Pathophysiology of Age-Related Bone Loss and Osteoporosis

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Aging is associated with significant bone loss in women and in men [1]. Fig. 1, which draws on numerous cross-sectional and longitudinal studies using areal bone mineral density (aBMD) by dual energy x-ray absorptiometry (DXA), depicts the overall pattern of bone loss in both sexes. The menopause in women is associated with a rapid loss of trabecular bone, as is present in the vertebrae, pelvis, and ultra-distal forearm. There is a less dramatic loss of cortical bone (present in the long bones of the body and as a thin rim around the vertebrae and other sites of trabecular bone) following the menopause. Approximately 8 to 10 years following menopause, slow, age-related phase of bone loss in trabecular and cortical bone becomes apparent and continues throughout life. Because men lack the equivalent of a menopause, they generally do not exhibit this rapid phase of bone loss. Men, however, have a very similar pattern of slow, age-related bone loss as is present in women.

Although DXA has provided important insights into the patterns of age-related bone loss, its utility is limited by the fact that it cannot clearly separate trabecular from cortical bone or provide information on possible changes in bone size/geometry with age. In recent studies, Riggs and colleagues [2] used central and peripheral quantitative CT (QCT) along with new image analysis software [3] to better define age-associated changes in bone volumetric density, geometry, and structure at different skeletal sites. As shown in Fig. 2, there were large decreases in volumetric BMD (vBMD) at the spine over life (predominantly trabecular bone), which

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seemed to begin even before middle life. These decreases were greater in women (approximately 55%) than in men (approximately 45%, $P < .001$). Even in this cross-sectional study, there was an apparent small midlife acceleration in the slope of the decrease in women that accounted for much of their significantly greater decrease in vertebral vBMD over life compared with men. In contrast to this pattern of changes in trabecular vBMD at the spine, cortical vBMD at the radius showed little change until midlife in either women or men (see Fig. 2). Thereafter, there were linear decreases in both sexes, but the decreases were greater in women (28%) than in men.

Fig. 1. Patterns of age-related bone loss in women and in men. Dashed lines represent trabecular bone and solid lines, cortical bone. The figure is based on multiple cross-sectional and longitudinal studies using DXA.

Fig. 2. (A) Values for vBMD (mg/cm$^3$) of the total vertebral body in a population sample of Rochester, Minn., 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. Color code is 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;19:1950; with permission.)
Aging also was associated with increases in bone cross-sectional area at various sites because of continued periosteal apposition throughout life. Bone marrow space, however, increased even more because of ongoing bone resorption. Thus, because endocortical resorption increased even more than periosteal apposition, there was a net decrease in cortical area and thickness [2]. This process, however, also resulted in outward displacement of the cortex, which increased the strength of bone to bending stresses and partially offset the decrease in bone strength resulting from decreased cortical area.

These age-associated changes in bone mass and structure lead, in turn, to a marked increase in the incidence of osteoporotic fractures in both sexes. As shown in Fig. 3, distal forearm (Colles) fractures increase sharply in women soon after menopause and then plateau after 10 to 15 years postmenopausally. The increase in incidence of vertebral fractures after menopause is more gradual but, in contrast to Colles’ fractures, vertebral fractures continue to increase throughout life. The rise in hip fractures follows that in vertebral fractures, and hip fractures increase markedly late in life. Men do not appear to have a measurable increase in Colles’ fractures with age (see Fig. 3), which may, in part, be because of their larger bones. With increasing age, however, there is a clear increase in the incidence of vertebral and hip fractures in men, although the onset of these fractures is delayed by about 10 years as compared with women, likely because of the absence of menopause and the associated accelerated bone loss present in women.

Based on these types of data, it has been estimated that 4 out of every 10 white women aged 50 years or older in the United States will experience a hip, spine, or wrist fracture sometime during the remainder of their lives; 13% of white men in this country also will suffer one of these fractures [4].
Although the risk of these fractures is lower in nonwhite women and men, it remains substantial. Collectively, osteoporotic fractures result in a significant financial burden on society, with estimated direct care expenditures of $12.2 to $17.9 billion each year, measured in 2002 dollars [5].

Pathogenesis of age-related bone loss in women

Menopause triggers a rapid phase of bone loss in women that can be prevented by estrogen replacement [6,7] and clearly results from loss of ovarian function. During the menopausal transition, serum estradiol levels fall to 10% to 15% of the premenopausal level, although levels of serum estrone, a fourfold weaker estrogen, fall to about 25% to 35% of the premenopausal level [8]. Serum testosterone levels also decrease following the menopause [9] although to a lesser extent, since testosterone continues to be produced by the adrenal cortex and by the ovarian interstitium. Bone resorption, as assessed by biochemical markers, increases by 90% at menopause, whereas bone formation markers increase by only 45% [10]. This imbalance between bone resorption and bone formation leads to accelerated bone loss. The rapid bone loss in this phase produces an increased outflow of calcium from bone into the extracellular pool, but hypercalcemia is prevented by compensatory increases in urinary calcium excretion [11], decreases in intestinal calcium absorption [12], and by a partial suppression of parathyroid hormone (PTH) secretion [13].

The cellular and molecular mechanisms by which estrogen mediates its effects on bone resorption are being worked out. Fig. 4 provides summarizes the cellular and molecular factors involved in osteoclast differentiation and function. The key, essential molecule for osteoclast development is the receptor activator of NF-κB ligand (RANKL) [14], which is expressed on the surface of bone marrow stromal/osteoblast precursor cells, T cells, and B cells [15]. RANKL binds its cognate receptor, RANK, on osteoclast lineage cells [16], and is neutralized by the soluble, decoy receptor osteoprotegerin (OPG), which also is produced by osteoblastic lineage cells [17]. Combined in vitro and in vivo studies have demonstrated that estrogen suppresses RANKL production by osteoblastic, T cells, and B cells [15] and also increases OPG production [18,19]. In addition to the effects of estrogen on RANKL and OPG expression, estrogen also regulates production of additional cytokines in osteoblasts or bone marrow mononuclear cells, thus modulating osteoclastic activity in a paracrine fashion [20]. There is an increasing body of evidence that bone-resorbing cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), macrophage colony-stimulating factor (M-CSF), and prostaglandins may be potential candidates for mediating the bone loss following estrogen deficiency. IL-1 and M-CSF production are increased in estrogen-deficient model systems [21,22]; this can be inhibited using specific antagonists [23–25]. Additionally, the
Bone resorptive effects of TNF-α are documented and can be reversed using a soluble type I TNF receptor [26]. Numerous other studies indicate that IL-6 plays a key role in mediating bone loss following estrogen deficiency [27,28]. It is likely, however, that, in vivo, multiple cytokines act cooperatively in inducing bone resorption following sex steroid deficiency, and that a single cytokine may account only partially for the effects of sex steroid deficiency on the skeleton. Finally, in addition to suppressing the production of proresorptive cytokines, estrogen also stimulates production of transforming growth factor (TGF)-β by osteoblastic cells [29]. TGF-β, in turn, has been shown to induce apoptosis of osteoclasts [30]. Estrogen also has direct effects on osteoclast lineage cells. Thus, it induces apoptosis of these cells [30] and can suppress RANKL-induced osteoclast differentiation by blocking RANKL/M-CSF-induced activator protein-1-dependent transcription through a reduction of c-jun activity [31,32]. The latter is caused by reduced c-jun expression and decreased phosphorylation. Moreover, estrogen also has been shown to inhibit the activity of mature osteoclasts through direct, receptor-mediated mechanisms [33].

Loss of these multiple actions of estrogen on restraining bone resorption thus triggers the rapid phase of bone loss, which generally subsides after 4 to 8 years. It has been suggested that estrogen deficiency alters the sensing of mechanical loading by the skeleton, perhaps through effects on osteocytes in bone [34]. Thus, for a given level of mechanical loading, bone mass may be perceived by these cells as being excessive in the setting of estrogen deficiency, leading to bone loss. Once sufficient bone is lost, however,
increased mechanical loading on the remaining bone may serve to limit additional bone loss, accounting for the cessation of the rapid phase of bone loss following estrogen deficiency.

In contrast to the trend for suppression of PTH levels during the rapid phase of bone loss, the late, slow phase of bone loss is associated with progressive increases in levels of serum PTH and in biochemical markers of bone turnover. These increases correlate with each other [13]. Moreover, when serum PTH levels were suppressed by a 24-hour calcium infusion in groups of young premenopausal and elderly postmenopausal women, the increases in biochemical markers in the postmenopausal women that were present on the control day were no longer present in the calcium infusion day, strongly suggesting that the increased serum PTH was the cause of the increase in bone turnover [35].

The increase in serum PTH with age represents secondary hyperparathyroidism, which likely has multiple etiologies. Certainly, vitamin D deficiency is common in elderly women [36] and leads to increases in PTH levels. In addition, however, it appears that longstanding estrogen deficiency may lead to chronic negative calcium balance because of loss of effects of estrogen on enhancing intestinal calcium absorption [12,37] and renal tubular calcium reabsorption [38,39]. It appears that unless this negative calcium balance is compensated for by very large increases in dietary calcium intake, it will result in secondary hyperparathyroidism and will contribute to the slow phase of bone loss.

In addition to increases in bone resorption, estrogen deficiency and aging are associated with impaired compensatory bone formation. The latter generally has been attributed to age-related factors, particularly to decreases in paracrine production of growth factors [40] or to decreases in circulating levels of growth hormone [41,42] and insulin-like growth factor (IGF)-I [43–45]. If estrogen stimulates bone formation, however, postmenopausal estrogen deficiency could be a contributing cause. Indeed, impaired bone formation becomes apparent soon after menopause [46]. Estrogen increases production of IGF-I [47], TGF-β [29], and procollagen synthesis by osteoblastic cells in vitro [47] and increases osteoblast life span by decreasing osteoblast apoptosis [48,49]. Direct evidence that estrogen can stimulate bone formation after cessation of skeletal growth was provided by Khastgir and colleagues [50], who obtained iliac biopsies for histomorphometry in 22 elderly women (mean age of 65 years) before and 6 years after percutaneous administration of high dosages of estrogen. They found a 61% increase in cancellous bone volume and a 12% increase in the wall thickness of trabecular packets. Tobias and Compston [51] have reported similar results. It is unclear whether these results represent only pharmacologic effects or are an augmentation of physiologic effects of estrogen that are ordinarily not large enough to detect. Thus, accumulating data implicate estrogen deficiency as a contributing cause of decreased bone formation with aging. Still, there is not a clear consensus on whether estrogen stimulates osteoblast function,
and, if it does, what is the relative contribution of increased proliferation function and decreased apoptosis.

Pathogenesis of age-related bone loss in men

Although osteoporosis is more common in women, men lose half as much bone with aging and have one third as many fragility fractures as women [13]. Because most men do not develop overt hypogonadism with aging, the prevailing opinion has been that sex steroid deficiency is not a major cause of age-related bone loss in men. It now is clear, however, that the failure of earlier studies to find major decreases in serum levels of total sex steroids was caused by the fact that they did not account for the confounding effect of a greater than twofold age-related rise in levels of serum sex hormone-binding globulin (SHBG) [52]. It generally is believed that circulating sex steroids that are bound to SHBG have restricted access to target tissues, whereas the 1% to 3% fraction that is free and the 35% to 55% fraction that is bound loosely to albumin are readily accessible. Although there are various methods to assess the bioavailable or non–SHBG-bound sex steroids, several groups have reported substantial decreases in serum levels of free or bioavailable sex steroid levels with aging [52,53]. Data from a population of 346 men from Rochester, Minn., are shown in Table 1. The precise cause of the age-related increase in serum SHBG levels and the failure of the hypothalamic-pituitary-testicular axis to compensate for this and maintain free or bioavailable sex steroids at young normal levels is unclear and the focus of ongoing studies.

As shown in Table 1, aging is associated with substantial decreases in bioavailable testosterone and estrogen levels. The traditional notion had been that because testosterone is the major sex steroid in men, it was the decrease in bioavailable testosterone levels that would be associated most closely with bone loss in men. The initial attempts to address this issue came from

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Percent change*</th>
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<tr>
<td>Bioavailable estrogen</td>
<td>−47</td>
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<tr>
<td>Bioavailable testosterone</td>
<td>−64</td>
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<tr>
<td>SHBG</td>
<td>+124</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>+285</td>
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<td>Follicle-stimulating hormone</td>
<td>+505</td>
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</table>

* P < 0.005.

cross-sectional observational studies in which sex steroid levels were related to BMD at various sites in cohorts of adult men. Slemenda and colleagues [54] found that BMD at various sites in 93 healthy men over age 55 years correlated with serum estradiol levels (correlation coefficients, depending on the site, of $+0.21$ to $+0.35$, $P = 0.01$ to 0.05) and, in fact, inversely with serum testosterone levels (correlation coefficients of $-0.20$ to $-0.28$, $P = 0.03$ to 0.10). Subsequent to this report, other similar cross-sectional studies have demonstrated significant positive associations between BMD and estrogen levels in men [52,53,55–59], particularly circulating bioavailable estradiol levels.

Although these findings are compatible with the hypothesis that estrogen plays an important role in maintaining bone mass in men, they suffer from two potential weaknesses. First, cross-sectional analyses cannot clearly dissociate the effects of estrogen to maintain or prevent bone loss from the effects of estrogen to achieve peak bone mass. For example, a particular individual with a relatively low bone mass at age 50 and low estradiol levels (relative to his age-matched peers) could have had life-long low estradiol levels going back to childhood. In this case, the low estradiol levels would reflect a deficiency in achieving peak bone mass, not necessarily an effect of estrogen to maintain or prevent bone loss. A second weakness of cross-sectional observational data is that correlation never proves causality.

To circumvent the first of these problems, Khosla and colleagues [60] studied, in a longitudinal manner, young (22 to 39 years) and older (60 to 90 years) men in whom rates of change in BMD at various sites over 4 years were related to sex steroid levels. These two different age groups permitted a separate comparison of the possible effects of estrogen on the final stages of skeletal maturation versus age-related bone loss. Forearm sites (distal radius and ulna) provided the clearest data, perhaps because of the greater precision of peripheral site measurements as compared with central sites such as the spine or hip. In the younger men, BMD at the forearm sites increased by 0.42% to 0.43% per year, whereas in the older men, BMD at these sites declined by 0.49% to 0.66% per year. Both the increase in BMD in the younger men and the decrease in BMD in the older men were associated with serum bioavailable estradiol levels more closely than with testosterone levels (Table 2). Moreover, further analysis of the data suggested that there may be a threshold bioavailable estradiol level of approximately 40 pmol/L (11 pg/mL), below which the rate of bone loss in the older men clearly was associated with bioavailable estradiol levels. Above this level, there did not appear to be any relationship between the rate of bone loss and bioavailable estradiol levels (Fig. 5). In these older men, the bioavailable estradiol level of 40 pmol/L (11 pg/mL) represented the median bioavailable estradiol level in these men and corresponded to a total estradiol level of approximately 114 pmol/L (31 pg/mL), which is close to the middle of the reported normal range for estradiol levels in men (10 to 50 pg/mL). Similar findings were reported by Gennari and
colleagues [61], where, in a cohort of elderly Italian men, those subjects with serum free estradiol levels below the median value lost bone over 4 years at the lumbar spine and femur neck, whereas the men with free estradiol levels above the median did not lose bone.

Although these studies helped to establish that estrogen levels are associated with skeletal maintenance in males, they could not establish causal relationships definitively. To address this issue, Falahati-Nini and colleagues [62] performed a direct interventional study to distinguish between the relative contributions of estrogen versus testosterone in regulating bone

Table 2

<table>
<thead>
<tr>
<th>Spearman correlation coefficients</th>
<th>Young</th>
<th>Middle-aged</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radius</td>
<td>Ulna</td>
<td>Radius</td>
</tr>
<tr>
<td>T</td>
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<td>-0.19</td>
<td>-0.18</td>
</tr>
<tr>
<td>E₂</td>
<td>0.33**</td>
<td>0.22*</td>
<td>0.03</td>
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<tr>
<td>E₁</td>
<td>0.35***</td>
<td>0.34**</td>
<td>0.17</td>
</tr>
<tr>
<td>Bio T</td>
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<td>-0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Bio E₂</td>
<td>0.30**</td>
<td>0.20</td>
<td>0.14</td>
</tr>
</tbody>
</table>

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

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


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Fig. 5. Rate of change in midradius BMD (A) and midulna BMD (B) as a function of bioavailable estradiol levels in elderly men. Model R² 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.)
resorption and formation in normal elderly men. Endogenous estrogen and testosterone production were suppressed in 59 elderly men using a combination of a long-acting gonadotropin-releasing hormone (GnRH) agonist and an aromatase inhibitor. Physiologic estrogen and testosterone levels were maintained by simultaneously placing the men on estrogen and testosterone patches delivering doses of sex steroids that mimicked circulating estradiol and testosterone levels in this age group. After baseline measurements of bone resorption (urinary deoxypyridinoline [Dpd] and N-telopeptide of type I collagen [NTx]) and bone formation (serum osteocalcin and amino–terminal propeptide of type I collagen [PINP]) markers, the subjects were randomized to one of four groups. Group A (−T, −E) discontinued both the testosterone and estrogen patches; group B (−T, +E) discontinued the testosterone patch but continued the estrogen patch. Group C (+T, −E) discontinued the estrogen patch but continued the estrogen patch, and group D (+T, +E) continued both patches. Because gonadal and aromatase blockade was continued throughout the 3-week period, separate effects of estrogen versus testosterone (in the absence of aromatization to estrogen) on bone metabolism could be delineated.

As shown in Fig. 6A, significant increases in both urinary Dpd and NTx excretion, (group A [−T, −E]), were prevented completely by continuing testosterone and estrogen replacement (group D [+T, +E]). Estrogen alone (group B) was almost completely able to prevent the increase in bone resorption, whereas testosterone alone (group C) was much less effective. Using a two-factor analysis of variance (ANOVA) model, the effects of estrogen on urinary Dpd and NTx excretion were highly significant (\(P = .005\) and \(P = .0002\), respectively). Estrogen accounted for 70% or more of the total effect of sex steroids on bone resorption in these older men, while testosterone could account for no more than 30% of the effect. Using a somewhat different design, Leder and colleagues [63] confirmed an independent effect of testosterone on bone resorption, although the data in the aggregate clearly favor a more prominent effect of estrogen for controlling bone resorption in men.

Fig. 6B shows the corresponding changes in the bone formation markers, serum osteocalcin and PINP. The reductions in both osteocalcin and PINP levels with the induction of sex steroid deficiency (group A) were prevented with continued estrogen and testosterone replacement (group D). Interestingly, serum osteocalcin, which is a marker of function of the mature osteoblast and osteocyte [64], was maintained by either estrogen or testosterone (ANOVA, \(P = 0.002\) and 0.013, respectively). By contrast, serum PINP, which represents type I collagen synthesis throughout the various stages of osteoblast differentiation [64], was maintained by estrogen (ANOVA, \(P = 0.0001\), but not testosterone.

Collectively, these findings provided conclusive proof of an important (and indeed, dominant) role for estrogen in bone metabolism in the mature skeleton of adult men. Similar findings were reported by Taxel colleagues.
in a study of 15 elderly men treated with an aromatase inhibitor for 9 weeks. Suppression of estrogen production resulted in significant increases in bone resorption markers and a suppression of bone formation markers. It appears, therefore, that similar to women, declining bioavailable estrogen levels in men may play a significant role in mediating age-related bone loss. Declining bioavailable testosterone levels may also contribute, however, because testosterone has some antiresorptive effects and is important for maintaining bone formation. Moreover, it provides the substrate for aromatization to estradiol. In addition, at least in rodents, testosterone has been shown to enhance periosteal apposition. Because larger bones are more resistant to fracture, effects of testosterone on increasing bone size in men may provide important protection against fracture risk.

As in aging women, serum PTH levels also increase with age in men. Because the higher ambient sex steroid levels in aging men as compared with elderly women may protect partially against the bone-resorbing effects of PTH, it has been more difficult to demonstrate a direct role for PTH in contributing to age-related increases in bone resorption in men. Thus, while secondary hyperparathyroidism likely also contributes to age-related bone loss in men, the data in support of this are not as clear as in women.
Other factors contributing to age-related bone loss in both sexes

The previous discussion focused on the role of declining sex steroid and increasing serum PTH levels in the pathogenesis of bone loss in women and in men. Multiple other factors, however, also contribute to age-related bone loss. The role of vitamin D deficiency in aggravating the secondary hyperparathyroidism of aging has been noted. In addition, although declining sex steroid levels may contribute to the age-related impairment in bone formation, this may be caused by other, sex steroid-independent factors, such as intrinsic reductions in the production of key growth factors important for osteoblast differentiation/function. Also, aging decreases the amplitude and frequency of growth hormone secretion [42], which leads to decreased hepatic production of IGF-I. Indeed, serum IGF-I levels decrease markedly with age, and there are also smaller decreases in serum IGF-II levels [43,44]. Thus, decreased systemic and skeletal production of IGFs may contribute to decreases in bone formation with aging.

Other changes in endocrine function with aging appear to make smaller contributions to bone loss. Among the weak adrenal androgens, levels of serum dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-SO₄) decrease by about 80% [68]. Because cortisol secretion remains constant or increases throughout life, the decrease in adrenal androgenic steroids leads to an increase in the catabolic/anabolic ratio of circulating adrenal steroid hormones with aging that could contribute to bone loss.

Peak bone mass also contributes to the risk of osteoporotic fractures later in life. Thus, those persons who achieve a higher peak bone mass are less likely to develop osteoporosis as age-related bone loss ensues, whereas those with low levels are at greater risk [69]. In addition, numerous sporadic factors that affect some, but not other, members of the aging population may contribute to fracture risk in 40% of men and 20% of women [70]. These include use of drugs such as corticosteroids; diseases such as malabsorption, anorexia nervosa, and idiopathic hypercalciuria; and behavioral factors such as smoking, alcohol abuse, and inactivity.

Finally, age-related osteopenia and sarcopenia are parallel processes. Frost [71,72] has suggested that the loss of muscle mass with aging is the principal cause of age-related bone loss. Although this contention remains controversial, it is likely that age-related decreases in muscle loading on bone may contribute to age-related bone loss.

Summary

Age-related bone loss in women and in men is driven, in large part, by changes in sex steroid production or availability and by secondary hyperparathyroidism. Superimposed on these mechanisms, other factors such as vitamin D deficiency, intrinsic defects in osteoblast function, impairments
in the growth hormone/IGF axis, reduced peak bone mass, age-associated sarcopenia, and various sporadic factors also contribute to bone loss and increased fracture risk in the elderly. An improved understanding of the relative importance of these various factors in the causation of bone loss should lead to enhanced preventive and therapeutic approaches for involutional osteoporosis, which, if left unchecked, is likely to impose an increasing health care burden on society.

References


