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Ego Seeman
Editor

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

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

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Bone's Material Composition

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

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

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

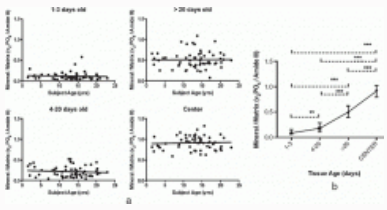

*Figure 1. (a) Scatter plots show that mineral/matrix ratio, expressed as the ratio of the integrated areas of the v_2PO_4 and amide III bands, was independent of subject age at all 4 tissue ages investigated in the present study. The linear regression line is also shown for the 4 different tissue ages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

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

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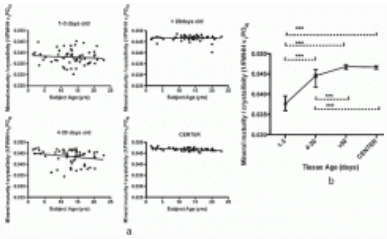


*band was independent of subject age at the 3 younger tissue ages analyzed. It was however dependent on subject age only at the oldest of the ages examined, namely at the trabecular center (Spearman r=0.360, p=0.005). It was also significantly dependent on tissue age. The linear regression line is also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

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

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

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

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

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

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

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

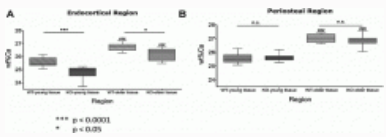
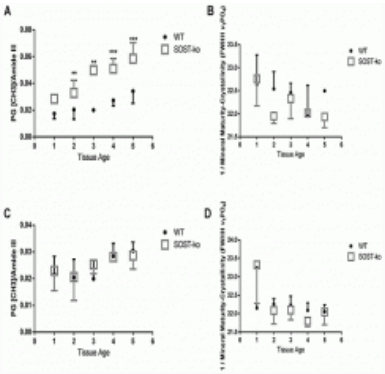


*Figure 3. Degree of mineralization (wt%Ca) in Sost KO mice and wildtypes. (A) Regions of young tissue age (5-15 days) as well as older regions (55-65 days) exhibit significantly lower mineralization (-1.9% [-0.47 wt%Ca] and -1.5% [-0.39 wt%Ca], respectively) at the site of endocortical bone apposition.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

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



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

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

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

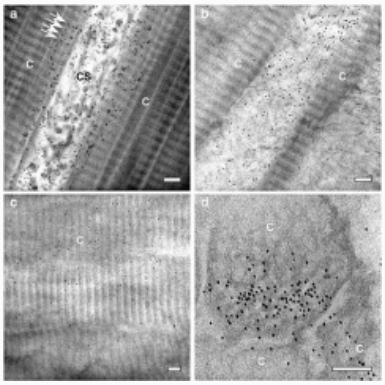


Figure 5. TEM images of immunolocalized OC stained with uranyl acetate. (a) Longitudinal tendon section with partial decalcification using 0.2% EDTA for 8 min shows immunolabeling of OC along collagen periodicity (arrows) as well as within interfibrillar collagen spaces (CS). (b, c) Longitudinal tendon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

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

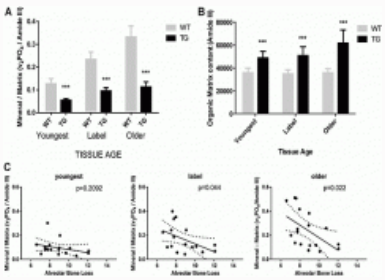


*Figure 6. (A) Mineral/matrix ratio at three distinct tissue ages at actively forming trabecular surfaces. TG animals had a significantly (***p<0.0001) lower ratio at all three. (B) Organic matrix content was significantly increased (***p<0.0001) in the TG animals at all three tissue ages considered.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

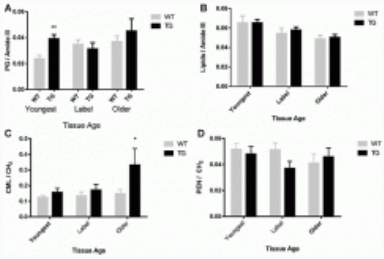


*Figure 7. (A) Relative proteoglycan content. TG animals had a higher content at the youngest tissue age (**p<0.001). (B) Relative lipids content. There were no differences between the WT and TG animals. (C) Relative CML content. The TG animals had elevated content at the oldest tissue age compared with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

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

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

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

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

Calcium Supplements in Men and Rodents

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

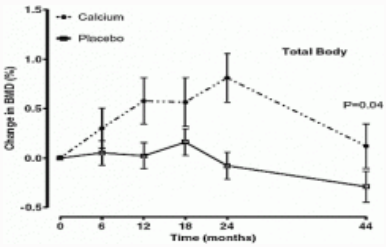


Figure 8. Change in total body BMD throughout the core trial period (up to year 2) and after discontinuation of intervention in men randomized to calcium 1200 mg/d or placebo. P values are for the between-group comparison of percent change from core trial baseline to 44 months. Data are mean ±SEM. In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

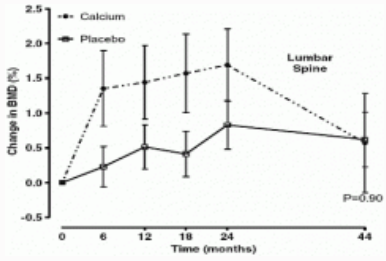


Figure 9. Change in BMD at spine throughout the core trial period (up to year 2) and after discontinuation of intervention in men randomized to calcium 1200 mg/d or placebo. P values are for the between-group comparison of percent change from core trial baseline to 44 months. Data are mean ±SEM. In the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

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

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

Risk Factors for Fractures

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

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

Antifracture Efficacy of Weekly PTH

Fujita et al reported a randomized, double-blind trial to assess the antifracture efficacy of 28.2 µg teriparatide vs. placebo (1.4 µg teriparatide) in 316 subjects studied for 131 weeks (15). Vertebral fractures occurred in 3.3% of subjects in the 28.2 µg teriparatide-treated group and 12.6% in placebo during 78 weeks; Kaplan-Meier estimates of risk after 78 weeks were 7.5 and 22.2 % in the teriparatide and placebo groups, respectively, with a relative risk reduction of 66.4% (P=0.008). Lumbar BMD in the 28.2 µg teriparatide group increased by 4.4±4.7% (P=0.001 relative to placebo).

Antifracture Efficacy of Clodronate

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

Antifracture Efficacy of Denosumab

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

Targeting Anabolic Therapy to Bone Using a Bisphosphonate

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

Anabolic Therapy
Blosozumab

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

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

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

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

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

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

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