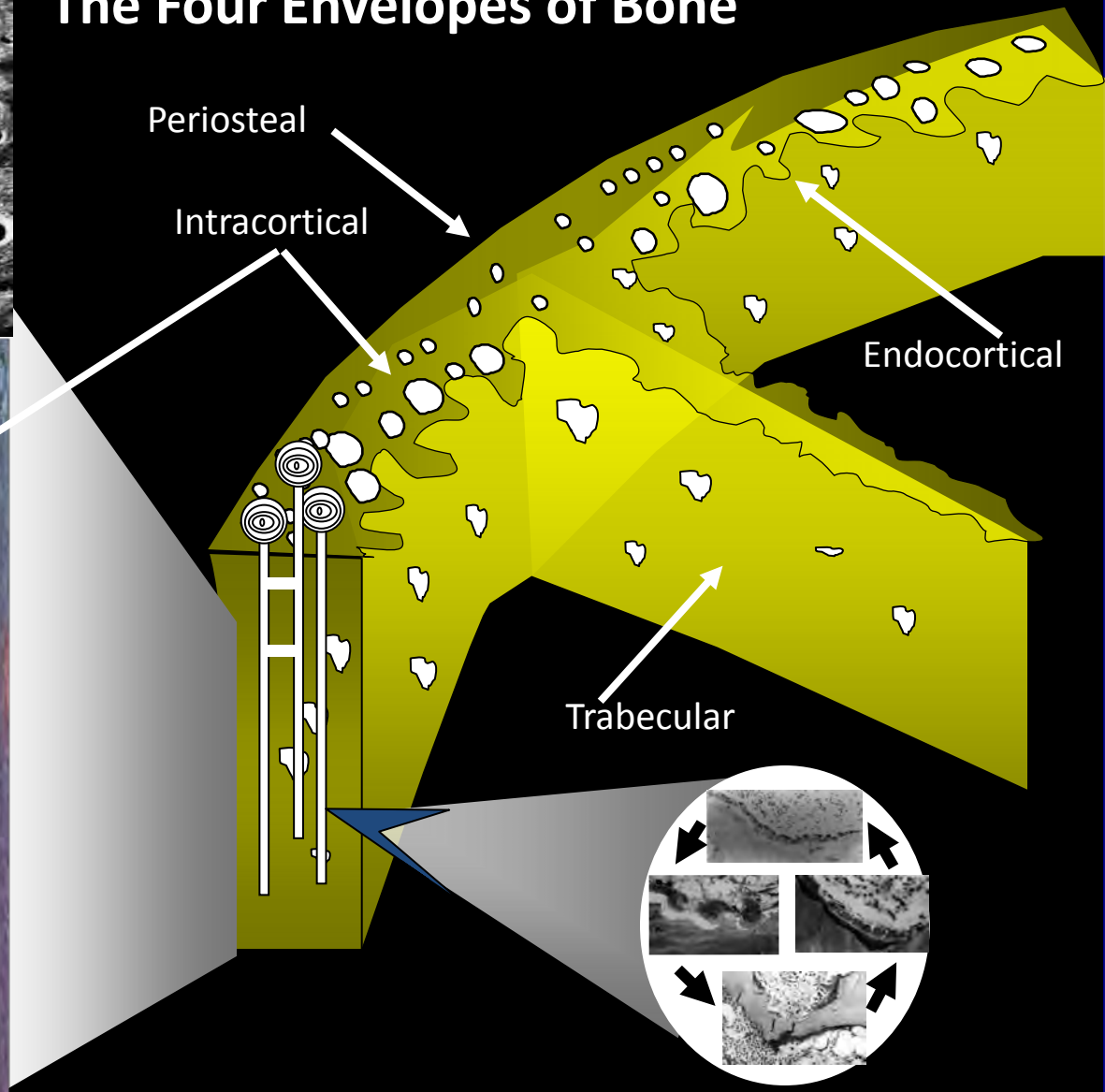
Zebaze et al 2010

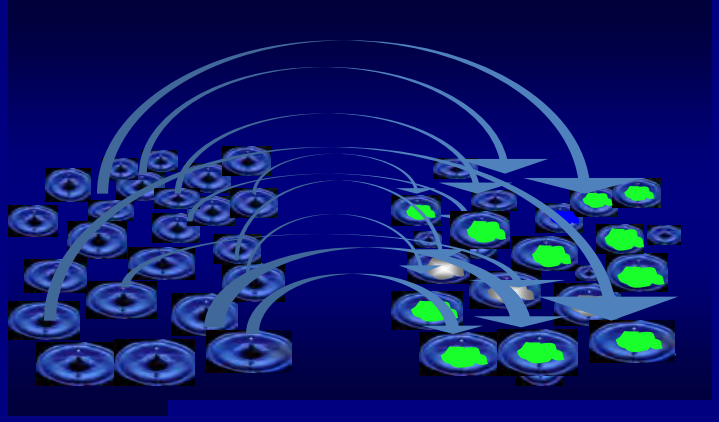




The Four Envelopes of Bone







Steady State

Perturbed

Restored, Slower

Higher density of a decreasing Bone Volume

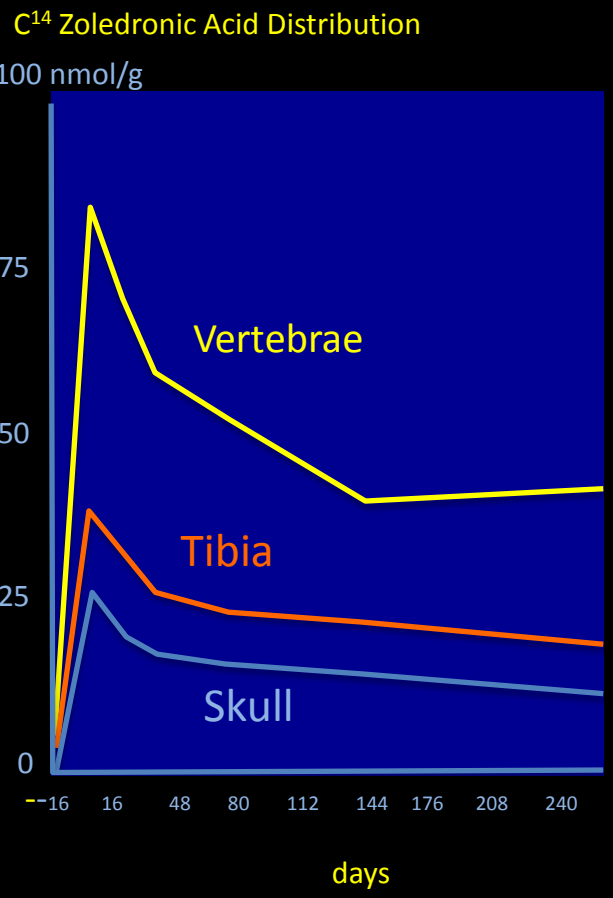
BMD

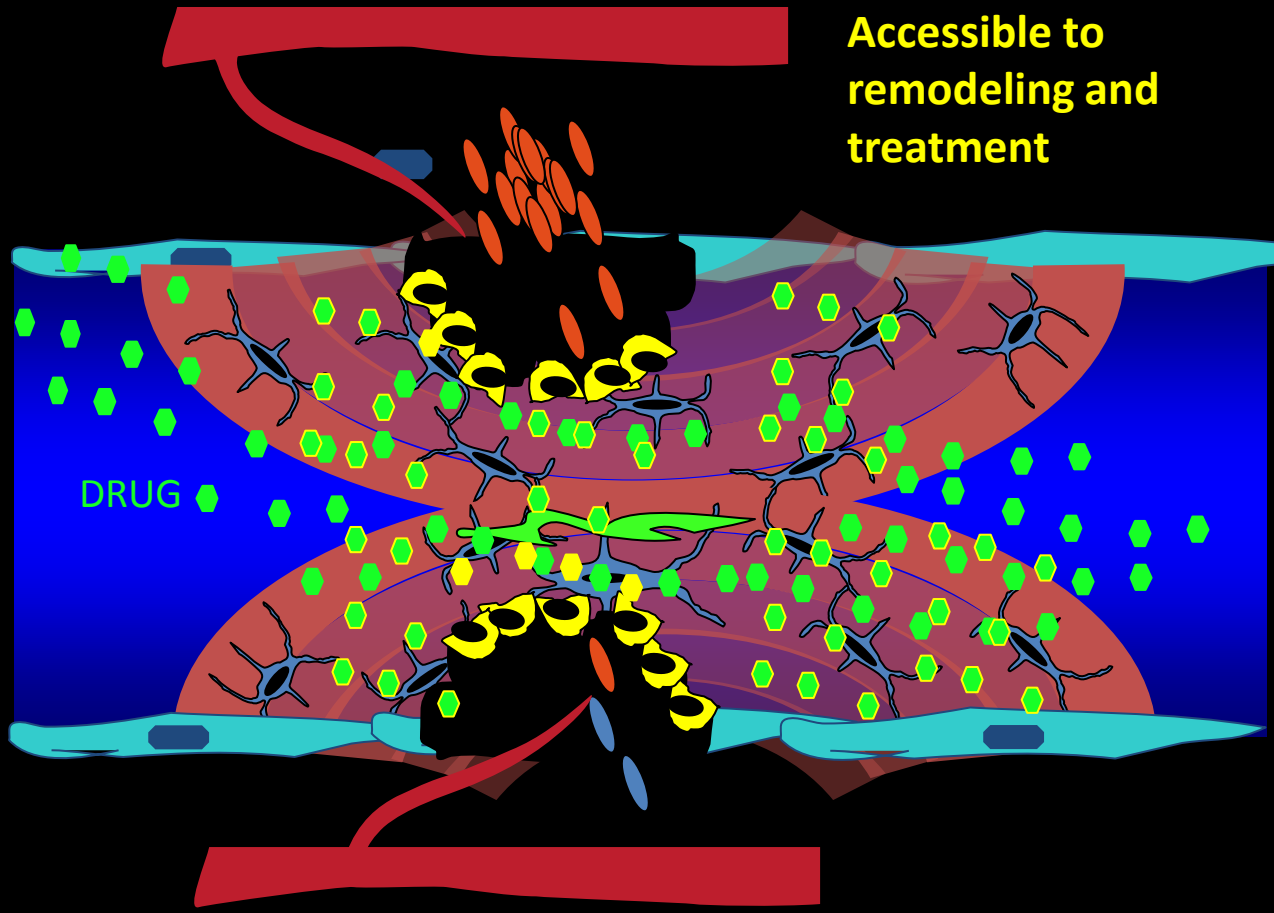
Untreated

Treat

Structural decay

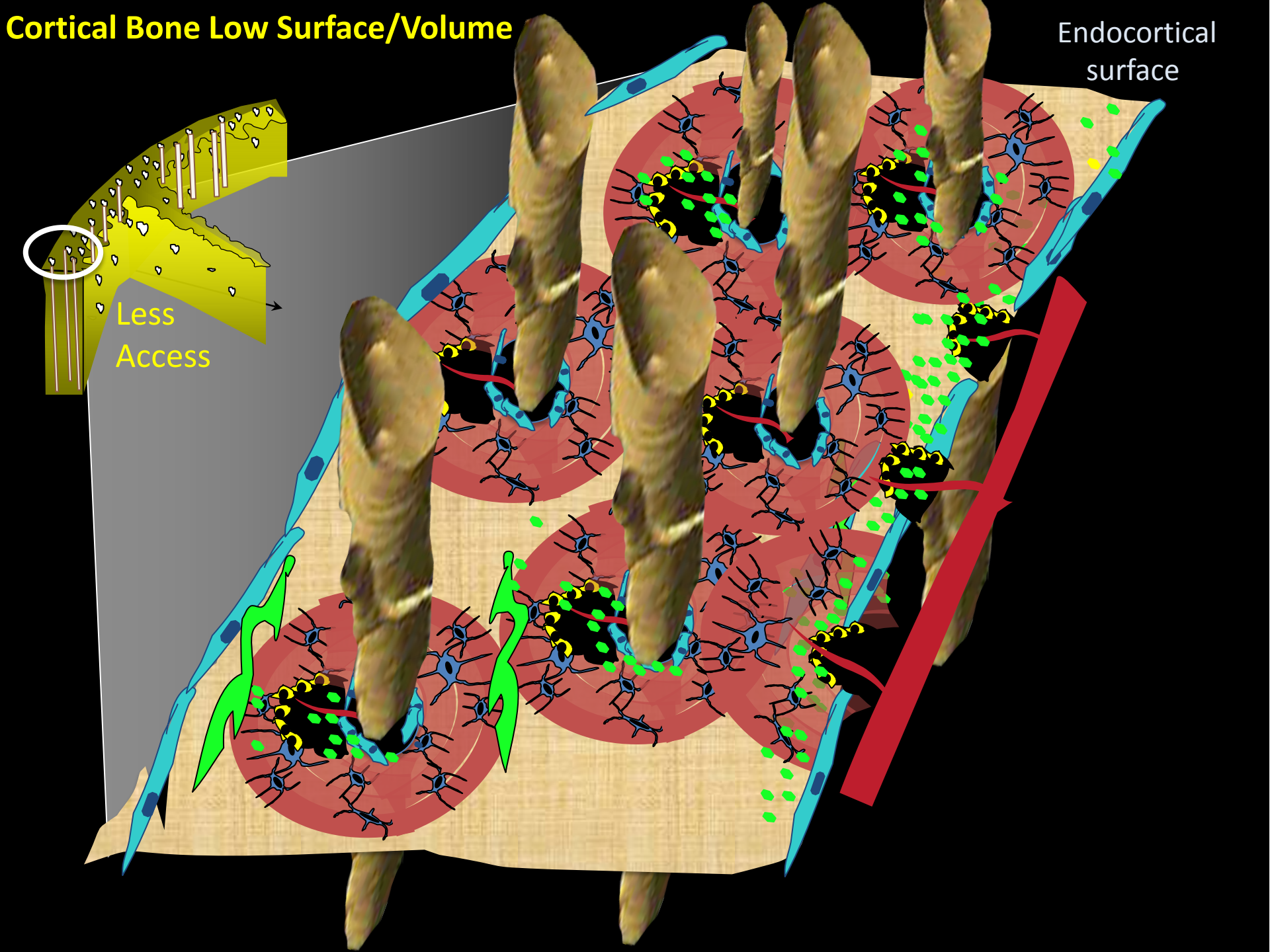
Trabecular Bone High Surface/Volume Configuration



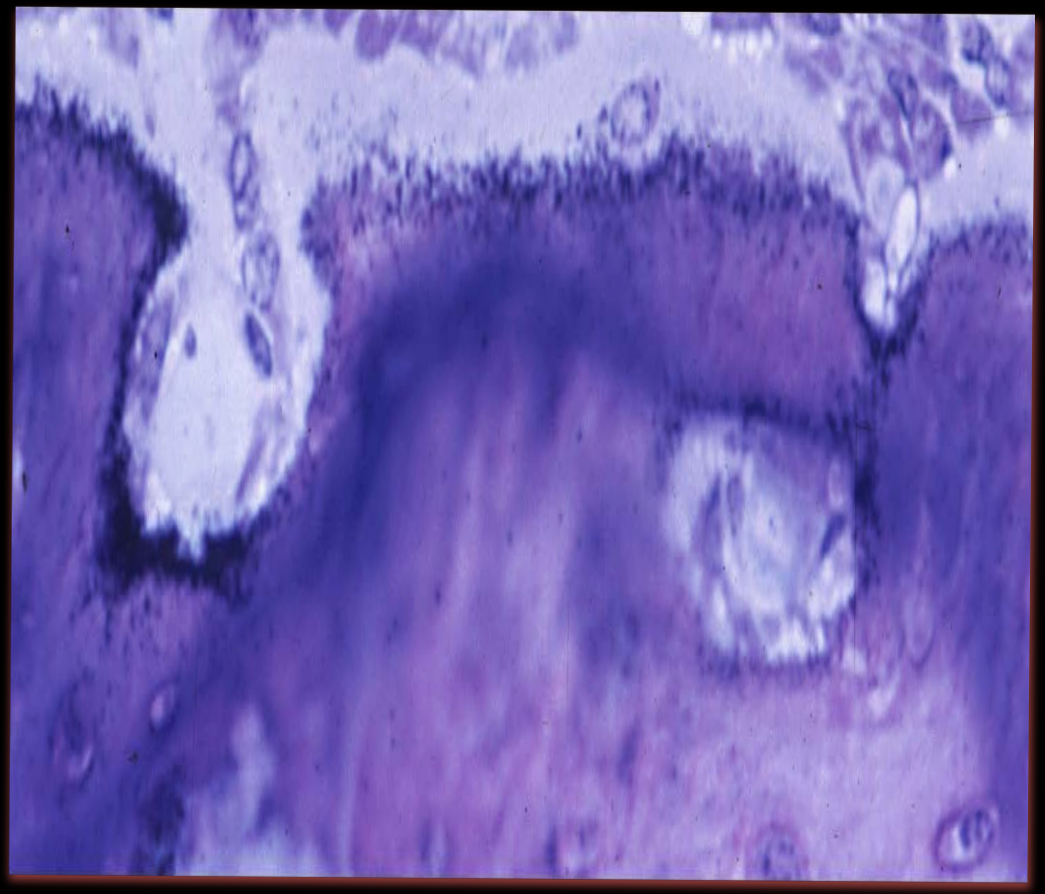


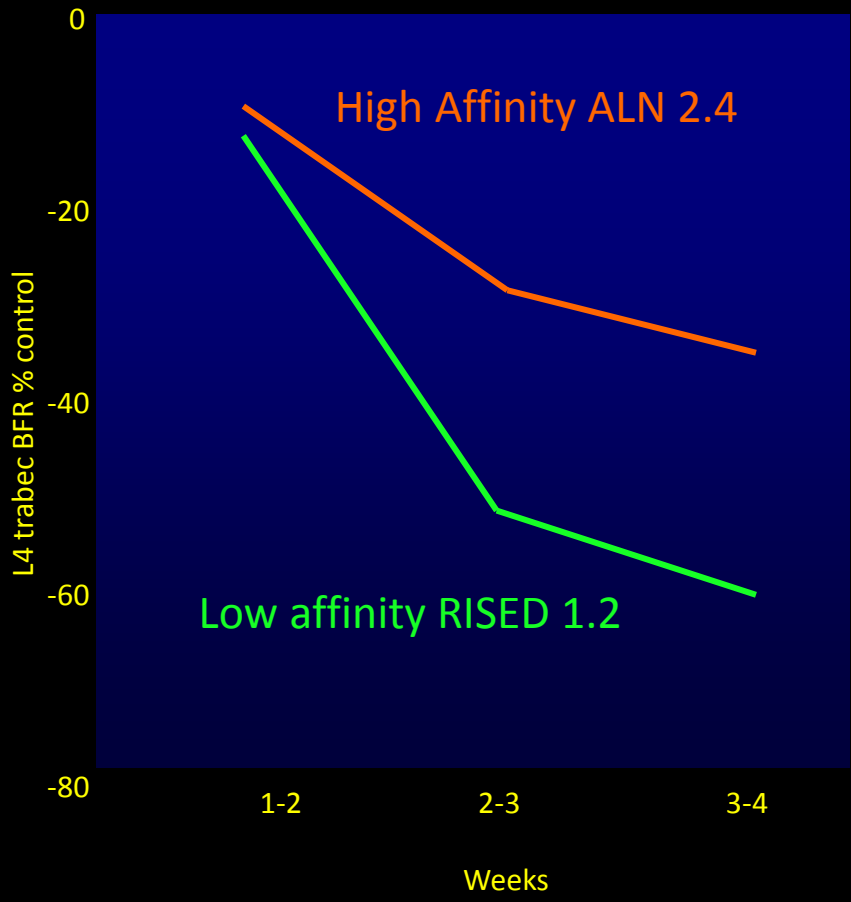
Accessible to remodeling and treatment

Weiss et al Drug Metab Distribut 2006;36:2043


Cortical Bone Low Surface/Volume
Endocortical surface
Less Access

BP on bone surfaces

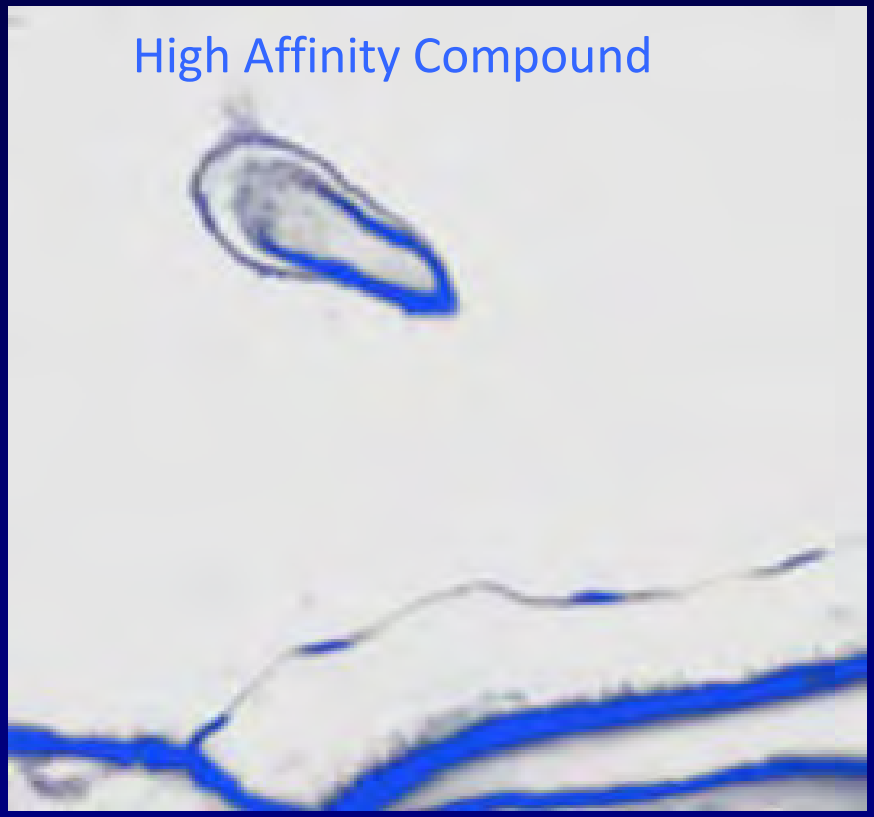


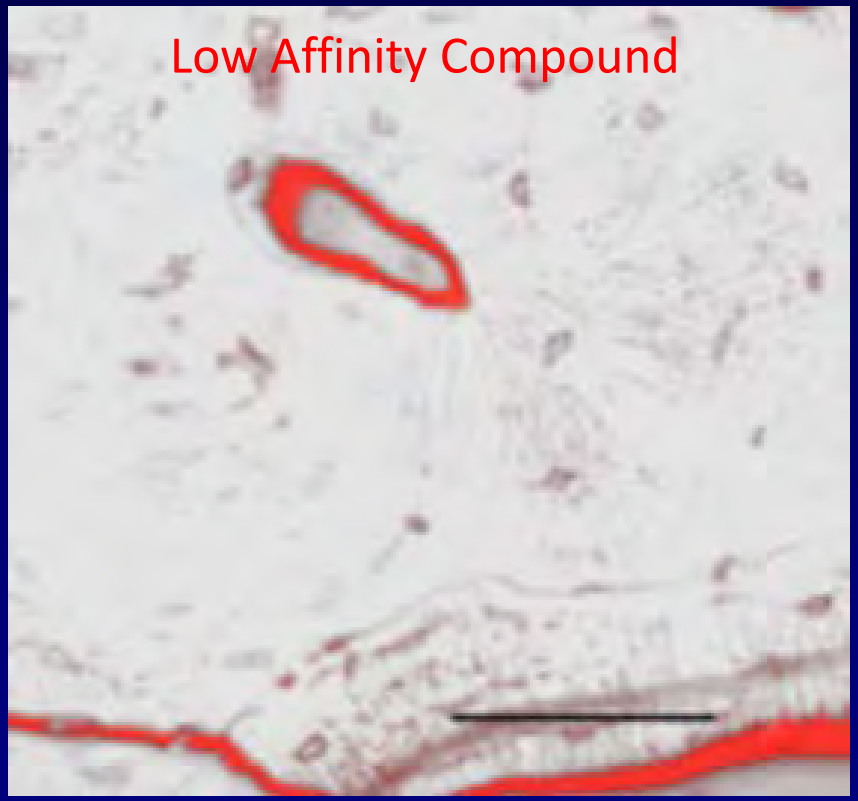


Mararachia et al Bone 1996;19:281

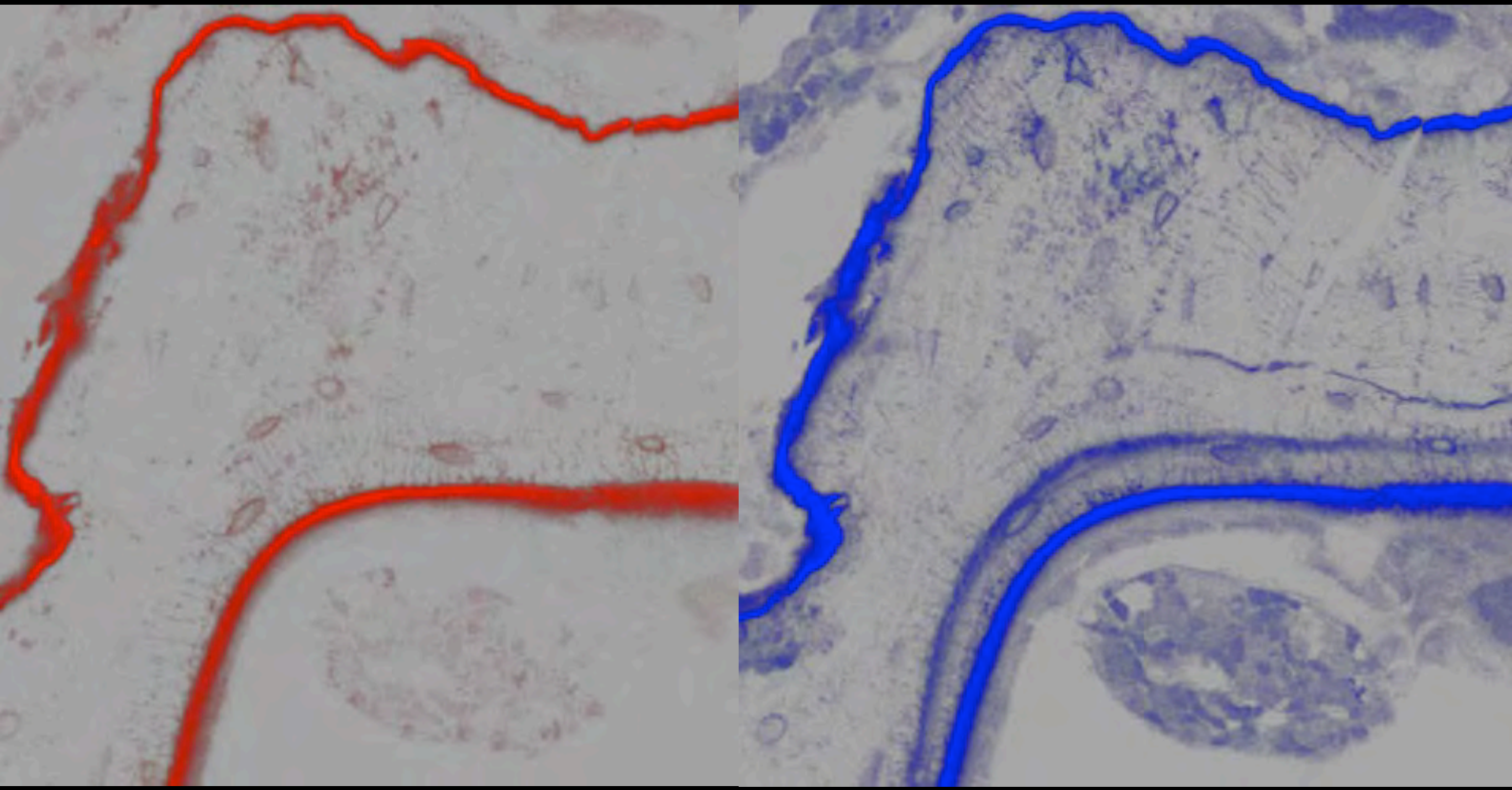
Allen et al Bone 2011;49:128

Penetration into Bone Matrix

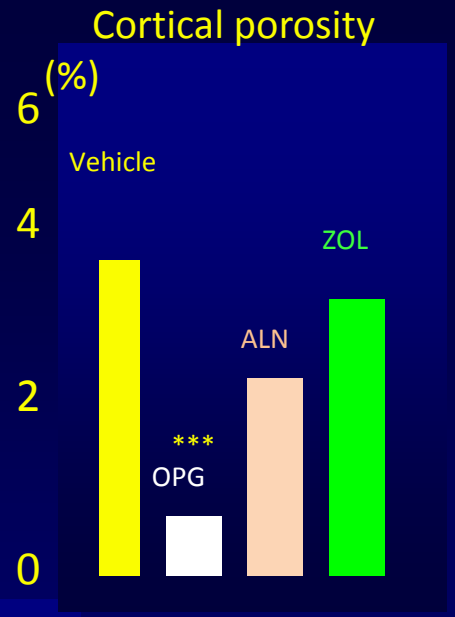


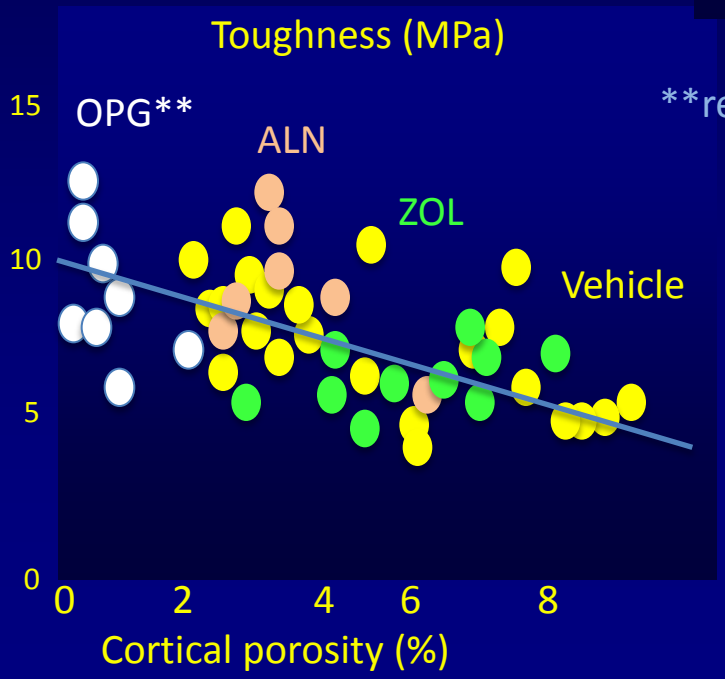


Turek et al Calcif Tissue Int 2012;90:202

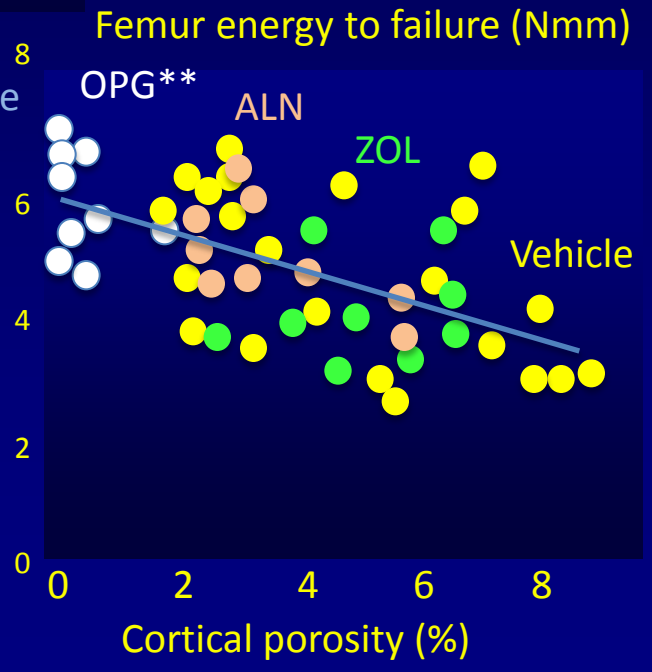


Mice constitutively activated PTH/PTHrP receptor have high porosity



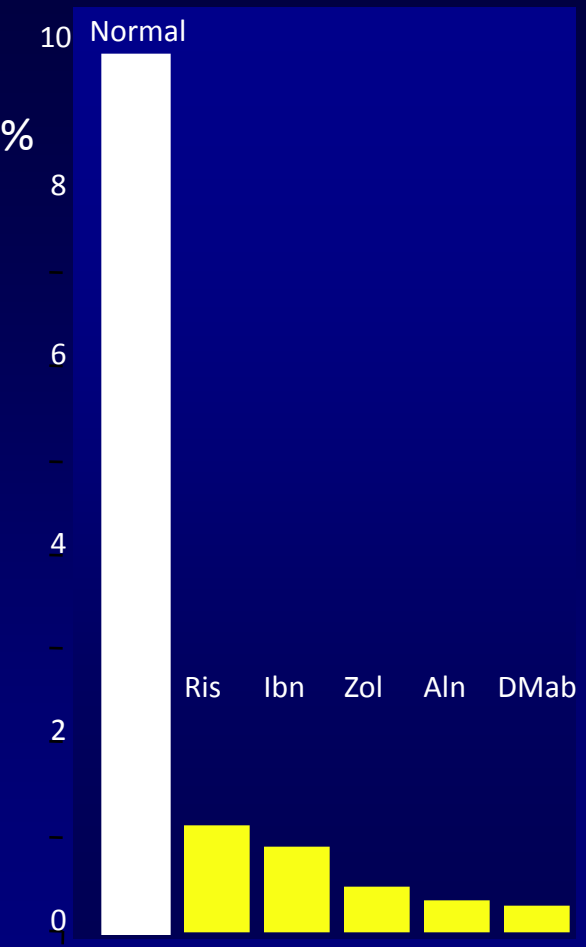


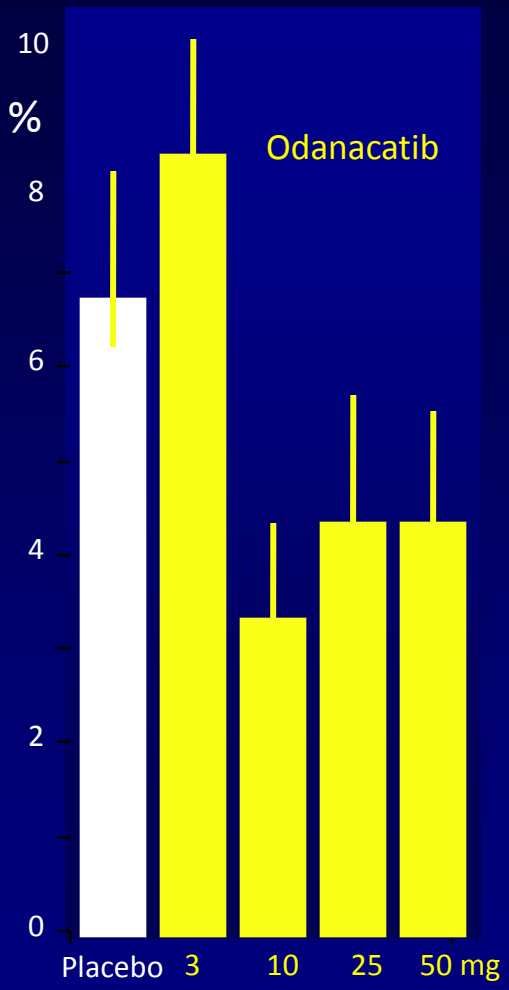
**relative to vehicle

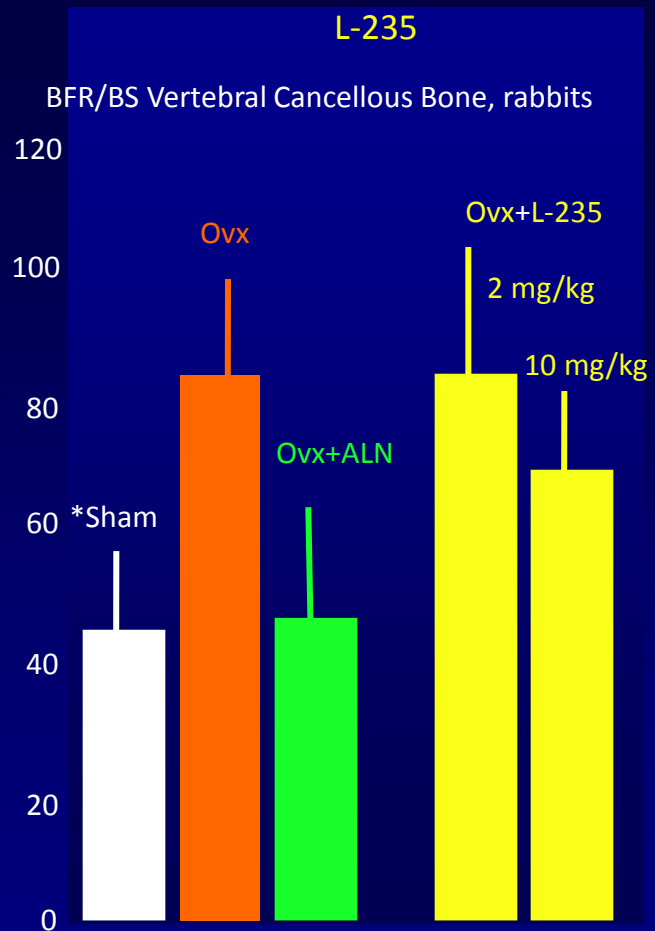


Ohishi et al Am J Pathol 2009;174:2160

Antiresorptive Therapies and the Surface Extent of Remodeling Reflected in the Mineralizing Surface MS/BS (%)



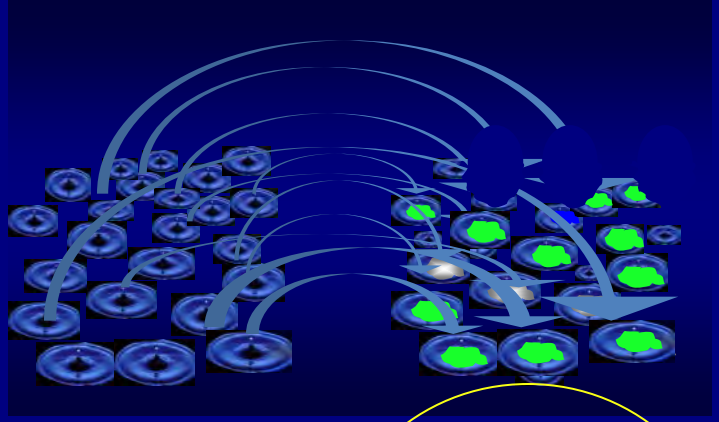




Recker JBMR 1988;31:133
Eriksen Bone 2002;31:620
Chavassieux JCI 1997;100:1475
Recker OI 2004;15:231
Recker JBMR 1008;23:6
Reid JBMR 2010

Bone H et al JBMR 2010

Pennypacker et al JBMR 2011



BP = fewer, same depth?

Steady State

Perturbed

Restored, same number, more shallow

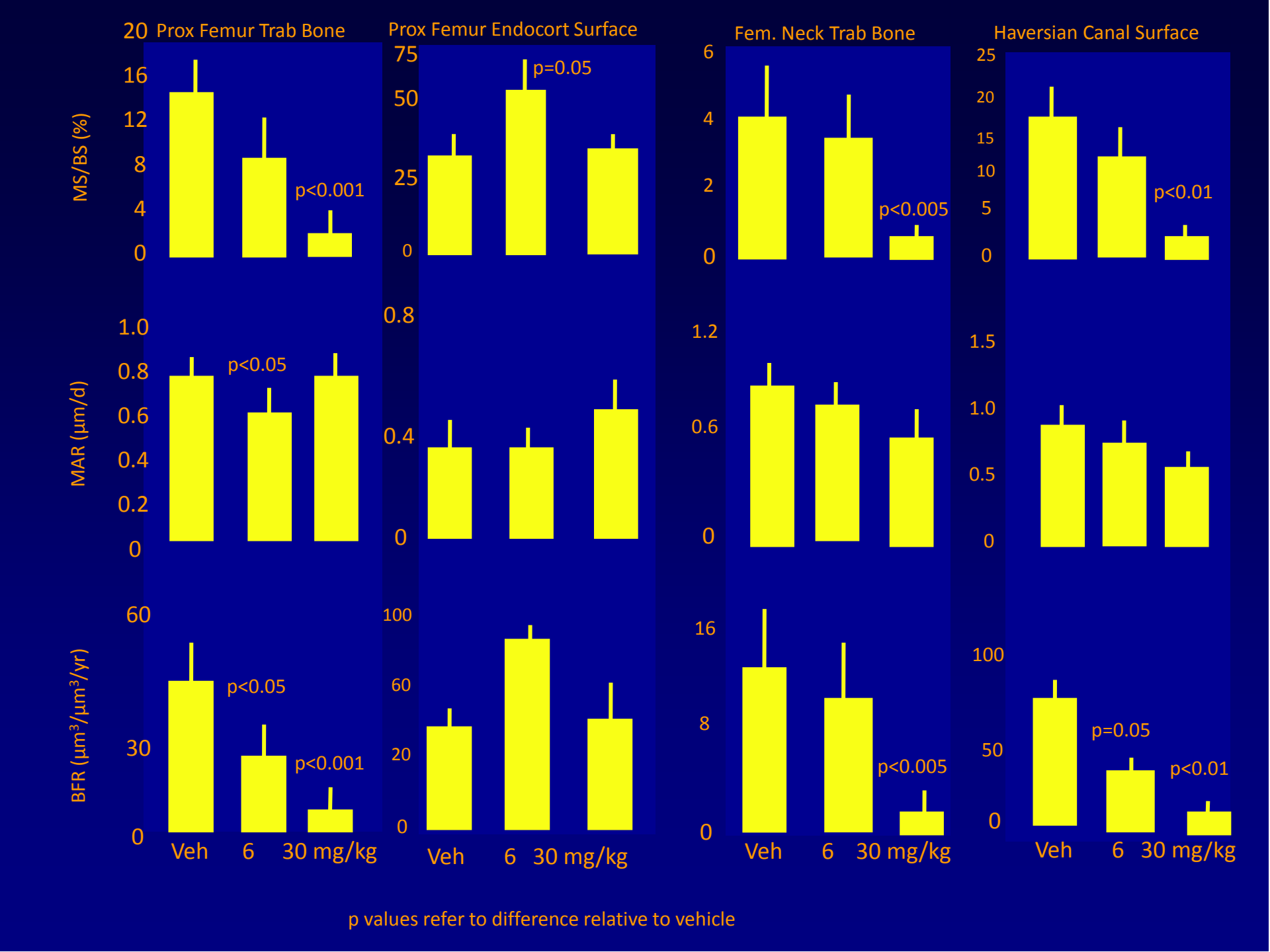
BMD

Steady state remodeling restored.
Whether there is bone loss, no loss or gain depends on bone balance.

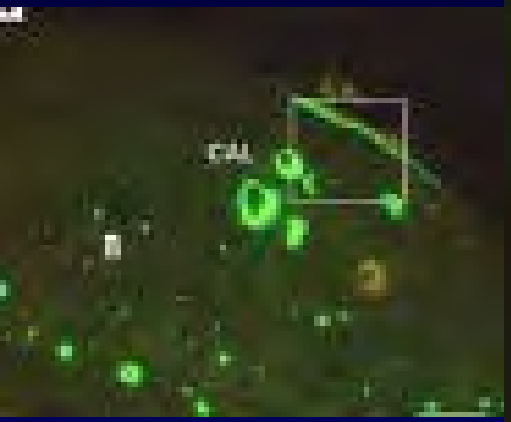
Untreated

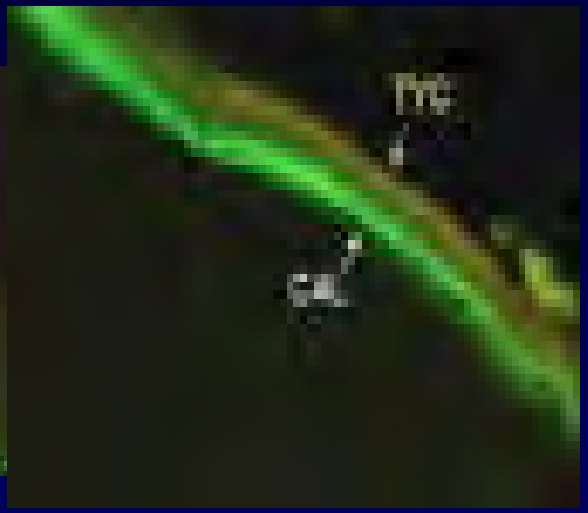
Treat

Structural decay

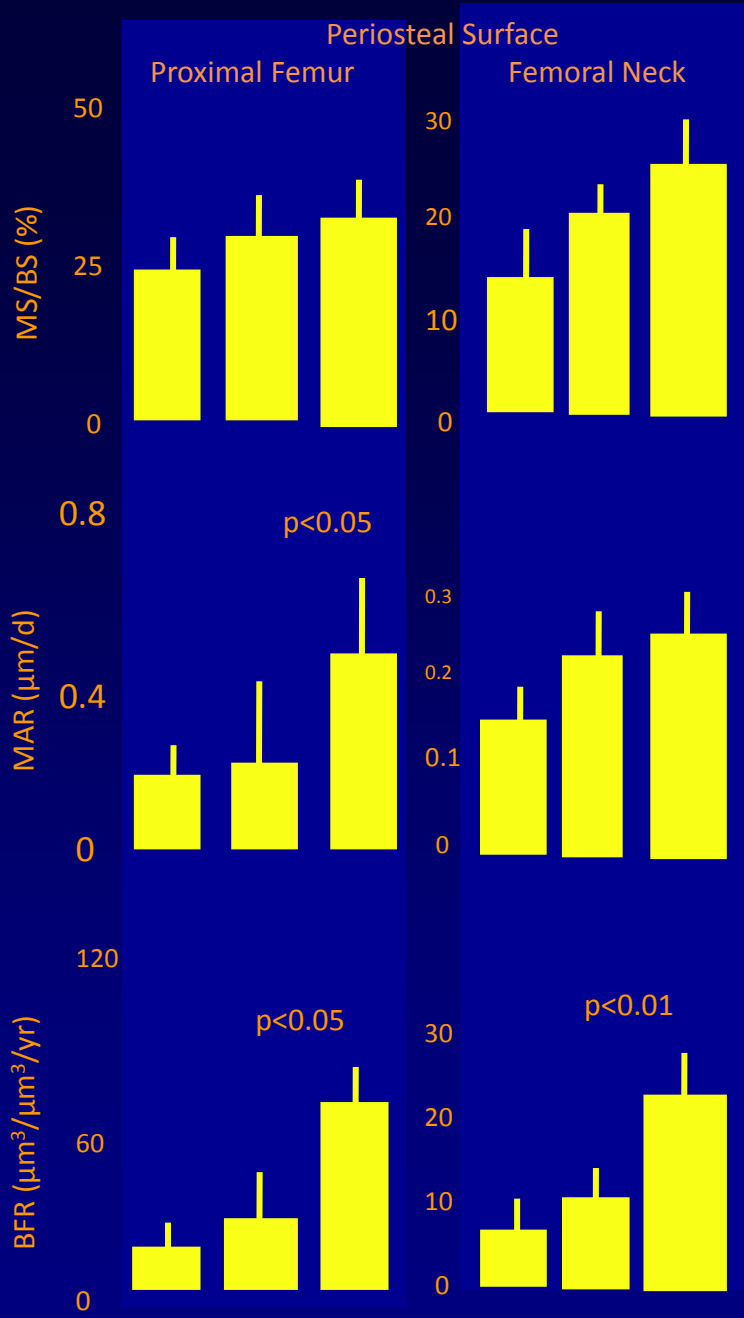

Prox Femur Trab Bone
Prox Femur Endocort Surface
Fem. Neck Trab Bone
Haversian Canal Surface
MS/BS (%)
MAR (µm/d)
BFR (µm³/µm³/yr)
p<0.001
p=0.05
p<0.005
p<0.01
p<0.05
p<0.001
p<0.05
p<0.005
p=0.05
p<0.01
Veh
6
30 mg/kg
p values refer to difference relative to vehicle

Vehicle



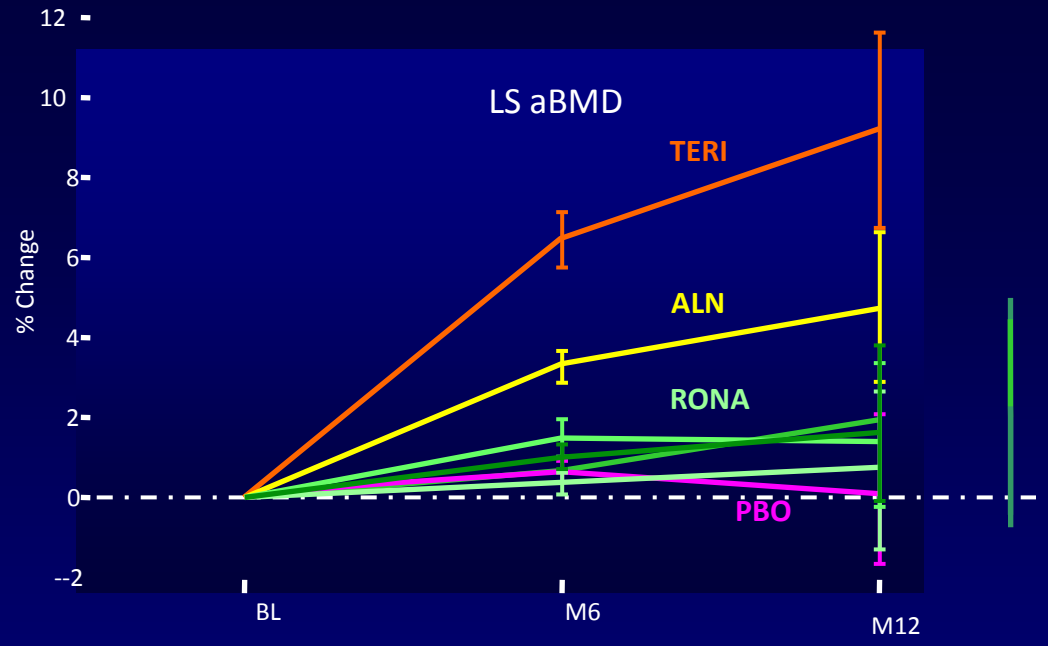


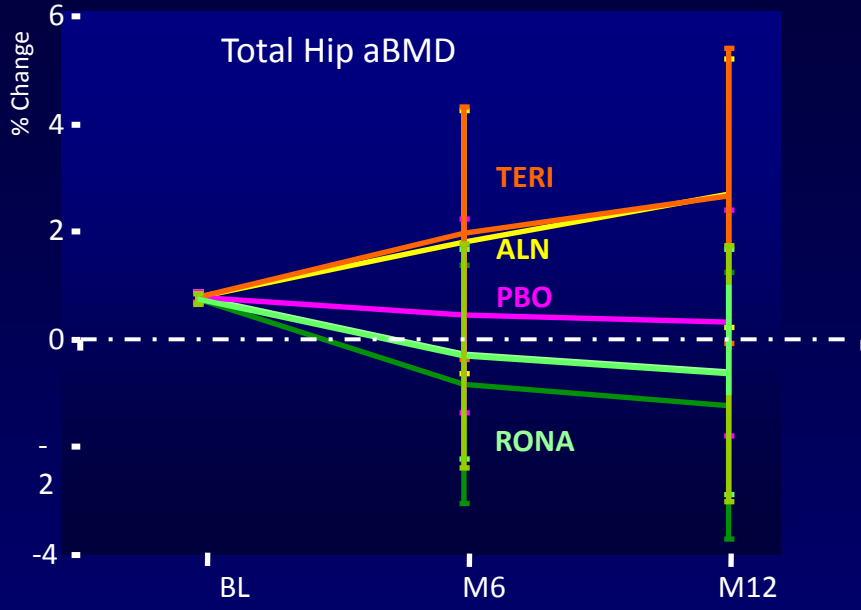
OD 30 mg/kg

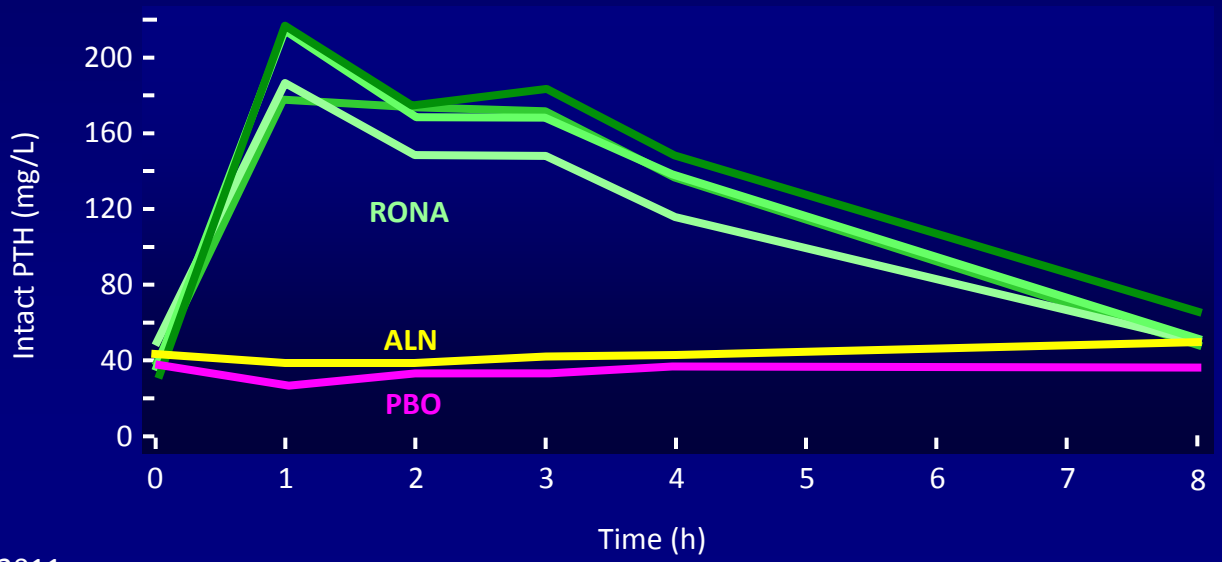


p values refer to difference relative to vehicle

Ronacalerat – Ca Receptor Antagonist







Fitzpatrick et al JBMR 2011