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Physiology of Bone Loss

Bart L. Clarke, MD^{a,b} and **Sundeep Khosla, MD^{c,d}**

^a Associate Professor of Medicine, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, Minnesota

^b Consultant, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota

^c Professor of Medicine, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, Minnesota

^d Consultant, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota

Introduction

Significant bone loss occurs with normal aging in both women and men [1]. Development of osteoporosis, usually in old age, is the natural consequence of age-related bone loss if left untreated. Multiple population-based cross-sectional and longitudinal studies over the last 25 years using areal bone mineral density (aBMD) assessed by dual energy x-ray absorptiometry (DXA) have helped define the general pattern of bone loss with normal aging (Figure 1). Both sexes lose aBMD at relatively slow rates starting at around age 40, with women losing aBMD more rapidly than men with onset of menopause in their late 40s or early 50s. Postmenopausal women lose trabecular BMD rapidly in their vertebrae, pelvis, and ultradistal wrist. There is less rapid cortical bone loss in the long bones and vertebrae after the menopause. About 8–10 years after menopause, slower age-related bone loss becomes prominent, and continues for the rest of life. Men, who do not experience sudden loss of gonadal sex steroid secretion, do not experience accelerated bone loss in their early 50s, as seen in women, but have slower age-related bone loss throughout their adult life past about age 40.

However, because DXA BMD is not able to differentiate changes occurring in trabecular and cortical bone with age, and because DXA BMD cannot assess age-related changes in bone geometry and/or size, more recent studies have utilized quantitative CT (QCT) scanning [2] to assess bone loss in greater detail. Both peripheral and central QCT, with new image analysis software [3], have been used to better define the age-related changes in bone volumetric density, geometry, and structure at multiple skeletal sites.

Riggs et al. [2] reported large decreases in lumbar spine volumetric BMD (vBMD) with normal aging in a cross-sectional study of men and women aged 20 to 97 years in Rochester, Minnesota, predominantly due to vertebral trabecular bone loss beginning in the third decade. The decrease in lumbar spine vBMD was larger in women than men (55% vs. 45%, $P < 0.001$). The rate of

^aCorresponding author for proof and reprints: Bart L. Clarke, M.D., Mayo Clinic W18-A, 200 1st Street SW, Rochester, MN 55905, 507–266–4322, 507–284–5745 (fax), Clarke.Bart@Mayo.edu.
Coauthor address: Sundeep Khosla, M.D., Mayo Clinic Endocrine Research Unit, Guggenheim 7, 200 1st Street SW, Rochester, MN 55905, 507–255–6663, 507–293–3853 (fax), Khosla.Sundeep@Mayo.edu

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bone loss appeared to increase in middle age in women, accounting for the greater decrease in vBMD seen with aging in women compared to men (Figure 2). Assessment of changes in radial cortical vBMD at the wrist showed that cortical bone loss did not begin until middle age in either women or men. After middle age, there were linear decreases in cortical vBMD in both women and men, but the decreases were greater in women than men (28% vs. 18%, $P < 0.001$). Normal aging was associated with increases in cross-sectional area at the femoral neck and radius because of continued periosteal apposition with normal aging. The bone marrow space increased more rapidly than cross-sectional area due to continued endosteal bone resorption. Because the rate of periosteal apposition was slower than the rate of endosteal resorption, cortical area and thickness decreased with aging. However, because periosteal apposition increased bone diameter, the ability of bone to resist biomechanical forces increased, partially offsetting the decrease in bone strength resulting from decreased cortical area.

Khosla et al. [4] subsequently showed that the structural basis for bone loss in the ultradistal radius with aging is different between men and women. Men have thicker trabeculae in young adulthood, and sustain primarily trabecular thinning without a net change in trabecular number or spacing, whereas women lose trabecular number and have increased trabecular spacing. These changes result in less microstructural damage with aging in men than women, which likely explains the lack of increase in wrist fractures seen in men. Khosla et al. [5] then demonstrated that in young men, the apparent conversion of thick trabeculae into more numerous, thinner trabeculae is most closely associated with declining IGF-I levels. By contrast, sex steroids were the major hormonal determinants of trabecular microstructure in elderly men and women. In a subsequent study, Riggs et al. [6] showed that the late onset of cortical bone loss is temporally associated with sex steroid deficiency. However, the early-onset, substantial trabecular bone loss in both sexes during sex steroid sufficiency is unexplained, and indicates that current paradigms on the pathogenesis of osteoporosis are incomplete.

These studies showed that these age-related changes in bone density and structure correlated with the observed increased fracture risk seen in this population in both women and men. Previous studies had shown that distal forearm (Colles') fractures increase rapidly in women after menopause, and then remain constant from about 10 to 15 years after menopause until the end of life (Figure 3). In contrast, vertebral fractures increase more slowly after menopause, but continue to increase exponentially during later life. Hip fractures in women increase more slowly than vertebral fractures after menopause, but continue to increase throughout life, and increase rapidly in later life. In men, however, distal forearm fractures do not appear to increase with normal aging, probably due to their larger bone size. Vertebral and hip fractures increase gradually with aging in men, beginning about a decade later compared to women, likely due to their lack of significant gonadal steroid deficiency later in life.

Based on these and other studies, it is estimated that 40% of Caucasian women aged 50 years or older will develop a vertebral, hip, or wrist fracture sometime during the remainder of their lives, and that this risk increases to about 50% if non-clinical vertebral fractures detected by radiological imaging are included in the estimate [7]. It is estimated that about 13% of Caucasian men will sustain similar fractures. The risk of these fractures is somewhat lower in non-Caucasian women and men. It is estimated that osteoporotic fractures cost the U.S. between \$12.2 to \$17.9 billion each year, as measured in 2002 dollars [8].

Pathophysiology of Age-Related Bone Loss in Women

Accelerated Postmenopausal Bone Loss Due to Gonadal Sex Steroid Deficiency

Menopause is associated with onset of rapid bone loss in most women. This is thought to be due to decreased ovarian function, leading to decreased estrogen secretion. This rapid bone

loss can be prevented by estrogen or hormone replacement [9,10]. During the menopause transition, serum 17 β -estradiol levels decrease by 85–90% from the mean premenopausal level, and serum estrone levels decrease by 65 to 75% from premenopausal levels [11]. Serum estrone has one-fourth the biological effect of serum 17 β -estradiol. Serum testosterone also decreases following menopause, but to a lesser extent, because testosterone continues to be produced by the adrenal cortex and interstitial cells in the ovary [12]. Khosla et al. showed that there may be a threshold level of serum bioavailable (non-sex hormone binding globulin [SHBG]-bound) estradiol in postmenopausal women below 11 pg/mL, at which trabecular bone loss occurs, whereas a threshold level below 3 pg/mL for bioavailable estradiol leads to cortical bone loss [13]. Some longitudinal clinical studies show that increased bone turnover in perimenopausal women correlates with elevated serum FSH, as well as serum estradiol [14]. The perimenopausal rise in FSH is due to a selective decrease in ovarian inhibin B (InhB). Decreases in inhibin levels across the menopause transition are associated with increasing bone turnover, independent of changes in sex steroids or FSH [14].

Bone resorption increases by 90% after menopause, as assessed by markers of bone resorption, whereas bone formation also increases, but only by 45% as assessed by markers of bone formation [15]. The difference between bone resorption and formation favors greater bone resorption, which leads to accelerated bone loss during the first 8–10 years after menopause. Increased bone resorption leads to an efflux of calcium from the skeleton into the extracellular pool, but compensatory increased renal calcium excretion [16], decreased intestinal calcium absorption [17], and partially suppressed parathyroid hormone secretion [18] prevent development of hypercalcemia.

The cellular and molecular mechanisms by which estrogen deficiency leads to bone loss are increasingly well understood (Figure 4). Estrogen deficiency increases receptor activator of nuclear factor kappa B ligand (RANKL) [19], leading to increased osteoclast recruitment and activation and decreased osteoclast apoptosis. RANKL is the final key molecule required for osteoclast development, and is normally expressed by bone marrow stromal/osteoblast precursor cells, T-lymphocytes, and B-lymphocytes [20,21]. RANKL binds to its receptor RANK on osteoclast lineage cells [22], and is neutralized in the bone microenvironment by its soluble decoy receptor osteoprotegerin (OPG), which is produced and secreted by osteoblast lineage cells [23]. Combined in vitro and in vivo studies have shown that estrogen normally suppresses RANKL production by osteoblastic cells and T- and B-lymphocytes [20,21], and increases OPG production by osteoblastic cells [24,25], so that estrogen deficiency leads to an alteration in the RANKL/OPG ratio that favors bone resorption.

Estrogen also modulates production of additional cytokines by bone marrow stromal mononuclear cells and osteoblasts, thereby controlling osteoclast activity by paracrine action [25]. Estrogen is thought to suppress production of bone-resorbing cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α , macrophage colony-stimulating factor (M-CSF), and prostaglandins by the appropriate cells [26]. Estrogen-deficient model systems have shown that increased IL-1 and M-CSF levels [27,28] can be reduced by specific antagonists to these molecules [29–30]. The bone-resorptive activity of TNF- α is able to be inhibited by soluble type I TNF receptor [33]. Estrogen deficiency is associated with increased IL-6 levels [34,35]. In vivo, however, it is likely that estrogen suppresses production and activity of multiple cytokines in premenopausal women that would otherwise act cooperatively to cause bone loss. With estrogen deficiency, each cytokine likely accounts for only part of cytokine-mediated age-related bone loss. It is not yet clear that there is a dominant cytokine contributing to estrogen-deficiency associated bone loss.

Estrogen normally also increases the production of transforming growth factor (TGF)- β by osteoblast precursor cells [36]. TGF- β induces apoptosis of osteoclasts [37]. Estrogen also

directly stimulates apoptosis of osteoclast precursor cells, and decreases osteoclast precursor differentiation by blocking RANKL/M-CSF-induced activator protein-1-dependent transcription by reducing c-jun activity [38,39]. C-jun activity is reduced by decreasing c-jun transcription and decreasing phosphorylation. Estrogen is also capable of inhibiting the activity of mature osteoclasts by direct, receptor-mediated mechanisms [40].

Loss of these multiple estrogen-induced restraining actions on osteoclast bone resorption leads to upregulation of rapid bone loss shortly after onset of menopause. The rapid phase of bone loss is sustained for 8–10 years before gradually subsiding. Why rapid bone loss gradually subsides after this duration is not yet clear, but it may be that estrogen deficiency alters biomechanical sensing of skeletal mechanical loading by osteocytes within the bone [41]. It is hypothesized that for a given level of skeletal mechanical loading during estrogen deficiency, bone mass is sensed as being excessive by the osteocytes, which then signal the osteoclasts to resorb more bone and/or the osteoblasts to form less bone, leading to net rapid bone loss. Once enough bone is lost, however, it is thought that the proportionately increased skeletal mechanical loading on remaining bone is sufficient to limit further rapid bone loss.

Age-Related Bone Loss Due to Secondary Hyperparathyroidism

While gonadal steroid deficiency may be a major cause for postmenopausal bone loss, other important factors also play a role. During the rapid phase of early postmenopausal bone loss, there is mild suppression of PTH secretion, but during the slower phase of later postmenopausal bone loss there is gradually increasing PTH secretion, with corresponding increasing markers of bone resorption. The increases in serum PTH and markers of bone turnover correlate with each other. Transient suppression of PTH secretion by an intravenous 24-hour calcium infusion in younger premenopausal and elderly postmenopausal women is associated with suppression of markers of bone turnover, strongly suggesting that increased serum PTH was the proximate cause of the increased bone turnover [42].

The reason for gradually increasing levels of PTH secretion with age is likely multifactorial. Vitamin D deficiency is common in postmenopausal women [43], and is associated with increased serum PTH levels. Longstanding estrogen deficiency also leads to chronic negative calcium balance because of loss of estrogen effects increasing intestinal calcium absorption [16,44] and renal tubular calcium reabsorption [45,46]. Unless these changes leading to negative calcium balance are compensated for with adequate calcium supplementation, secondary hyperparathyroidism inevitably develops, leading to age-related bone loss.

Bone Loss Due to Decreased Bone Formation

Postmenopausal and age-related bone loss is due not just to accelerated bone resorption, but also to decreased bone formation. Decreased bone formation has generally been attributed to decreased paracrine production of growth factors [47], and/or decreased GH [48,49] and IGF-1 levels [50–52]. If estrogen directly stimulates bone formation, estrogen deficiency may also directly result in bone loss. Impaired bone formation is detectable in early menopause [53]. Estrogen increases production of IGF-1 [54], TGF- β [36], and procollagen synthesis by osteoblast precursor cells in vitro [54], and increases osteoblast life span by decreasing osteoblast apoptosis [55,56]. Khastgir and colleagues provided direct evidence that estrogen can stimulate bone formation after cessation of skeletal growth by evaluating iliac crest bone biopsies from 22 elderly women of mean age 65 years before, and 6 years after, percutaneous administration of high doses of estrogen [57]. They found that cancellous bone volume increased by 61%, and trabecular wall thickness by 12%. Tobias and Compston reported similar results [58]. It is not yet clear whether these results are due to the pharmacological doses of estrogen used, or augmentation of physiological effects that are normally not of sufficient magnitude to detect. Accumulating data implicate estrogen deficiency as a contributing cause

of decreased bone formation with aging, but there is not yet a clear consensus on whether estrogen directly stimulates osteoblast function, and if it does, what the relative magnitude of increased proliferation or decreased apoptosis are.

Pathophysiology of Age-Related Bone Loss in Men

Age-related bone loss due to gonadal steroid deficiency

Although osteoporosis more commonly affects women, men lose about half as much bone with aging as women, and suffer one-third the number of fragility fractures as women [59,60]. Since most men do not develop overt hypogonadism with normal aging, it was thought for many years that gonadal sex steroid deficiency was less significant a cause of bone loss in men than in women. However, multiple studies over the last decade have shown that lack of apparent age-related gonadal sex steroid deficiency in men is due to the doubling of SHBG with aging in men [61,62], with consequent near-preservation of serum total testosterone and estradiol, but decreased bioavailable and free gonadal sex steroid levels. Serum sex steroids are bound predominantly to circulating albumin or SHBG, but a small fraction circulates in free form. It is estimated that 35–55% of circulating testosterone and estradiol is loosely bound to albumin, 42–64% circulates bound to SHBG, and that 1–3% circulates in free form [63]. Since SHBG binds to testosterone and estradiol with high avidity, this form of gonadal sex steroid is not generally available to diffuse into target tissue cells from the circulation, bind to sex steroid receptors, and exert sex steroid action. The fraction of circulating testosterone and estradiol bound to albumin or circulating free represents bioavailable testosterone and estradiol capable of interacting with sex steroid receptors in target tissues.

A variety of methods have been used to assess serum bioavailable testosterone and estradiol, and multiple groups have reported decreased serum free or bioavailable sex steroids with aging [64–66]. Khosla et al. [61] showed in a cross-sectional study of 346 men from age 23 to 90 in Rochester, Minnesota, that bioavailable testosterone decreased by 64%, and bioavailable estrogen by 47%, and that SHBG increased by 124%, LH by 285%, and FSH by 505% (Table 1). Similar data were recently reported from men in the MrOS Study in Sweden [67]. The proximate cause for the increase in SHBG in men, and the failure of the hypothalamic-pituitary-gonadal axis to compensate for decreased circulating bioavailable sex steroids in men are not yet clear, and remain under investigation [62].

For many years it was assumed that decreased serum testosterone was responsible for age-related bone loss in men, because it has traditionally been viewed as the dominant gonadal steroid in men. However, a number of cross-sectional observational studies that correlated serum sex steroid levels to BMD at various skeletal sites reported that bone loss in aging men correlated better with serum estradiol than testosterone. The earliest study to report this finding, by Slemenda et al. [65], found correlation coefficients between serum total estradiol and BMD at different skeletal sites ranging from +0.21 to +0.35 ($P = 0.01$ – 0.05), with inverse correlation coefficients between serum total testosterone and BMD at various skeletal sites ranging from -0.21 to -0.28 ($P = 0.03$ – 0.10). A number of other cross-sectional studies subsequently confirmed these findings in other male population samples, with positive correlations between serum total or bioavailable estradiol and BMD [66,67,69–73].

These studies strongly suggested that estrogen deficiency plays the dominant role in age-related bone loss in men, as well as women. However, the cross-sectional nature of these studies did not allow discrimination of the effect of estradiol on peak bone density from the effect on preservation or prevention of bone loss with normal aging. Men with low BMD and low estradiol levels may have had low estradiol levels for much or all of their lives, and this would likely have caused low BMD due to decreased acquisition of peak bone density, as well as more rapid bone loss with aging. In addition, correlation studies can never prove causality.

To assess the effect of estrogen deficiency on bone loss in men, Khosla et al. [73] evaluated rates of bone loss at different skeletal sites longitudinally over 4 years in young men aged 22 to 39 years, and older men aged 60 to 90 years. Study of these two populations allowed separation of the effects of gonadal sex steroids on men reaching peak bone density, from the effects on age-related bone loss. Forearm BMD assessment provided the clearest data, perhaps because of the greater precision of measurement at this site, compared to the lumbar spine and hip sites. In the younger men, forearm BMD increased by 0.42 to 0.43% per year, whereas forearm BMD decreased in the older men by 0.49 to 0.66% each year. The rates of BMD change at the wrist site correlated better with serum bioavailable estradiol levels than serum bioavailable testosterone levels (Table 2). Further analysis suggested that there was a serum bioavailable estradiol threshold of 11 pg/mL (40 pmol/L), below which the rate of BMD loss correlated with estradiol. Above this threshold, there was no correlation between rate of bone loss and serum estradiol (Figure 5). The threshold level corresponded to the median serum bioavailable estrogen level in these men, with the corresponding serum total estradiol level 31 pg/mL, which is near the middle of the normal range for estradiol of 10 to 50 pg/mL in these men. Similar findings were reported by Gennari et al. [74] in a cohort of elderly Italian men, with men with serum free estradiol levels below the median for the group losing lumbar spine and femoral neck BMD over 4 years, and men with serum free estradiol levels above the median maintaining their BMD at these sites.

Although these cross-sectional studies helped establish that serum estrogen levels are associated with BMD in men, they could not prove that estrogen deficiency was the primary cause of bone loss in aging men. A pivotal experiment giving strong support for estrogen deficiency being more important than testosterone deficiency in causation of bone loss in aging men was performed by Falahati-Nini et al. [75]. The authors treated 59 normal elderly men of mean age 68 years with a long-acting gonadotropin-releasing hormone (GnRH) agonist to suppress GnRH, LH, and FSH secretion, and an aromatase inhibitor to block peripheral conversion of testosterone to estrogen, for three weeks. Physiological estrogen and testosterone levels were maintained during suppression of LH and FSH secretion and aromatase blockade by placing the men on estrogen and testosterone patches that mimicked circulating estrogen and testosterone levels for age. After baseline assessment at three weeks of the bone resorption markers urinary deoxypyridinoline and NTx-telopeptide, and bone formation markers osteocalcin and PINP, the men were randomized to one of four treatment groups for three further weeks. Men in group A (-T, -E) discontinued both their testosterone and estrogen patches; those in Group B (-T, +E) discontinued their testosterone patch but continued their estrogen patch; those in Group C (+T, -E) continued their testosterone patch but discontinued their estrogen patch; and men in Group D (+T, +E) continued both patches. Because GnRH agonist and aromatase inhibitor treatment was maintained during the three weeks of patch therapy, the authors were able to independently assess the effects of testosterone and estrogen on bone metabolism in the men.

The study showed that men in Group A, without either testosterone or estrogen replacement, had significant increases in both markers of bone resorption, whereas these increases were completely blocked in men in Group D, with both testosterone and estrogen replacement (Figure 6). Men in Group B, who received estrogen but not testosterone, had minimal increases in bone resorption markers, whereas men in Group C, who received testosterone but not estrogen, had significant increases in bone resorption markers. Using a two-factor analysis of variance (ANOVA) model, the effects of estrogen on urinary deoxypyridinoline and NTx-telopeptide excretion were highly significant ($P = 0.005$ and 0.0002 , respectively). Estrogen accounted for more than 70% or more of the total effect of sex steroids on bone resorption in the men, while testosterone accounted for no more than 30% of the effect.

Gonadal steroid-deficient men in Group A had reduced bone formation marker levels, whereas men in Group D, given combination testosterone and estrogen treatment, maintained normal bone formation markers. Men in Groups B and C, given either testosterone or estrogen treatment, maintained their levels of osteocalcin, which is a marker of function of mature osteoblasts and osteocytes [73] (ANOVA, $P = 0.002$ and 0.013 , respectively). Men in Groups B and C maintained their levels of P1NP, representing type I collagen synthesis throughout the various stages of osteoblast differentiation, only with estrogen, but not testosterone (ANOVA, $P = 0.0001$).

Leder et al. [77] used a slightly different trial design to confirm an independent effect of testosterone on bone resorption, but the cumulative data to date suggest a more prominent role of estrogen in preventing bone resorption in men. Similar findings were reported by Taxel et al. [78] in a study of 15 elderly men treated with an aromatase inhibitor for 9 weeks. Suppression of estrogen production caused significant increases in bone resorption markers, and suppression of bone formation markers. In another study, Sanyal et al. [79] showed that the effects of estrogen on bone in older men were independent of changes in FSH.

The data from these various investigations show that estrogen plays an important and dominant role in bone metabolism in the skeleton of aging men. It therefore appears that decreasing bioavailable estrogen levels in men play a significant role in mediating age-related bone loss in men, similar to women [80]. Declining testosterone levels also play a role, however, because testosterone has antiresorptive effects and is important for maintaining bone formation. Testosterone also is the substrate for aromatase, which converts testosterone to estrogen. Testosterone has been shown to increase periosteal apposition in bone, at least in rodents [81]. Testosterone also likely contributes to reduced fracture risk in men because of its influence on increasing bone size in men during growth and development.

Age-related bone loss due to secondary hyperparathyroidism

PTH secretion also increases in aging men, similar to what is seen in aging women [18,59, 60]. Because higher circulating gonadal sex steroid levels in aging men may help protect against bone resorption promoted by increased PTH levels, it has been more difficult to demonstrate a direct role for PTH in causation of age-related bone loss in men [82].

Factors Contributing to Age-Related Bone Loss in Both Sexes

Age-related bone loss may be driven primarily by gonadal sex steroid deficiency and physiological secondary hyperparathyroidism, but multiple other factors also contribute to this process. Vitamin D deficiency, widely prevalent in postmenopausal women with osteoporosis, and common among children and adults without osteoporosis in many countries around the world, worsens age-related physiological secondary hyperparathyroidism [43]. Age-related decreased bone formation may be due in part to sex steroid deficiency, but other sex steroid-independent factors likely contribute to decreased bone formation. Age-related decreases in production of growth factors necessary for osteoblast differentiation and function most likely contribute to decreased bone formation. The age-related decrease in amplitude and frequency of GH production by the pituitary leads to decreased liver production of IGF-1 [49]. IGF-1 levels decrease markedly with age, and IGF-2 levels also decrease, but less rapidly [50,51]. Decreased systemic and local skeletal production of IGF-1 and -2 likely contribute to decreased bone formation with aging. Growth factor binding proteins may also play a role in regulation of age-related bone loss. Amin et al. [83] showed that higher serum IGFBP-2 predicts lower BMD, and is associated with increased markers of bone resorption independent of age, body mass, and sex hormones. The association between IGFBP-2 and markers of bone formation may reflect coupling with increased bone resorption, which is not adequate to maintain BMD.

Other changes in endocrine function with aging likely also contribute to the physiology of bone loss. The less potent adrenal androgens DHEA and DHEA-sulfate both decrease by about 80% with aging, with much of the decrease occurring in young adults [84], whereas cortisol secretion remains relatively constant throughout life. The decrease in adrenal androgens early in adult life may therefore change the ratio of adrenal catabolic/anabolic hormone activity. This change may contribute to younger adult trabecular bone loss.

Leptin secreted by adipocytes has been demonstrated in mice and humans to regulate bone remodeling through studies of loss-of-function mutations of this hormone or of its receptor. It has been assumed, but not formally demonstrated, that this regulation occurs through neuronal means, possibly via the sympathetic nervous system. It has been difficult to dissociate the influence leptin exerts on appetite and energy expenditure from this function. Shi et al. [85] recently showed that deletion of the leptin receptor in mouse neurons results in increased bone formation and bone resorption, resulting in high bone density as seen in leptin-deficient mice. In contrast, osteoblast-specific leptin receptor deletion did not influence bone remodeling. These findings established that leptin regulates bone mass accrual in vivo by acting through neuronal means, and provided a direct demonstration that leptin functions to regulate bone remodeling independently of its regulation of energy metabolism.

Recent studies have demonstrated an important role for circulating serotonin in regulating bone mass in rodents [86]. In addition, patients treated with selective serotonin reuptake inhibitors (SSRIs) have reduced aBMD. The potential physiological role of serotonin in regulating bone mass in humans remains unclear. Mödder et al. [87] measured serum serotonin levels in a population-based sample of 275 women and related these to total body and spine aBMD assessed by DXA, femur neck total and trabecular vBMD, and vertebral trabecular vBMD assessed by QCT, and bone microstructural parameters at the distal radius assessed by HRpQCT. Serotonin levels were inversely associated with body and spine aBMD (age-adjusted $R = -0.17$ and -0.16 , $P < 0.01$, respectively), and with femoral neck total and trabecular vBMD (age-adjusted $R = -0.17$ and -0.25 , $P < 0.01$ and < 0.001 , respectively), but not lumbar spine vBMD. Bone volume/tissue volume, trabecular number, and trabecular thickness at the radius were inversely associated with serotonin levels (age-adjusted $R = -0.16$, -0.16 , and -0.14 , $P < 0.05$, respectively). Serotonin levels were also inversely associated with body mass index (BMI, age-adjusted $R = -0.23$, $P < 0.001$). Multivariable models showed that serotonin levels remained significant negative predictors of femur neck total and trabecular vBMD, as well as trabecular thickness at the radius, after adjusting for age and BMI. Collectively, these data provide support for a physiological role for circulating serotonin in regulating bone mass in humans.

Lower peak bone density at 25–35 years of age also contributes to risk of osteoporosis and fractures later in life. Individuals with lower peak bone density for whatever cause will develop low bone density or osteoporosis sooner than those with higher peak bone density, assuming the rate of bone loss is equivalent as they age [88].

It has been suggested that bone strength is homeostatically adapted to habitual skeletal loading conditions and that bone loss could, therefore, result simply from age-related reductions in physical activity and muscle mass. In a stratified random sample of Rochester, Minnesota, women and men 21–97 years of age, Melton et al. [89] estimated indices of bone strength, flexural rigidity, and axial rigidity from central QCT measurements at the femoral neck and lumbar spine, and pQCT measurements at the ultradistal radius. Habitual skeletal loading was assessed using lean body mass, total skeletal muscle mass, body weight, and physical activity. This study showed that there was not a close correspondence between changes in habitual load and changes in bone strength, nor any consistent pattern. Moreover, inter-individual variation

in the strength-to-load ratios was substantial. These data suggest that the hypothesis that reduced skeletal loading is the primary basis for age-related bone loss may be oversimplified.

Numerous sporadic secondary causes of bone loss play a role in age-related bone loss by various mechanisms. It is estimated that about 40% of women, and 20% of men, have an identifiable sporadic cause of bone loss [90], such as glucocorticoid therapy, subtle or clinically evident malabsorption, anorexia nervosa, idiopathic hypercalciuria, or behavioral factors such as excess alcohol intake, cigarette smoking, high-caffeine or high-sodium diet, or physical inactivity.

Age-related bone loss and sarcopenia proceed in parallel. It has been suggested that age-related muscle loss is the main factor causing age-related bone loss [91,92]. Although not yet proven, it is likely that age-related muscle loss, causing decreased muscle loading on the skeleton, contributes significantly to age-related bone loss.

Summary

Age-related bone loss in women and men is caused in large part by gonadal sex steroid deficiency and physiological secondary hyperparathyroidism. Other factors also play key roles, including vitamin D deficiency, intrinsic defects in osteoblast function, impairment of the GH/IGF axis, reduced peak bone mass, age-associated sarcopenia, and various sporadic secondary causes. Further understanding of the relative contributions of each of these factors to age-related bone loss and fracture risk will lead to improved preventive and therapeutic approaches for osteoporosis.

Synopsis

The physiology of bone loss in aging women and men is largely explained by the effects of gonadal sex steroid deficiency on the skeleton. In women, estrogen deficiency is the main cause of early rapid postmenopausal bone loss, where as hyperparathyroidism and vitamin D deficiency are thought to explain age-related bone loss later in life. Surprisingly, estrogen deficiency also plays a dominant role in the physiology of bone loss in aging men. Many other factors contribute to bone loss in aging women and men, including defective bone formation by aging osteoblasts, impairment of the growth hormone/IGF axis, reduced peak bone mass, age-associated sarcopenia, leptin secreted by adipocytes, serotonin secreted by the intestine, and a long list of sporadic secondary causes. Further elucidation of the relative importance of each of these factors will lead to improved preventive and therapeutic approaches for osteoporosis.

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Figure 1.

Patterns of age-related bone loss in women and men. Dashed lines represent trabecular bone and solid lines, cortical bone. The figure is based on multiple cross-sectional and longitudinal studies using DXA. (*Reproduced from Khosla S, Riggs BL. Pathophysiology of age-related bone loss and osteoporosis. Endocrinol Metab Clin N Am 2005;34(4):1017; with permission.*)

Figure 2.

(A) Values for vBMD (mg/cm^3) of the total vertebral body in a population sample of Rochester, Minnesota, women and men between the ages of 20 and 97 years. Individual values and smoother lines are given for premenopausal women in red, for postmenopausal women in blue, and for men in black. (B) Values for cortical vBMD at the distal radius in the same cohort, with color code as in (A). All changes with age were significant ($P < .05$). (*Reproduced from* Riggs BL, Melton LJ 3rd, Robb RA, et al. A population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J Bone Miner Res* 2004;19(12):1950; with permission.)

Figure 3.

Age-specific incidence rates for proximal femur (hip), vertebral (spine), and distal forearm (wrist) fractures in Rochester, Minnesota, women (A) and men (B). (*Adapted from Cooper C, Melton LJ. Epidemiology of osteoporosis. Trends Endocrinol Metab 1992;3(6):225; with permission.*)

Figure 5.

Rate of change in mid-radius BMD (A) and mid-ulna BMD (B) as a function of bioavailable estradiol levels in elderly men. Model R^2 values were 0.20 and 0.25 for the radius and ulna, respectively, both less than 0.001 for comparison with a one-slope model. Solid circles correspond to subjects with bioavailable estradiol levels below 40 pmol/L (11 pg/mL) and open circles those with values above 40 pmol/L. (*Reproduced from Khosla S, Melton LJ 3rd, Atkinson EJ, et al. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86(8);3558; with permission.*)

Figure 6.

Percent changes in (A) bone resorption markers (urinary deoxypyridinoline [Dpd] and N-telopeptide of type I collagen [NTx]) and (B) bone formation markers (serum osteocalcin and N-terminal extension peptide of type I collagen [PINP]) in a group of elderly men (mean age 68 years) made acutely hypogonadal and treated with an aromatase inhibitor (Group A), treated with estrogen alone (group B), treated with testosterone alone (Group C), or both (Group D). Significance for change from baseline: * $P < .05$; ** $P < .01$; *** $P < .001$. (Adapted from Falahati-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest* 2000;106(12):1556–7; with permission.)

Table 1

Changes in serum sex steroids and gonadotropins over life in a random sample of 346 men (Rochester, Minnesota) aged 23–90 years. (*Adapted from* Khosla S, Melton LJ 3rd, Atkinson EJ, et al. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab* 1998;83(7):2268; with permission.)

Hormone	Percent Change [*]
Bioavailable estrogen	–47
Bioavailable testosterone	–64
Sex hormone binding globulin	+124
Luteinizing hormone	+285
Follicle stimulating hormone	+505

*
P < 0.005

Spearman correlation coefficients relating rates of change in bone mineral density at the radius and ulna to serum sex steroid levels among a sample of men (Rochester, Minnesota) stratified by age. (*Reproduced from* Khosla S, Melton LJ 3rd, Atkinson EJ, et al. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab* 2001;86(8):3558, with permission.)

Table 2

Spearman correlation coefficients	Young		Middle-aged		Elderly	
	Radius	Ulna	Radius	Ulna	Radius	Ulna
T	-0.02	-0.19	-0.18	-0.25*	0.13	0.14
E2	0.33**	0.22*	0.03	0.07	0.21*	0.18*
E1	0.35***	0.34**	0.17	0.23*	0.16	0.14
Bio T	0.13	-0.04	0.07	0.01	0.23**	0.27**
Bio E2	0.30**	0.20	0.14	0.21*	0.29**	0.33***

Abbreviations: Bio, bioavailable; E1, estrone, E2, estradiol; T, testosterone.

* P < 0.05;
** P < 0.01;
*** P < 0.001.