Osteoporos Int (2003) 14 (Suppl 3): S2–S8
DOI 10.1007/s00198-002-1340-9

REVIEW ARTICLE

Reduced bone formation and increased bone resorption: rational targets for the treatment of osteoporosis

Ego Seeman

Received: 2 May 2002 / Accepted: 20 August 2002 / Published online: 19 March 2003
© International Osteoporosis Foundation and National Osteoporosis Foundation 2003

Abstract The *net* amount of bone lost during aging is determined by the difference between the amount of bone removed from the endocortical, trabecular and intracortical components of its endosteal (inner) envelope and formed beneath its periosteal (outer) envelope. Endosteal bone loss is determined by the remodeling rate (number of basic multicellular units, BMUs) and the negative balance (the difference between the volumes of bone resorbed and formed in each BMU). Bone loss already occurs in young adult women and men and is probably due to a decline in the volume of bone formed in each BMU. The rate of loss is slow because the remodeling rate is low in young adulthood. Bone loss accelerates in women at menopause because remodeling intensity increases and BMU balance becomes more negative as estrogen deficiency reduces osteoblast lifespan and increases osteoclast lifespan. The high remodeling rate also reduces the mineral content of bone tissue. The negative BMU balance results in trabecular thinning, disappearance and loss of connectivity, cortical thinning and increased intracortical porosity. These changes compromise the material and structural properties of bone while concurrent age-related subperiosteal bone formation increases the cross-sectional area (CSA) of bone partly offsetting endosteal bone loss and the loss of structural and material strength. Thus, treatments aimed at reducing the progression of bone fragility, and reversing it, should reduce activation frequency and so reduce the number of remodeling sites, reduce osteoclastic resorption in the BMU, and so reduce the volume of bone resorbed on each of the three components of the endosteal surface thereby reducing the progression of trabecular thinning, loss of connectivity, cortical thinning and porosity. If treatment also increases periosteal bone formation, the CSA of the whole bone and its cortical area will increase. If treatment also increases endosteal bone formation in the BMU, bone balance will be less negative, especially if resorption depth is reduced. This may produce thickening of trabeculae provided activation frequency is not too low. If treatment can increase de novo bone formation at quiescent endosteal surfaces, this will increase cortical and trabecular thickness, and reduce intracortical porosity. In this way, drugs directed at both the resorptive and formative aspects of remodeling, and bone modeling may (i) increase compressive and bending strength of cortical bone by increasing the diameter of the whole bone, its CSA and the distance the cortical mass is placed from the neutral long bone axis; (ii) maintain or increase peak compressive stress and peak strain in trabecular bone, preventing microcracks and buckling; and (iii) increase the material density of bone tissue, an effect that probably should not be permitted to reach a level which reduces resistance to microdamage accumulation and progression (toughness).

Keywords Bone formation · Bone resorption · Osteoporosis · Treatment

E. Seeman
Department of Endocrinology,
Austin and Repatriation Medical Centre,
3084 Heidelberg, Melbourne, Australia
E-mail: ego@austin.unimelb.edu.au
Tel.: +61-3-94965489
Fax: +61-3-94963365

Structural abnormalities in bone and their biomechanical consequences

The mineralized skeleton is defined externally by its periosteal surface and internally by the endocortical, trabecular and intracortical components of its endosteal surface [1]. Cellular activity on these surfaces modifies the external size and shape, internal architecture, total mass, and thus the material and structural strength of the skeleton. Periosteal bone formation defines the bone's cross-sectional area (CSA) while endocortical bone formation or resorption determine the proximity of the endocortical and periosteal surfaces, and thus

cortical thickness and the distance the cortical shell is positioned from the neutral or long axis of the bone, a geometric feature important in determining bending strength of the whole bone [2].

During aging, endocortical bone remodeling with net resorptive loss of cortical bone narrows the cortex so that the same axial load is distributed on a smaller CSA, so load per unit area (stress) increases, which in turn imposes greater tensile strain on the convex surface and compressive strain on the concave surface of the long bone. Increased remodeling with increased resorptive excavation of intracortical tunnels and reduced bone formation within each increases the number and size of intracortical pores, which further reduces cortical mass and CSA, predisposing to local stress and microdamage. In old age, intracortical pores coalesce reducing the CSA of the cortex further [3].

Bone resorption on each side of the trabecular network of plates produces trabecular thinning and perforation. Trabecular area decreases so that the same loads are greater in relative terms; i.e., the load per unit area on the vertical trabeculae increases predisposing to bending, while shear stresses on horizontal trabeculae may induce cracks [4]. As horizontal trabeculae disappear, the vertical trabeculae are predisposed to buckling (Fig. 1). By contrast, bone formation on each side of the trabeculae thicken them, but whether this compensatory modeling occurs is uncertain.

Periosteal bone formation at the axial and appendicular skeleton partly offsets endosteal bone loss and structural damage so that the net loss of bone from these regions is a function of all of these surface-specific changes. Women and men with spine fractures have reduced vertebral bone mineral density (BMD) because vertebral CSA is reduced due to lower than average periosteal bone formation during growth, aging or both [5, 6, 7]. BMD is also reduced because the smaller bone contains less bone within its periosteal envelope, i.e., volumetric bone mineral density (vBMD) is reduced.

The structural basis of the lower vBMD may be a reduction in bone tissue mass such as thinner cortices, increased porosity (number and size), thinner and fewer trabeculae and/or a reduction in the bone mineral content of the bone tissue mass (regrettably called "true" density). An individual may have lower vBMD because a high remodeling rate reduces the mineral content of the tissue, but the tissue volume may not differ. Techniques such as densitometry or quantitative computed tomography "see" the mineralized mass of bone, not the tissue mass, so it is not possible to determine whether the deficit in vBMD is due to structural changes produced by remodeling imbalance, a reduced mineral content of the tissue or both.

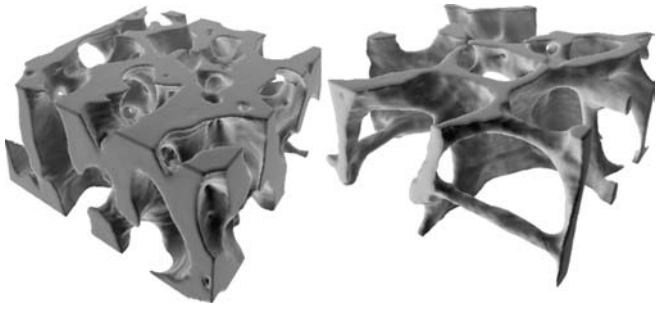

Fig. 1 Trabecular thinning and loss results in a reduction in mass and cross-sectional area of bone so that the same load is now relatively greater, increasing the risk of structural failure (from [8], with permission)

Both the reduction in tissue mineral density of a long bone's cortical shell and a reduction in the thickness of the cortical shell reduce the bone's ability to tolerate bending during loading. A reduction in trabecular number has more severe consequences for peak compressive strength than trabecular thinning or a reduction in trabecular tissue density (which may increase peak tolerable strains) [8]. Thus, vBMD may be reduced because the mineral content of the bone tissue mass is reduced, because the cortices are thin and porous, and the trabeculae are thin or have disappeared [9]. In women with hip fractures, femoral neck diameter may be reduced, normal or increased, while cortices are thin and porous [10, 11, 12, 13, 14, 15]. How do these structural abnormalities develop?

Bone "loss" during aging

Irreversible bone loss

Bone remodeling is achieved by teams of osteoclasts, which resorb a volume of bone on the endosteal surfaces at regions called basic multicellular units (BMUs). Resorption of a volume of bone is followed by bone formation by osteoblasts in the same region. Provided that the volumes of bone removed and replaced within each focal BMU are the same, no net bone loss *or* structural damage occurs. The necessary and sufficient structural requirement for bone to be irreversibly "lost" is that the volume of bone resorbed is greater than the volume of bone formed [1]. This may be the result of a reduction in the volume of bone formed, an increase in the volume of bone resorbed, or both.

BMD decreases at the spine and proximal femur in women before menopause [16, 17, 18, 19]. It is likely that there is a subtle reduction in bone formation in premenopausal women and in young adulthood in men. Evidence for this is lacking because of the lack of histomorphometric data in young women. There is a some, albeit weak, evidence for a linear decrease in mean wall thickness across age in men and in women (Fig. 2) [20]. Whether this is an "appropriate" response to reduced loading in sedentary individuals, or an "abnormality" produced by reduced osteoblast precursor production, reduced formation of mature osteoblasts, reduced osteoblast activity or lifespan, increased osteoclast generation, activity or lifespan, is uncertain but the effect is bone loss and structural damage.

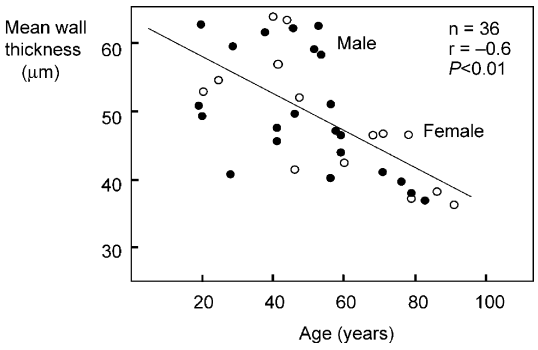

Fig. 2 Mean wall thickness, reflecting bone formation in the basic multicellular unit, declines with age (from [20], with permission)

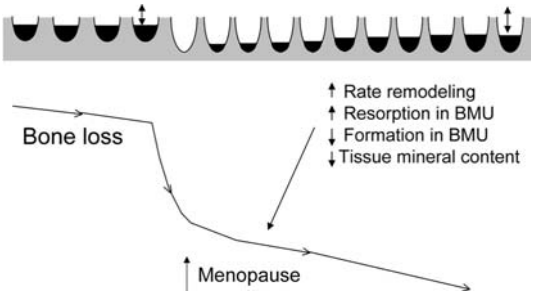

Fig. 3 After menopause there is a rapid decline in bone mineral density (BMD) because of the delay in filling of the remodeling space. BMD decline slows as steady state is restored at the higher remodeling rate but continues to decline because of the worsening negative bone balance in the basic multicellular unit (E. Seeman, with permission)

Bone loss accelerates in women at menopause because estrogen withdrawal is associated with increased remodeling intensity (activation frequency); many more discrete foci on the endosteal surfaces remodel bone, each producing bone loss because of the negative BMU balance. The initial accelerated loss of bone is due to the rapid fall in bone mineral mass produced by the increase in numbers of BMUs, which increase the porosity of bone as increased bone remodeling expands the reversible remodeling space [21, 22]. The rapid fall in BMD is a consequence of the delay in bone formation within each of the many more and new remodeling sites (Fig. 3). Bone formation (which is coupled with resorption) proceeds in these high numbers of remodeling sites while new resorptive cavities form. Bone loss continues from the lower BMD at a more rapid rate than before menopause (but slower than immediately after menopause) for three reasons: (1) BMU balance becomes more negative, (2) the remodeling rate is higher, and (3) the high remodeling rate reduces the tissue mineral content of the bone by replacing older, more densely mineralized bone with younger, less densely mineralized bone. The BMU balance is more negative because estrogen deficiency increases the lifespan of osteoclasts so more bone is resorbed in the BMU, while the lifespan of osteoblasts decreases so less bone is formed as well [23, 24]. The increased numbers of remodeling sites and the

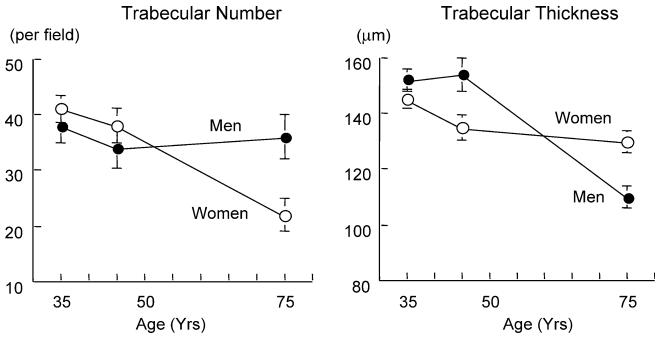

Fig. 4 Trabecular bone volume declines in women because of a decline in trabecular number with a modest decline in trabecular thickness, while trabecular thinning is greater in men than in women (from [25])

deeper resorption lacunae produce loss of connectivity in women.

Men do not undergo a midlife acceleration in bone remodeling. The loss of trabecular bone in men proceeds with thinning of trabeculae, unlike the complete loss of trabecular plates in women (Fig. 4) [25]. Bone loss is the result of a reduction in the volume of bone formed rather than the result of an increase in the volume of bone removed in the BMU, so trabecular connectivity is better maintained in men. As trabeculae are lost, the trabecular surface available for remodeling decreases. However, the surface available for trabecular remodeling in old age is better preserved in men and is greater than in women. Therefore, men may continue to lose bone from the trabecular compartment longer than women in old age. Despite the accelerated loss of bone in women, the overall loss of trabecular bone in men and women is similar in quantitative terms (suggesting trabecular bone loss continues in men longer than in women).

Late in life, endocortical and intracortical remodeling increase and bone loss comes primarily from cortical bone because remodeling is surface-based and the surfaces within cortical bone increase due to increased intracortical porosity. Cortical porosity increases with age or may decline as pores coalesce, predisposing to fractures at cortical sites such as the proximal femur [3, 26]. Cortical bone effectively becomes "trabecularized," particularly on its inner third. The total surface available for bone remodeling does not diminish with age: it moves from the trabecular to the cortical compartment.

Secondary hyperparathyroidism may increase remodeling further in elderly men and women. Bone loss accelerates in old age because the already thinner porous cortices and thinner and fewer trabeculae are subjected to the same or higher intensity of remodeling so that the same or a larger volume of bone is removed from an ever-decreasing mass of bone. Consequently, structural damage and bone fragility increase out of proportion to the reduction in bone mass. Loss of bone mineral occurs out of proportion to the loss of bone mass (produced by the negative BMU balance) because the high remodeling

produces a fall in mineral content of bone tissue. Old bone that has undergone more complete secondary mineralization is replaced by younger bone that has undergone primary, but less complete secondary, mineralization.

Periosteal bone formation during aging

As endosteal bone loss proceeds, periosteal apposition occurs concurrently, increasing the CSA of bone and reducing the net loss of bone [27]. Cortical bone loss is less in men than in women because periosteal bone formation is greater, *not* because endosteal resorption is lower (Fig. 5) [27]. Thus, bone "loss" reflects the *net* result of all the periosteal bone formed during aging minus all the bone irreversibly removed from the endosteal surface, itself a function of the size of the negative bone balance in each BMU and the number of BMUs (the remodeling rate). The hormonal factors that determine the greater periosteal apposition in men than in women are unstudied.

It is feasible that the periosteal apposition is an adaptive response to increased loads on subperiosteal bone surface which increase strains produced as trabeculae disappear and cortices become more porous and thinner. There is no evidence to support this plausible adaptive response to increased relative loading.

Thus, women and men who sustain fractures may have a range of structural abnormalities that reflect the heterogeneous nature of structural and material changes that accompany aging of the skeleton. There may be "excessive" or more rapid bone loss than the rest of the population due to a more negative bone balance in the BMU, which itself may be the result of a greater volume of bone resorbed in each BMU, a lower volume of bone formed in each BMU, or both. Alternatively, if BMU imbalance is not more negative than in age-matched controls, greater bone loss may be due to a higher remodeling rate than in controls. Histomorphometric and biochemical evidence for higher resorption in the BMU, lower bone formation in the BMU, or a higher remodeling rate in fracture cases than in controls is conflicting [28, 29, 30, 31, 32, 33, 34, 35]. Although a higher group mean for indices of resorption or a lower group mean for indices of bone formation in fracture cases is reported, there is wide scatter so that many patients have normal or reduced bone resorption while many have reduced bone formation or no histologic parameters outside the reference range, suggesting reduced vBMD may be the result of a reduced peak vBMD with bone loss proceeding at a rate no different from controls. Thus, could greater antifracture efficacy result if drug therapy were targeted to the underlying abnormality (anabolic therapy for individuals with reduced bone formation, antiresorptive therapy for patients with increased resorption, or both drugs for individuals with both abnormalities)?

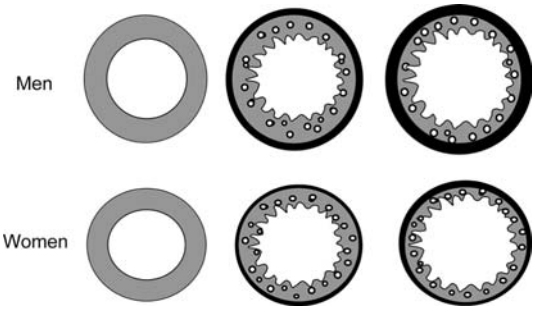

Fig. 5 Cortical bone loss is less in men than in women because periosteal bone formation is greater in men, not because endocortical resorption is less (E. Seeman, with permission)

Antiresorptives increase the mineral content of the more slowly diminishing mass of bone

Antiresorptive agents reduce the rate at which bone is remodeled. Fewer sites excavate bone on its endosteal (trabecular, endocortical, intracortical) surfaces so that less of the existing volume of the mineralized skeleton is "turned over." The reduced remodeling rate results in slowing in the progression of trabecular and cortical thinning, trabecular perforation and cortical porosity. The reduced turnover of the skeletal mass results in an increase in the mineral content of the existing bone, which increases the bending stiffness of cortical and trabecular bone. This increase in mineral density of the bone tissue, together with the initial filling of the reversible or transient remodeling space when remodeling slows down, accounts for most of the increase in BMD found with antiresorptive agents (Fig. 6). Older osteons at various stages of secondary mineralization are no longer removed and replaced by young bone but rather undergo more complete secondary mineralization.

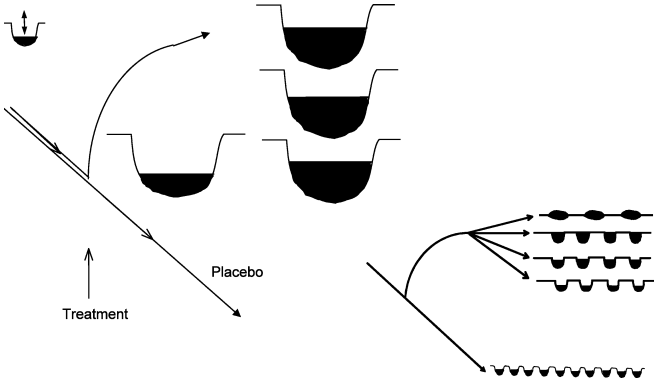

Fig. 6 Bone mineral density increases with antiresorptive therapy because filling of the reversible remodeling space deficit proceeds when the larger number of resorptive cavities from the cycle before the drug was given complete their remodeling cycle. *Inset*: From this higher level bone loss resumes or stops depending on the rate of remodeling and the size of the negative bone balance in each basic multicellular unit (E. Seeman with permission)

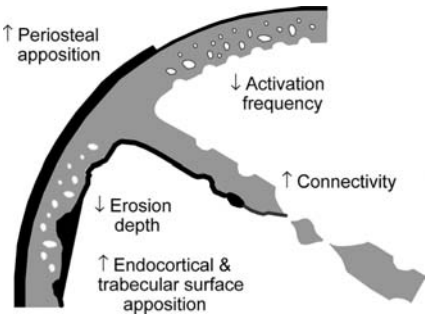

Fig. 7 Combined approach to treatment reducing the resorptive side of remodeling (activation frequency, resorption depth) and bone formation on the periosteum, in the basic multicellular unit and de novo on quiescent endosteal surfaces, may restore the structure and mass of bone (E. Seeman with permission)

Antiresorptives may also reduce the magnitude of the BMU imbalance by reducing the lifespan of the osteoclast and increasing the lifespan of the osteoblast. The increase in mineral density of the tissue may increase the stiffness of the bone allowing accumulation and spread of microdamage, as more homogeneously mineralized bone is less resistant to crack propagation (i.e., bone becomes less tough) [36, 37].

Thus, the antiresorptive agents combat the three mechanisms causing bone loss: they reduce the rate of remodeling, they may reduce the negative balance in the BMU by producing shallower resorption cavities and they increase the mineral content of the bone. Studies in beagles suggest residronate reduces resorption depth and increases mean wall thickness while alendronate reduces cortical porosity [38, 39]. There is no compelling evidence of an increase in trabecular bone volume on iliac crest bone biopsy specimens. This should occur if the remodeling space is reduced but changes may be difficult to detect. There is no consistent evidence that these drugs eliminate the negative bone balance or make it positive; the latter would thicken the cortices and trabeculae were it not for the slow remodeling rate.

The drugs do slow the progression of bone fragility by reducing the remodeling rate but at no stage is there an increase in bone mass beyond that produced by reduction in the reversible remodeling space. Indeed, bone tissue mass continues to decrease, albeit more slowly, while the mineral content of the decreasing tissue mass increases because bone turnover is reduced. This is documented using alendronate [39] and is likely to occur to varying degrees with agents that reduce the remodeling rate, such as calcium supplements, estrogen, raloxifene, and risedronate as well. The increase in mineral content of the existing bone may partly account for the early reduction in fracture risk. Whether the continued increase in the mineral content reduces or increases bone fragility in the longer term is uncertain [36, 37]. Antiresorptive agents do not restore the strength of bone by increasing its mass and refashioning this mass into its pristine architectural form.

Prospects for restoring the structure of bone using formation-stimulating agents

One of the most encouraging advances in the field of osteoporosis is the emergence of evidence that bone-forming agents such as intermittent parenteral parathyroid hormone therapy and daily oral strontium ranelate reduce the risk of fractures [40, 41, 42, 43]. Intermittent parathyroid hormone administration increases the CSA of bone by stimulating both periosteal and endocortical apposition, increases trabecular thickness and may increase trabecular connectivity.

More recently, evidence of the antifracture efficacy of strontium ranelate in spine fractures has been reported in abstract form. This orally active agent appears to have bone-forming and antiresorptive activity [44]. In preclinical evaluation, strontium ranelate was reported to increase bone mass and mechanical properties of bones [43].

Summary and conclusion

Antiresorptive agents reduce the remodeling rate and the magnitude of the negative bone balance by reducing osteoclast lifespan and increasing osteoblast lifespan. Focal remodeling is reduced and erosion cavities are more shallow, so that trabecular thinning, perforation and cortical thinning proceed more slowly. Antiresorptive drugs may reduce the severity of the negative bone balance but they do not make bone balance positive, so they cannot restore or "build" bone. As bone turnover is reduced, older osteons undergo more complete secondary mineralization so that the more slowly declining mass of bone has a higher mineral content.

Reduced bone formation plays a central role in the pathogenesis of bone loss and bone fragility. Increasing bone formation appears to be a rational approach to the reversal of bone fragility provided that anabolic treatment can (i) increase periosteal and endocortical apposition and so increase bone size and cortical thickness; (ii) increase trabecular thickness, number and connectivity and (iii) allow normal bone mineralization to occur (Fig. 7). There seems to be progress in this direction.

References

1. Parfitt AM. Skeletal heterogeneity and the purposes of bone remodelling; implications for the understanding of osteoporosis. In: Marcus R, Zfeldman D, Kelsey J, editors. San Diego: Academic Press, 2001:433–444.
2. Ruff CB, Hayes WC. Sex differences in age-related remodeling of the femur and tibia. J Orthop Res 1988;6:886–96.

3. Jordan GR, Loveridge N, Bell KL, Power J, Rushton JN, Reeve J. Spatial clustering of remodeling osteons in the femoral neck cortex: a cause of weakness in hip fracture? Bone 2000;26:305–13.
4. Fyhrie DP, Schaffler MB. Failure mechanisms in human vertebral cancellous bone. Bone 1994;15:105–9.
5. Duan Y, Parfitt M, Seeman E. Vertebral bone mass, size and volumetric bone mineral density in premenopausal women, and postmenopausal women with and without spine fractures. J Bone Miner Res 1999;14:1796–802.
6. Seeman E, Duan Y, Fong C, Edmonds J. Fracture site-specific deficits in bone size and volumetric density in men with spine or hip fractures. J Bone Miner Res 2001;16:120–7.
7. Vega E, Ghiringhelli G, Mautalen C, Valzacchi GR, Scaglia H, Zylberstein C. Bone mineral density and bone size in men with primary osteoporosis and vertebral fractures. Calcif Tissue Int 1988;62:465–9.
8. Keaveny TM, Morgan EF, Niebur GL, Yeh OC. Biomechanics of trabecular bone. Annu Rev Biomed Eng 2001;3:307–33.
9. Meunier PJ, Sellami S, Briancon D, Edouard C. Histological heterogeneity of apparently idiopathic osteoporosis. In: Deluca HF, Frost HM, Jee WSS, Johnston CC, Parfitt AM, editors. Osteoporosis: recent advances in pathogenesis and treatment. Baltimore: University Park Press, 1990:293–301.
10. Beck TJ, Ruff CB, Scott WW Jr, Plato CC, Tobin JD, Quan CA. Sex differences in geometry of the femoral neck with aging: a structural analysis of bone mineral data. Calcif Tissue Int 1992;50:24–9.
11. Boonen S, Koutri R, Dequeker J, Aerssens J, Lowet G, Nijs J, et al. Measurement of femoral geometry in type I and type II osteoporosis: differences in hip axis length consistent with heterogeneity in the pathogenesis of osteoporotic fractures. J Bone Miner Res 1995;10:1908–12.
12. Cheng XG, Lowet G, Boonen S, Nicholson PHF, Brys P, Nijs J, et al. Assessment of the strength of proximal femur in vitro: relationship to femoral bone mineral density and femoral geometry. Bone 1997;20:213–8.
13. Karlsson KM, Sernbo I, Obrant KJ, Redlund-Johnell I, Johnell O. Femoral neck geometry and radiographic signs of osteoporosis as predictors of hip fracture. Bone 1996;18:327–30.
14. Duan Y, Seeman E. Proximal femoral dimensions in women and men with hip fractures. Unpublished data.
15. Beck TJ, Oreskovic TL, Stone KL, Ruff CB, Ensrud K, Nevitt MC, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: the study of osteoporotic fractures. J Bone Miner Res 2000;16:1106–19.
16. Kalender WA, Felsenberg D, Louis O, Lopez P, Klotz E, Osteaux M, et al. Reference values for trabecular and cortical vertebral bone density in single and dual-energy quantitative computed tomography. Eur J Radiol 1989;9:75–80.
17. Riggs BL, Wahner HW, Melton LJ III, Richelson LS, Judd HL, Offord KP. Rate of bone loss in the axial and appendicular skeleton of women: evidence of substantial vertebral bone loss prior to menopause. J Clin Invest 1986;77:1847–91.
18. Gilsanz V, Gibbens DT, Carlson M, Boechat I, Cann CE, Schulz ES. Peak trabecular bone density: a comparison of adolescent and adult. Calcif Tissue Int 1987;43:260–2.
19. Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. J Clin Invest 1994;93:799–808.
20. 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;10:13–7.
21. Parfitt AM. Morphological basis of bone mineral measurements: transient and steady state effects of treatment in osteoporosis. Miner Electrolyte Metab 1980;4:273–87.
22. Heaney RP. The bone-remodeling transient: implications for the interpretation of clinical studies of bone mass change. J Bone Miner Res 1994;9:1515-23.
23. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 2000;21:115–37.
24. Hughes DE, Dai A, Tiffee JC, Li HH, Mundy GR, Boyce BF. Estrogen promotes apoptosis of murine osteoclasts mediated by TGF-beta. Nat Med 1996;2:1132–6.
25. Aaron JE, Makins NB, Sagreiy K. The microanatomy of trabecular bone loss in normal aging men and women. Clin Orthop 1987;215:260–71.
26. Bousson V, Meunier A, Bergot C, Vicant E, Rocha MA, Morais MH, et al. Distribution of intracortical porosity in human midfemoral cortex by age and gender. J Bone Miner Res 2001;16:1308–17.
27. Duan Y, Turner CH, Kim BT, Seeman E. Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. J Bone Miner Res 2001;16:2267–75.
28. Oleksik A, Ott SM, Vedi S, Bravenboer N, Compston J, Lips P. Bone structure in patients with low bone mineral density with or without vertebral fracture. J Bone Miner Res 2000;15:1368–75.
29. Eriksen EF, Hodgson SF, Eastell R, Cedel SL, O'Fallon WM, Riggs BL. Cancellous bone remodeling in type I (postmenopausal) osteoporosis: quantitative assessment of rates of formation, resorption, and bone loss at tissue and cellular levels. J Bone Miner Res 1990;5:311–9.
30. Hordon LD, Raisi M, Aaron JE, Paxton SK, Beneton M, Kanis JA. Trabecular architecture in women and men of similar bone mass with and without vertebral fracture. I. Two-dimensional histology. Bone 2001;27:271–6.
31. Kimmel DB, Recker RR, Gallagher JC, Vaswani AS, Aloia JF. A comparison of iliac bone histomorphometric data in postmenopausal osteoporotic and normal subjects. Bone Miner 1990;11:217–35.
32. Foldes J, Parfitt AM, Shih M-S, Rao DS, Kleerekoper M. Structural and geometric changes in iliac bone: relationship to normal aging and osteoporosis. J Bone Miner Res 1991;6:759–66.
33. Legrand E, Chappard D, Pascaretti C, Duquenne M, Krebs S, Rohmer V, et al. Trabecular bone microarchitecture, bone mineral density and vertebral fractures in male osteoporosis. J Bone Miner Res 2000;15:13–19.
34. Brown JP, Delmas PD, Malavel L, Edouard C, Chapuy MC, Meunier PJ. Serum bone Gla-protein: a specific marker for bone formation in postmenopausal osteoporosis. Lancet 1984;I:1091–3.
35. Eastell R, Delmas PD, Hodgson SF, Eriksen EF, Mann KG, Riggs BL. Bone formation rate in older normal women: concurrent assessment with bone histomorphometry, calcium kinetics, and biochemical markers. J Clin Endocrinol Metab 1988;67:741–8.
36. Mashiba T, Hirano T, Turner CH, Forward MR, Johnson CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000;15:613–20.
37. Currey JD. The mechanical consequences of variation in the mineral content of bone. J Biomech 1969;2:1–11.
38. Boyce RW, Paddock CL, Gleason JR, et al. The effect of risedronate on canine cancellous bone remodeling: three dimensional kinetic reconstruction of the remodeling site. J Bone Miner Res 1995;10:211–21.
39. Roschger P, Rinnerthaler P, Yates J, Rodan GA, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone 2001;29:185–91.
40. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.

41. Seeman E, Delmas PD. Reconstructing the skeleton with intermittent parathyroid hormone. Trends Endocrinol Metab 2001;12:281–3.
42. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis: a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87:2060–6.
43. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. Calcif Tissue Int 2001;69:121–9.
44. Meunier PJ, Roux C, Ortolani S, Badurski J, Kaufman JM, Spector T, et al. Strontium ranelate reduces the vertebral fracture risk in women with postmenopausal osteoporosis. World Congress on Osteoporosis, Lisbon, Portugal. Osteoporos Int 2002;13:520–22 (045).