Update in Male Osteoporosis

Sundeep Khosla

Endocrine Research Unit, College of Medicine, Mayo Clinic, Rochester, Minnesota 55905

Context: Osteoporosis in men is becoming an increasingly important public health problem. One in five men over the age of 50 yr will suffer an osteoporotic fracture during their lifetime, and men who sustain fractures have an increased mortality risk.

Evidence Acquisition: Evidence was obtained by PubMed search and author's knowledge of the field.

Evidence Synthesis: Studies using computed quantitative tomography and high-resolution peripheral computed quantitative tomography have provided new insights into the bone structural changes with aging in men, including the somewhat surprising demonstration of significant, ongoing trabecular bone loss starting in young adult life. In addition, there are now data demonstrating that serum estradiol levels are important predictors of fracture risk in men and that there is a threshold estradiol level below which not only bone loss but also fracture risk increases markedly. Criteria for diagnosing and managing osteoporosis in men are also evolving, including the application of the fracture risk assessment tool to derive 10-yr fracture risks in men. Three bisphosphonates (alendronate, risedronate, and zolendronic acid) and teriparatide are currently U.S. Food and Drug Administration approved for the treatment of osteoporosis in men, with a number of new compounds, including a monoclonal antibody against receptor activator of nuclear factor-κB ligand, selective estrogen receptor modulators, and selective androgen receptor modulators in varying stages of development.

Conclusions: Despite significant advances, there remain a number of key unresolved issues regarding the pathogenesis and management of male osteoporosis, not the least of which is increasing public awareness of this important cause of morbidity and mortality in men. (*J Clin Endocrinol Metab* 95: 3–10, 2010)

With the aging of the population, osteoporosis in men is becoming an increasingly important public health problem. Aging men lose bone mineral density (BMD) at a rate of approximately 1% per year (1), and one in five men over the age of 50 yr will suffer an osteoporotic fracture during their lifetime (2). Of all osteoporotic fractures, hip fractures contribute to the greatest morbidity and mortality, and almost 30% of all hip fractures occur in men (3). Although there is increasing recognition of the problem of male osteoporosis, there remain considerable gaps in knowledge regarding this disorder as well as in the care of these patients; for example, men are far less likely than women to receive a diagnosis of osteoporosis or treatment after a fracture (4). This brief update provides a summary of recent developments in the epidemiology, pathogenesis, and management of male osteoporosis, along with highlighting areas where additional work is needed to better understand and treat this disease.

Epidemiology

Johnell and Kanis (3) recently updated the worldwide prevalence of osteoporotic fractures using data from published sources. Of the annual incidence of 9 million fractures, 39% were in men. Thirty percent of hip, 20% of
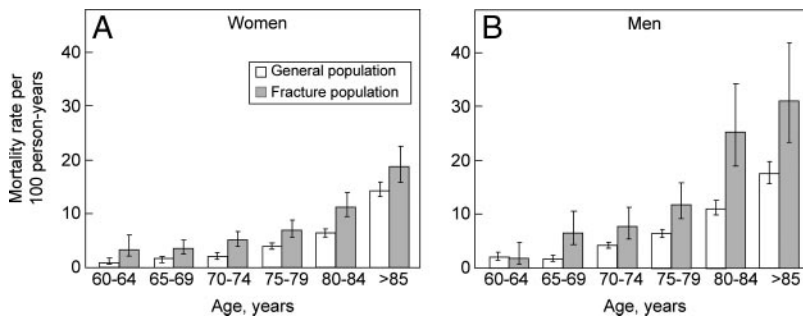
Abbreviations: BMD, Bone mineral density; CI, confidence interval; DHEA, dehydroepiandrosterone; HR, hazard ratio; HRpQCT, high-resolution peripheral quantitative computed tomography; MrOS, Osteoporotic Fractures in Men Study; QTL, quantitative trait loci; RH, relative hazard; SARM, selective androgen receptor modulator; SERM, selective estrogen receptor modulator; vBMD, volumetric BMD.

FIG. 1. Mortality rates for the general participants and fracture patients according to age from the Dubbo Osteoporosis Epidemiology Study in women (A) and men (B). In this population, there were 2245 women and 1760 men aged 60 yr and older. Of the fracture patients, 952 were women and 343 were men. *Error bars* indicate 95% CI. [Reproduced with permission from D. Bliuc *et al.*: *JAMA* 301:513, 2009 (10). ©American Medical Association.]

forearm, 42% of clinical vertebral, and 25% of humerus fractures occurred in men. As is the case in women, there appears to be geographic variation in the probability of hip fractures. Thus, for each 10° increment in latitude, there is a 0.3% increase in the 10-yr probability of hip fracture (5).

There are now clear data in men, as was previously reported in women (6), that the risk of subsequent fracture is markedly increased after a low-trauma fracture. In data from the Dubbo Osteoporosis Epidemiology Study of community-dwelling women and men aged 60 yr or older followed up for 16 yr, Center *et al.* (7) found that after a low-trauma fracture (caused by a fall from a standing height or less) at any skeletal site (excluding skull fractures and those due to underlying malignancy or Paget disease), the relative risk of subsequent fracture was 1.95 (95% confidence interval [CI], 1.70–2.25) in women and 3.47 (95% CI, 2.68–4.48) in men. As a result of the higher relative risk in men, the absolute risk of subsequent fracture was similar in women and men. These findings thus indicate that as for women, a careful fracture history and appropriate assessment for preexisting vertebral fractures, using either vertebral fracture assessment by dual energy x-ray absorptiometry (8) or spine x-rays, is essential in men.

Interestingly, although low-trauma fractures have been associated with BMD, Mackey *et al.* (9) demonstrated that in women and men, high-trauma fractures (*e.g.* due to motor vehicle crashes and falls from greater than standing height) are also associated with low BMD. In this study, each 1-SD reduction in total hip BMD in women was similarly associated with an increased risk of high-trauma fracture [multivariate relative hazard (RH), 1.45; 95% confidence interval (CI), 1.23–1.72] and low-trauma fracture (RH, 1.49; 95% CI, 1.42–1.57). Results were concordant in men (high-trauma fracture RH, 1.54; 95% CI, 1.20–1.96; low-trauma fracture RH, 1.69; 95% CI, 1.49–

1.91). These findings have particular implications for osteoporosis clinical trials and observational studies, because it appears that high-trauma fractures should be included as outcomes in these studies. From a clinical perspective, the possibility of underlying skeletal fragility should also be considered in patients sustaining high-trauma fractures.

In a subsequent study, the Dubbo group also demonstrated that all low-trauma fractures were associated with increased mortality risk for 5–10 yr (10) (Fig. 1). As is evident, for all ages, mortality after fracture was higher for men than for women, and this was most marked in the older age groups. Examination of death certificates suggested no difference between causes of death in the fracture group and general population, with cardiac, respiratory, cerebrovascular disease, and malignancy being the major causes. Thus, the precise cause of the excess mortality after fracture in men (or in women) remains unclear.

The past several years have seen a marked increase in studies on the genetics of BMD and osteoporosis (for review, see Ref. 11), a detailed discussion of which is beyond the scope of this brief update. However, two recent studies are worth highlighting. In the first of these, Styrkarsdottir and colleagues (12) performed a quantitative trait analysis of data from 5861 Icelandic subjects where they examined the association between 301,019 single-nucleotide polymorphisms and BMD of the hip and lumbar spine. They then tested for an association between 74 single-nucleotide polymorphisms from this initial discovery set in replication sets of Icelandic, Danish, and Australian subjects (4165, 2269, and 1491 subjects, respectively). As in previous studies, however, the majority of the subjects were women (87% in the Icelandic population and 61–100% in the test populations). This analysis identified sequence variants in five genomic regions that were significantly associated with BMD in both the discovery and replications sets. Three regions were close to or within genes known to be relevant for bone metabolism: receptor activator of nuclear factor-κB ligand (RANKL), osteoprotegerin (OPG), and estrogen receptor 1 (ESR1). The other two regions were close to the zinc finger and BTB domain-containing 40 gene (ZBT40) and the major histocompatibility complex region. Somewhat disappointing was the finding that although statistically highly significant, these genes combined accounted for only approximately 3% of the total variation in hip and spine BMD. Thus, they are unlikely to be clinically useful but do provide further insights into the biochemical pathways underlying osteoporosis. Because the vast majority of subjects in this, and

other, genetic studies of osteoporosis have been women, Peacock *et al.* (13) measured spine and hip BMD in 515 pairs of brothers, aged 18–61 yr, and performed linkage analysis in this sample as compared with results in a previous sample of 774 sister pairs to identify possible sex-specific quantitative trait loci (QTL). In this analysis, the investigators identified significant QTL (LOD > 3.6) for BMD on chromosome 4q21 (hip), 7q34 (spine), 14q32 (hip), 19p13 (hip), 21q21 (hip), and 22q13 (hip). By comparison with the previous female data, the QTL on chromosomes 7, 14, and 21 were male specific, whereas the others were not sex specific. Collectively, these data highlight the complexity of the genetics of a trait such as BMD as well as the fact that the genes determining BMD are likely at least partly gender specific.

Pathogenesis

Male osteoporosis remains a heterogeneous entity, with multiple underlying causes. In addition, several different factors may contribute to bone loss in a given individual. Conceptually, however, it is useful to separate male osteoporosis into primary causes (age-related and idiopathic osteoporosis) and secondary causes (those due to clearly identifiable diseases or drugs).

   Recent studies using central and peripheral quantitative computed tomography (QCT), including high-resolution peripheral QCT (HRpQCT), have allowed for a clearer definition of age-associated changes in volumetric BMD (vBMD), geometry, and microstructure. In cross-sectional studies, Riggs *et al.* (14) found large decreases in vBMD at the spine (which consists principally of trabecular bone) over life, with a similar pattern of changes in trabecular bone at the femur neck, distal radius, and distal tibia, which seemed to begin in the third decade in both men and women. By contrast, cortical vBMD at the distal radius, distal tibia, and femur neck showed little change until midlife in either men or women, with linear decreases in both sexes thereafter. These cross-sectional findings were confirmed by longitudinal data (15), which showed significant trabecular bone loss at the spine, distal radius, and distal tibia before midlife in men, with an apparent attenuation in rates of trabecular bone loss at the distal radius and tibia, but not at the spine, in older men (Fig. 2, A–C). By contrast, cortical vBMD remained relatively stable until age 65–70 yr, with loss of cortical bone thereafter (Fig. 3, A and B). Essentially similar findings were present in women. These cross-sectional and longitudinal studies thus indicate that in both sexes, trabecular bone loss begins in young adult life, whereas cortical bone loss begins after midlife.

   Studies using HRpQCT, which allows for *in vivo* assessment of bone microstructure, demonstrated that at the
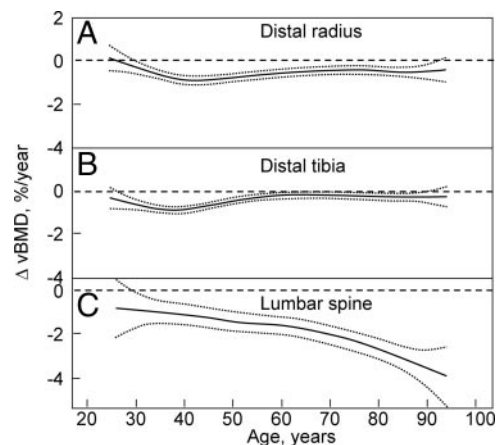

FIG. 2. Age-specific rates of change in vBMD at trabecular scanning sites in men at the distal radius (A), distal tibia (B), and lumbar spine (C). Data are shown with a smoothing spline and the 95% CI. [Reproduced with permission from B. L. Riggs *et al.*: *J Bone Miner Res* 23:205, 2008 (15). ©American Society for Bone and Mineral Research.]

distal radius, women undergo loss of trabeculae with aging, whereas men primarily sustain trabecular thinning (16), findings that are similar to previous data from cadaveric transiliac bone biopsies (17). Because decreases in trabecular number have been shown by finite element modeling (18) to have a much greater impact on bone strength compared with decreases in trabecular thickness, these findings may help explain the lower lifelong risk of fractures in men, especially their virtual immunity to age-related increases in distal forearm fractures.

   Recent studies have also further defined the relative contributions of estrogen and testosterone toward fracture risk in men. Previous work had demonstrated that estrogen played an important, and perhaps dominant, role in regulating bone density (19), bone resorption (20, 21), and bone loss (22) in elderly men. In addition, there appeared to be a threshold serum estradiol level below which the male skeleton became estrogen deficient (22, 23). Consistent with previous studies (19), Orwoll and colleagues (24) demonstrated that in men age 65 yr and older from the Osteoporotic Fractures in Men Study (MrOS), testosterone and estradiol levels, and their free fractions, declined
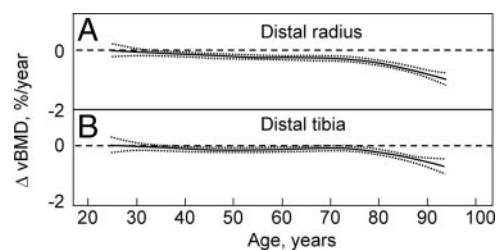

FIG. 3. Age-specific changes in vBMD at cortical scanning sites at distal radius (A) and distal tibia (B) in men. Data are shown with a smoothing spline and the 95% CI. [Reproduced with permission from B. L. Riggs *et al.*: *J Bone Miner Res* 23:205, 2008 (15). ©American Society for Bone and Mineral Research.]

significantly with age. Although free estradiol and free testosterone were modestly correlated (r = 0.20; $P <$ 0.001), at any level of free testosterone, there was considerable variation in free estradiol levels. Amin and colleagues (25) related these declining sex steroid levels in aging men from the Framingham Study to the risk for hip fractures. In this study, 793 men (mean age, 71 yr) evaluated between 1981 and 1983 were followed until the end of 1999. The men were stratified into three groups, according to serum estradiol and testosterone levels. Based on 39 men who sustained a hip fracture during follow-up, incidence rates for hip fracture (per 1000 person-years) were 11.0, 3.4, and 3.9 for the low (2.0–18.1 pg/ml), middle (18.2–34.2 pg/ml), and high (≥34.3 pg/ml) estradiol groups, respectively. After adjustment for age, body mass index, height, and smoking status, the adjusted hazard ratios (HRs) for men in the low and middle estradiol groups, relative to the high estradiol group, were 3.1 (95% CI, 1.4–6.9) and 0.9 (95% CI, 0.4–2.0), respectively, consistent with the presence of a threshold estradiol level around 18 pg/ml below which fracture risk increased in the men. By contrast, in similar adjusted analyses evaluating men by their testosterone levels, the investigators found no significant increased risk for hip fracture associated with low testosterone levels.

Somewhat contrasting findings were reported from men in the Dubbo cohort by Meier and colleagues (26), who found that although serum testosterone was not related to lumbar spine or femoral neck BMD in 609 men over the age of 60 yr, lower testosterone levels were stronger predictors of low-trauma fractures than were estradiol levels, despite the fact that estradiol was significantly associated with spine and hip BMD in these men. These findings suggested that the effect of testosterone on fracture risk in elderly men may be mediated via nonskeletal factors, such as muscle strength and/or fall risk.

The most definitive data addressing this issue have come from the MrOS cohort. In the first of these studies, Mellström *et al.* (27) analyzed sex steroids using gas chromatography-mass spectroscopy in 2639 elderly men (mean age, 75 yr) from the Swedish arm of MrOS and evaluated fractures over a mean follow-up period of 3.3 yr. In multivariable proportional hazards regression models, free estradiol and SHBG, but not free testosterone, were independently associated with fracture risk. In further subanalyses, free estradiol was inversely associated with clinical vertebral fractures (HR per SD decrease, 1.57; 95% CI, 1.36–1.80), nonvertebral osteoporotic fractures (HR per SD decrease, 1.42; 95% CI, 1.23–1.65), and hip fractures (HR per SD decrease, 1.44; 95% CI, 1.18–1.76). Furthermore, consistent again with a threshold effect, the inverse relation between serum estradiol and fracture risk was non-
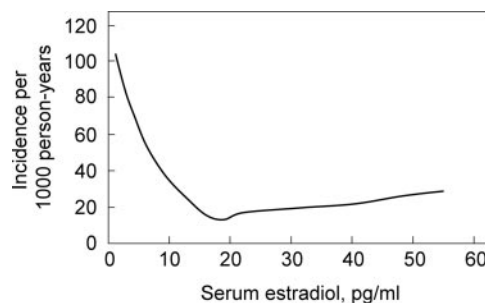

FIG. 4. Yearly incidence of fractures as a function of serum estradiol levels in subjects from MrOS Sweden. Poisson regression models were used to determine the relation between serum estradiol levels and fracture risk. [Reproduced with permission from Mellström *et al.*: *J Bone Miner Res* 23:1552, 2008 (27). ©American Society for Bone and Mineral Research.]

linear (Fig. 4). Specifically, the yearly incidence of fractures was inversely associated with serum estradiol levels at estradiol levels less than 16 pg/ml; above this level, there was no relationship between fracture incidence and estradiol levels.

LeBlanc *et al.* (28) have subsequently expanded these findings to include the larger U.S. cohort of MrOS involving 5995 men age 65 yr and older, of which they randomly selected a subcohort of 1436 white men and all 446 minority participants, plus all subjects with incident hip and other nonvertebral fractures. Consistent with the previous data and with the notion of a threshold, they found that men in the lowest bioavailable (non-SHBG bound) estradiol quartile (<11.4 pg/ml) or highest SHBG quartile (>59.1 nM) had greater risk of all nonvertebral fractures; by contrast, men with the lowest bioavailable testosterone level had no increased fracture risk after adjustment for bioavailable estradiol. However, these investigators did observe an interesting interaction (P = 0.03) between SHBG and bioavailable testosterone: men with low bioavailable testosterone and high SHBG did have an increase in fracture risk, with the highest risk of fracture occurring in men with low bioavailable estradiol, low bioavailable testosterone, and high SHBG.

Taken together, these studies using fracture as outcomes have provided further support for a key role for estradiol in determining fracture risk in aging men as well as the presence of a threshold estradiol level (which may vary, depending on the particular assay used) below which fracture risk increases in men. Testosterone may also contribute to fracture risk, particularly in the setting of high SHBG levels. Moreover, it is probable that a significant component of the testosterone effect on risk of fracture is mediated by nonskeletal effects, such as on muscle mass, balance, or risk of falls, although further studies directly addressing this issue are needed.

These findings also have potential clinical implications. First, from a diagnostic standpoint, measurement of serum sex steroid levels, particularly estradiol levels, in men with

osteoporosis may be useful. However, this has to await further evaluation after standardization of sex steroid assays, likely using mass spectroscopy. Second, these data strengthen the rationale for assessing the use of selective estrogen receptor modulators (SERMs) in preventing bone loss in aging men. Third, these findings raise potential concerns about the utility of nonaromatizable selective androgen receptor modulators (SARMs) in preventing bone loss in men, because to the extent that the major sex steroid effect on bone is mediated by estrogen, these non-aromatizable compounds may have minimal skeletal effects, at least in humans. Nonetheless, SARMs may be useful in enhancing muscle strength and reducing fall risk and have antifracture effects through these nonskeletal actions.

Although there are a large number of possible secondary causes of osteoporosis in men, one has received considerable attention recently, the use of selective serotonin reuptake inhibitors. In a cross-sectional analysis of MrOS data, Haney *et al.* (29) found that mean BMD among men who used selective serotonin reuptake inhibitors (n = 160) was 3.9% lower at the total hip and 5.9% lower at the lumbar spine compared with BMD in men not on antidepressants (n = 5708; $P = 0.002$ for total hip; $P < 0.001$ for spine). By contrast, other antidepressants (trazodone hydrochloride and tricyclic antidepressants) were not associated with decreased BMD. These clinical findings are of particular interest given recent provocative data by Yadav and colleagues (30) showing that duodenum-derived serotonin inhibits bone formation, unveiling perhaps an entirely novel enteroskeletal regulatory system. In women, serum serotonin levels have recently been found to be inversely associated with bone mass and structural parameters at various skeletal sites (31); whether similar associations are present in men and the precise role for serotonin in regulating bone turnover in humans remains an area of active investigation.

Management

The original World Health Organization criteria for diagnosing osteoporosis were developed for women (32), and since then, there has been a vigorous debate regarding whether male- or female-referent T-scores should be used to diagnose osteoporosis in men. There are data indicating that the relationship between the absolute level of BMD and fracture risk is the same in men and women (33), arguing for the use of female-specific T-scores, even in men. By contrast, other studies have noted sex differences in the relationship between BMD and fracture risk, which are most apparent at younger ages and become less evident in older men (34). Currently, most densitometer reports

provide gender-specific T-scores for men. However, the new World Health Organization fracture risk assessment tool (FRAX) uses the absolute femoral neck BMD (independent of sex) or, if T-scores are used, the calculator uses NHANES reference values for women aged 20–29 yr (*i.e.* a female-referent T-score) (35). The FRAX tool for predicting absolute 10-yr fracture risk can be used with or without BMD and includes key risk factors identified from nine prospective, population-based cohorts: a prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and daily alcohol consumption of three or more units daily. For women and men, the National Osteoporosis Foundation (NOF) has recently performed a U.S.-specific cost-effectiveness analysis, which incorporates the cost and health consequences of hip, spine, forearm, shoulder, rib, pelvis, and lower leg fractures, and identifies a 10-yr hip fracture probability of 3% or greater [or major osteoporotic (spine, forearm, hip, or shoulder) fracture of 20% or greater] as being sufficient to justify treatment (36). In contrast to this approach, the United Kingdom National Osteoporosis Guideline Group has adopted a variable threshold for treatment that at each age is set at a risk equivalent to that associated with a prior fracture and, therefore, rises with age (37). Both groups, however, clearly recommend pharmacological treatment for men or women with a prior history of fragility fracture.

The FRAX algorithm for the United States has just recently been revised (38), and just how FRAX and the new NOF guidelines for the treatment of osteoporosis in men (or women) will impact clinical practice remains to be determined. For example, there is concern that a substantial number of men (or women) with femoral neck BMD in the osteopenic range may be recommended for treatment based on the NOF guidelines. However, evidence that these men will have a reduction in fractures after therapy (as opposed to those subjects with T-scores below −2.5) is lacking. At the least, however, the ability of physicians to provide information to patients on absolute risks of fracture (rather than simply the somewhat abstract concept of a T-score) should lead to more informed decisions by the physician and patient regarding the initiation of pharmacological therapy.

In terms of therapy, given the critical role discussed above for estrogen in bone metabolism in men, a logical hypothesis is whether low doses of estrogen or SERMs may be effective as treatment modalities for osteoporosis in men. Although neither is currently approved for use in men, raloxifene does reduce bone turnover in men with low endogenous estradiol levels (39, 40) and has been found to have positive effects on BMD at multiple sites in

men undergoing gonadal suppression therapy for prostate cancer (41). A more recent study of 1389 men with prostate cancer on androgen deprivation therapy found that another SERM, toremifene, significantly reduced vertebral fractures (42). Thus, SERMs do hold promise in the treatment of hypogonadal bone loss in men with prostate cancer, but further studies are needed to assess their possible efficacy in aging men not undergoing gonadal suppression.

The question of whether SARMs might also represent a useful option for the treatment of osteoporosis in men has received considerable attention in recent years. Although there is preclinical animal data on a number of compounds in this class that appear to have beneficial effects on bone and muscle without adverse effects on the prostate (43), there are currently no published human data on the skeletal or nonskeletal effects (particularly effects on muscle mass and function) or safety of these compounds.

The issue of testosterone and/or the adrenal androgen dehydroepiandrosterone (DHEA), treatment of elderly men for preservation of bone and muscle mass as well as overall quality of life remains an active area of debate and discussion. In a recent study, Nair and colleagues (44) performed a 2-yr placebo-controlled, randomized, double-blind study involving 87 elderly men with low levels of DHEA-sulfate and bioavailable testosterone (defined as below the 15th percentile for young normal men). Over 2 yr of treatment, DHEA had no effect on body composition, and neither hormone altered the peak volume of oxygen consumed per minute, muscle strength, or insulin sensitivity. Men who received testosterone transdermally had a slight increase in fat-free mass, and men in both treatment groups had a modest (~2%) increase in BMD at the femur neck but not at the spine, total hip, or radius. Neither treatment had an effect on the quality-of-life measures tested or had major adverse effects, including on prostate-specific antigen levels. These findings using transdermal testosterone at doses that had only modest effects on serum testosterone levels contrast with previous studies that used im testosterone administration and achieved higher circulating testosterone levels (45). In the latter, testosterone therapy was associated with more clinically significant increases in bone mass and muscle strength and improved body composition. Based on the current state of uncertainty regarding testosterone treatment of aging men, the Institute of Medicine has recommended that a series of clinical trials be done to help determine the efficacy of testosterone for several important outcomes, including bone (46).

As is the case in women, the mainstays of therapy for osteoporosis in men are the bisphosphonates. Currently,

alendronate, risedronate, and zolendronic acid are U.S. Food and Drug Administration (FDA) approved for use in men. In addition, for patients at high risk of fracture, use of teriparatide in men has also been approved by the FDA. Because the general approach to the use of these drugs is similar to that in women, this is not discussed in detail here, and a more detailed description of bisphosphonate use in men has recently been presented elsewhere (47). The most recent option that is currently pending review by the FDA is denosumab, a fully monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL). In a double-blind, multicenter study, Smith *et al.* (48) randomly assigned men receiving androgen deprivation therapy for prostate cancer to receive denosumab at a dose of 60 mg sc every 6 months or placebo (734 patients in each group). At 24 months, lumbar spine BMD increased by 5.6% in the denosumab group, as compared with a 1.0% loss in the placebo group ($P < 0.001$); denosumab was also associated with significant increases in BMD at the total hip, femoral neck, and distal radius. At 36 months, patients on denosumab had a 62% decreased incidence of new vertebral fractures (1.5 *vs.* 3.9% in the placebo group, $P = 0.006$). Thus, as for women, therapeutic options for treating osteoporosis in men are continuing to expand.

Key Unresolved Issues

Although there have been considerable advances in our understanding and management options for male osteoporosis, there are a number of important gaps in knowledge. Thus, although the FRAX algorithm has adopted the use of absolute femoral neck BMD and female-referent T-scores, the issue of whether male or female reference ranges should be used to define osteoporosis in men remains an active area of debate. This obviously impacts the question of the true prevalence of male osteoporosis. In terms of pathogenesis of bone loss, a better understanding is needed of the hormonal and nonhormonal factors causing bone loss in men, particularly the underlying mechanisms for the significant, ongoing trabecular bone loss in men (and women) in young adult life. Further studies are also needed regarding the potential utility of measuring serum estradiol levels, in addition to serum testosterone levels, using standardized mass spectroscopy assays in the evaluation of men with low bone mass. Additional studies on the use of SERMs, SARMs, and the skeletal, as well as nonskeletal, benefits *vs.* risks of testosterone treatment of aging men with declining total and bioavailable testosterone levels also need to be done. Finally, given that osteoporosis in men remains an underdiagnosed and undertreated disorder (4), increasing public awareness of this important cause of morbidity and mortality in men is key

to ensure that as men age, they are spared the consequences of this disabling but now eminently preventable and treatable disease.

Acknowledgments

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