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Osteoporosis in Men: Insights For the Clinician

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Abstract and Introduction

Abstract

Osteoporosis has finally been recognized as an important disorder in men. Men have osteoporotic fractures about 10 years later in life than women. Owing to increasing life expectancy, more fractures are predicted. Important risk factors for men include advancing age, smoking or chronic obstructive pulmonary disease, glucocorticoid therapy, and androgen deprivation therapy for prostate cancer. Other groups at risk for osteoporosis include those with alcohol abuse, men on enzyme-inducing antiseizure drugs, and those with malabsorption or history of surgery for peptic ulcer disease. History and physical examination will likely reveal secondary causes of osteoporosis. Some, but not all organizations, recommend screening for osteoporosis in men older than age 70. In the USA, The Department of Veterans Affairs recommends case finding rather than screening. Evaluation starts with bone mineral density testing by dual energy X-ray absorptiometry of the spine, hip, and in some cases forearm. A few laboratory tests can be helpful, including measurement of 25-hydroxyvitamin D. Most studies of osteoporosis therapy in men are small; but alendronate, risedronate, zoledronic acid, and teriparatide are FDA-approved to increase bone density in men with osteoporosis. A new potent antiresorptive agent, denosumab, increased bone density dramatically in men on androgen deprivation therapy and is approved for this indication in Europe. Recognition, diagnosis, and treatment of osteoporosis in men should lead to fewer fractures and probably fewer deaths.

Introduction

The difference between the most recent *National Osteoporosis Foundation Clinicians Guide* and the previous edition is emblematic of the change in recognition that men are at risk for osteoporosis and fracture. Only in the most recent edition (available at http://www.nof.org) are there recommendations for evaluation and management of male osteoporosis. There is good evidence that osteoporosis in men is underdiagnosed and undertreated [Feldstein *et al.* 2005]. Indeed, about one third of all hip fractures occur in men [Burge *et al.* 2007] and men are less likely to survive [Bass *et al.* 2007] or regain independence after hip fracture. As reported in a study from Denmark [Kannegaard *et al.* 2010], the excess post-hip-fracture mortality is not explained by comorbidities or medication. However, more studies than ever have been reported such that a body of literature now exists to help the clinician. Nonetheless, osteoporosis medication advertisements target women only, and many clinicians still believe that osteoporosis is just a disorder of postmenopausal women. The purpose of this paper is to highlight some of the recent additions to our knowledge base and to present some suggestions for evaluation and treatment of male osteoporosis.

Etiology of Osteoporosis in Men

While the risk for fracture in men increases with age, as it does in women, there is a subgroup of men who present in middle age, usually with vertebral fractures. Some of the men may have obvious secondary causes, such as glucocorticoid-induced osteoporosis [Pearce *et al.* 1998]. These men may have chronic obstructive pulmonary disease, inflammatory bowel disease, or a rheumatologic condition requiring oral glucocorticoids. Another relatively common cause is hypercalciuria. In addition there are a few unusual disorders that have been associated with fractures and/or low bone mineral density (BMD) in middle-aged men. One group of osteoporotic younger men have low serum levels of insulin-like growth factor-I (IGF-I) associated with specific alleles in a variable region of the *IGF-I* gene [Rosen *et al.* 1998]. These men have normal growth hormone secretion and respond very well to standard therapy [Kurland *et al.* 2000]. Another genetic disorder has been described in male family members in Belgium [van Pottelbergh *et al.* 2004]. These men have osteoporosis and fractures apparently due to low levels of bioavailable

estradiol. As we describe in the following, in aging men, estrogen plays an important role in male osteoporosis.

There have been a few other interesting syndromes of early osteoporosis in men, but by and large most fractures occur in men older than 70, with the incidence rising with further aging. We are beginning to learn why some men fracture and others do not. In an important systematic review [Papaioannou *et al.* 2009] of reasons for low BMD in older men, the following risk factors were found: advancing age, low body weight, smoking, decreased physical activity, and previous adult fracture. In a large study [Trimpou *et al.* 2010] of men who suffered a hip fracture during a 30-year period, low BMD, smoking, tall stature, stroke, dementia, and inadequate leisure activity were found to predict fracture risk. As in women, the older man who has amassed the largest skeleton during growth has more bone to lose with aging. Delayed puberty in a male is associated with lower peak bone mass [Finkelstein *et al.* 1996]. It is likely that genetics also play a role in the attainment of peak bone mass, and delayed puberty is one example of how sex steroids affect bone mass. In addition, with aging, bioavailable estradiol levels are more closely associated with BMD [Khosla *et al.* 1998] than testosterone levels, although in the MrOS cohort, men with lower bioavailable testosterone as well as lower bioavailable estradiol and higher sex hormone binding globulin (SHBG) had significantly higher rates of bone density loss over time [Cauley *et al.* 2010]. An example of profound hypogonadism is the use of androgen deprivation therapy for prostate cancer. Both estradiol and testosterone are dramatically reduced by this treatment, which leads to markedly increased fracture risk [Adler, 2011; Shahinian *et al.* 2005].

Screening for Osteoporosis in Men

Owing to the increasing fracture risk with aging, the American College of Physicians [Qaseem *et al.* 2008], the International Society for Clinical Densitometry [Baim *et al.* 2008] and the American College of Preventive Medicine [Lim *et al.* 2009] advocate screening men at or after age 70 by dual energy X-ray absorptiometry (DXA) of the spine and hip. For men younger than 70, the presence of risk factors for fracture would also trigger DXA evaluation. When the spine DXA cannot be interpreted because of arthritic changes, a forearm region of interest, usually the distal one third radius should be measured [Binkley and Adler, 2010]. In contrast, in the recent report of the United States Preventive Services Task Force [US Preventive Services Task Force, 2011], DXA screening of men based upon age was not dvocated because there are no randomized, controlled trials demonstrating that benefits of such screening outweigh potential harms. In the USA, The Department of Veterans Affairs also does not advocate population screening but rather case finding. Thus, only an adult man at increased risk for osteoporosis and fracture (Table 1) would be considered for DXA. This approach is likely to identify more men at risk for fracture, but studies of case finding *versus* population screening will be needed to determine sensitivity, specificity, and cost effectiveness of the different approaches.

Table 1. Risk factors for osteoporosis and fracture in men that may indicate the need for dual energy X-ray absorptiometry.

Age
Low body weight
Low trauma fracture after age 50
Oral glucocorticoid therapy
Androgen deprivation therapy for prostate cancer
Other hypogonadism
Smoking and/or chronic obstructive pulmonary disease
Excess alcohol intake (>3 units daily)
Malabsorption, celiac disease
Surgery for peptic ulcer disease

Bariatric surgery
Enzyme-inducing antiseizure medications
Hyperthyroidism
Osteopenia/fracture noted on X-ray
Height loss
Mobility disorders (Parkinson's disease, stroke, multiple sclerosis, etc.)

For the man who has suffered a fragility fracture or has osteoporosis determined by DXA, evaluation and treatment are indicated. However, in men as in women, there will be more fractures in those men who have so-called osteopenia on DXA testing simply because so many more men have osteopenia. If osteoporosis is defined as a BMD 2.5 standard deviations or more below the normal young mean (*T*-score ≤ −2.5), then osteopenia is a BMD between 1 and 2.4 standard deviations below the normal young mean (*T*-score between −1 and −2.4). The problem facing the clinician with an osteopenic patient is to determine whether he is likely to fracture. New calculation tools can be used to estimate the 5- or 10-year fracture risk of an individual. The most widely used tool is the FRAX® constructed by the World Health Organization [Kanis *et al.* 2010] and available online (see http://www.shef.ac.uk/FRAX/). The clinician can enter the data requested (patient0s age, sex, weight, height, and femoral neck BMD as well as validated risk factors for osteoporosis: previous adult fracture, parental history of hip fracture, current smoking, alcohol intake of >3 units daily, oral glucocorticoid use, rheumatoid arthritis, other secondary osteoporosis). The tool then calculates the 10-year risk prediction for hip fracture and for any major osteoporotic fracture (vertebral, hip, forearm, or humerus). In the US, a study [Tosteson *et al.* 2008] concluded that it would be cost effective to treat patients with a 10-year hip fracture risk of 3% or a 10-year any major osteoporotic fracture risk of 20%. It should be noted that the FRAX uses the absolute value of bone density (in g/cm^2), which essentially means that the same normative database is used for men and women. On the other hand, most bone densitometers will report the *T*-score by comparing the patient's bone density with normal young men. Another fracture risk calculator that can be used in men is the Garvan nomogram, which is based on the Dubbo Study from Australia [Nguyen *et al.* 2008]. This calculator (see http://www.fractureriskcalculator.com) uses age, sex, number of non-major-trauma fractures since age 50, number of falls in last 12 months, and femoral BMD to predict 5- and 10-year risk of any osteoporotic fracture or hip fracture. In one validation study [Sandhu *et al.* 2010] in Australia, the Garvan nomogram was superior to FRAX in identifying male fracture patients, but it is not known whether this is true for other populations. There are other fracture risk calculators available, and at some point there may be agreement on what works for a given population of men. It is interesting that both FRAX and the Garvan nomogram include age as a risk factor for fracture, but in the CHAMP study, age was not an independent determinant of bone density [Bleicher *et al.* 2010]. This confirms the result of studies in women that age affects bone quality as well as quantity. The ethnic background of the patient may be important because DXA may predict fracture risk differently in different populations. Indeed, the clinician still must use judgment for many patients who may have risk factors not utilized by the calculation tools. Until there is a universally accepted fracture risk calculator applicable to all populations, clinicians will still have to weigh all the potential benefits and harms in a given patient. The fact that these risk calculators work for men is more evidence that the problem of male osteoporosis is receiving long-delayed attention.

Evaluation of Osteoporosis

For the man with osteoporosis determined by DXA or elevated fracture risk as determined by one of the calculations, history and physical examination are required to determine whether there is a so-called secondary cause of osteoporosis. At least in some cases of secondary osteoporosis, treatment of the underlying disorder often improves bone health. For example, oral glucocorticoid preparations decrease osteoblast function and increase fracture risk as early as 3 months after starting them [van Staa *et al.* 2000]. After stopping the glucocorticoids, fracture risk diminishes quickly. Crohn's disease or other inflammatory bowel disorders also lead to bone loss. Improvement in the

inflammatory bowel condition often leads to improvement in BMD and muscle mass, reducing fracture risk. The list of secondary causes is long [Painter *et al.* 2006], and it has been thought that men are more likely to have secondary osteoporosis than women. In some series [Deutschmann *et al.* 2002] the great majority of men have secondary osteoporosis, but this has not always been the case [McKiernan *et al.* 2010]. Regardless of the prevalence, however, it is clear that careful history and physical examination will likely lead to a diagnosis or at least suspicion of a diagnosis that can be confirmed by laboratory testing. An exception to this rule is celiac disease, which is being diagnosed more often than previously. Some patients with celiac disease do not have gastrointestinal symptoms, so the clinician needs to consider this in the man (particularly the younger man) who does not have other reasons for osteoporosis. Most other secondary disorders are found by history, physical examination, and a short list of laboratory tests [Ryan *et al.* 2011], as shown in Table 2.

Table 2. Laboratory evaluation of men at risk for osteoporosis and fracture.

Serum chemistries: calcium, creatinine (or estimated glomerular filtration rate), possibly phosphate, alkaline phosphatase
Serum 25-hydroxyvitamin D
Urinary calcium and creatinine (preferably in a 24-hour urine specimen)
Serum parathyroid hormone if serum calcium abnormal or if normocalcemic hyperparathyroidism is suspected*
Serum thyroid-stimulating hormone and free T4 if hyperthyroidism suspected
Serum testosterone, luteinizing hormone, follicle-stimulating hormone (possibly sex hormone binding globulin) if hypogonadism suspected
Complete blood count
Serum and urine electrophoresis (and possible light chain analysis) if multiple myeloma suspected
Antibodies for celiac disease

*Some experts believe that serum parathyroid hormone is helpful in the interpreting level of 25-hydroxyvitamin D.

As listed in Table 2, measurement of the main circulating vitamin D moiety, 25-hydroxyvitamin D, is recommended. Based on an exhaustive literature review, the Institute of Medicine (IOM) [Ross *et al.* 2011] determined that a level of 20 ng/ml (50 nmol/l) is the minimum needed for bone health. To achieve this, they recommended that diet and supplements provide 600–800 IU of Vitamin D daily. Osteomalacia, due to extremely low vitamin D levels, needs to be diagnosed and treated with vitamin D replacement. For the patient with osteoporosis, many experts believe that a serum level of more than 20 ng/ml is preferable for several reasons. First, patients do not take vitamin D supplements regularly [Jackson *et al.* 2006], so aiming beyond the minimum is more likely to ensure that the individual stays above that minimum serum concentration. Second, the quality of measurement of 25-hydroxyvitamin D has been variable [Binkley *et al.* 2009, 2004], with some assays overestimating the 25-hydroxyvitamin D level. Third, in obese patients, the larger storage depot (adipose tissue) may lead to increased vitamin D requirements. Finally, in a histological study, raising the serum 25-hydroxyvitamin D level to 30 ng/ml (75 nmol/l) eliminated any evidence of osteomalacia in bone biopsies [Priemel *et al.* 2010]. Indeed, the IOM stated that up to 4000 IU of vitamin D daily was probably safe. It is obvious that more study is needed to define a best value for all patients. Nonetheless, aiming for a 25-hydroxyvitamin D level a little above 20 ng/ml makes clinical sense.

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It is also important to consider an image of the spine. For the man with osteopenia (*T*-score between −1 and −2.4), the finding of a compression fracture (without a history of trauma to explain it) means the patient likely needs pharmacologic therapy. While standard X-rays of the lumbar and thoracic spine have been the usual method for diagnosis of compression fracture, there is a definite radiation dose associated with such X-rays. Vertebral fracture assessment (VFA) is an image performed by many DXA machines [Schousboe *et al.* 2008]. In addition to the convenience of performing VFA at the time of DXA, the technique is associated with a much lower radiation dose than standard X-rays. It should be noted that many individuals have compression deformities on spine imaging despite no recollection of acute back pain bad enough to bring them to medical attention. Compression fractures may also be noted on lateral chest X-rays obtained for other clinical reasons, although there are studies showing that many fractures are missed or not followed up [Bartalena *et al.* 2010].

If physical examination and/or history suggest a secondary cause of osteoporosis, and sometimes without such suggestions (e.g. a middle aged man with vertebral fractures), other tests may be indicated. For example, hyperthyroidism may lead to increased bone turnover and loss. Hypogonadism is an important cause of osteoporosis. Thus, early morning measurement of serum testosterone is suggested for many men. Depending on the clinical context and level of testosterone, measurements of the pituitary hormones luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin should be considered. In some men it may be necessary to measure bioavailable testosterone, which is calculated from the total testosterone, albumin, and SHBG, using a readily available calculation tool (see http://www.issam.ch/freetesto.htm).

Management of the Man with Osteoporosis by DXA and/or Increased Fracture Risk

All patients, including men, need some general measures to decrease fracture risk. Among these are smoking cessation and decreasing fall risk with home safety measures, improving lower body strength by weight-bearing exercise, maintaining visual acuity, and avoiding medications (and substances such as alcohol) that affect mental functioning. The latter is particularly important for elderly men. In addition, all contemporary trials of osteoporosis medications have included some supplementation of calcium and vitamin D. The IOM [Ross *et al.* 2011] has recently recommended 1000–1200 mg of calcium daily (in diet plus supplements when needed) and 600–800 IU of vitamin D daily. There is controversy about both substances with concern that too much may also be harmful. For the population at large, the IOM stated that doses of calcium up to 2000mg daily and vitamin D up to 4000 IU daily are probably safe. The reader is directed to some very recent articles on the calcium [Lewis *et al.* 2011; Bolland *et al.* 2010] and vitamin D [Heaney and Holick, 2011; Rosen, 2011] supplementation. There is also a recent summary on

nonpharmacologic management of osteoporosis [Kasturi and Adler, 2011].

The man with osteoporosis of the spine or hip (usually femoral neck and total hip are measured) is a good candidate for therapy because the studies (as described in the following) demonstrate that available therapies increase bone density and in some cases decrease morphological fractures. Some of the studies included men with osteopenia (usually a *T*-score in the spine or hip between −2 and −2.4) plus evidence of a minimal trauma fracture. A ground level fall is considered to be minimal trauma. The ISCD recommends measuring the distal one third radius bone density in those men in whom the spine DXA cannot be interpreted [Binkley and Adler, 2010], and as mentioned above this is also important for those men with arthritis in the hip [Chaganti *et al.* 2010] and particularly for men on androgen deprivation therapy for prostate cancer [Adler *et al.* 2010] or hyperparathyroidism. There are no studies demonstrating that a man with osteoporosis only in the forearm will respond to therapy, but some interesting information on forearm bone density response to therapy is discussed in the following.

The standard therapy for men with osteoporosis by DXA or osteopenia plus a history of a minimal trauma has been oral bisphosphonate treatment. The US Food and Drug Administration (FDA) has approved oral alendronate and risedronate to increase BMD in such men. The typical dose is 70mg of alendronate weekly or 35 mg of risedronate weekly. There is a 150 mg monthly dose of risedronate that has only been FDA approved for postmenopausal osteoporosis, but men have been treated off label with this convenient preparation. For patients having contraindications (e.g. esophageal motility disorders) to oral bisphosphonates or who have had gastrointestinal side effects from oral bisphosphonates, intravenous zoledronic acid is FDA approved to increase bone density in men and approved after hip fracture [Orwoll *et al.* 2010; Lyles *et al.* 2007]. This preparation is also convenient because it is given as a once yearly intravenous infusion (5mg over at least 15 minutes). All three bisphosphonates approved for men by the FDA will increase BMD in men and decrease bone turnover, surrogates for fracture reduction. In the main daily alendronate trial [Orwoll *et al.* 2000] spine bone density increased by 7.1% and femoral neck by 2.5% in 2 years, compared with baseline. In addition, there was some evidence that alendronate decreased morphologic vertebral fractures as measured by X-ray changes. As the comparator group in the zoledronic acid study, weekly alendronate increased bone density similarly to intravenous zoledronic acid [Orwoll *et al.* 2010]. Two years of weekly risedronate also has been shown to increase spine bone density by 6% compared with baseline and decrease bone turnover markers in men [Boonen *et al.* 2009]. In a small study in men with stroke [Sato *et al.* 2005], risedronate therapy was associated with a lower number of hip fractures. In the registration trial for zoledronic acid, the drug decreased the number of vertebral and hip fractures in postmenopausal women. The main trial in men was not placebo controlled; instead zoledronic acid was compared with oral alendronate [Orwoll *et al.* 2010]. Thus, from this trial no definitive fracture information can be obtained. Both bisphosphonates increased spine bone density by over 6% in 2 years. On the other hand, in a post-hip-fracture trial [Lyles *et al.* 2007], zoledronic acid, compared with placebo infusion, lowered the subsequent clinical fracture rate in men and women, although a separate analysis of the men has not been reported. In addition, mortality was decreased in those postfracture patients who received zoledronic acid. These studies are illustrative of the fact that most studies in men are too small to have fracture outcomes. Instead, fracture surrogates are used, with the assumption made that if a drug affects the surrogates similarly in men and women, then it is likely the medication will also have the same salutary impact on fracture risk. Given the number of women in the zoledronic acid registration trial (almost 8000) and the cost (many millions of dollars), any trial in men, with their lower overall fracture rate, would likely require many more subjects and millions of dollars in cost.

Bisphosphonates are generally well tolerated but have to be taken with water in a fasting patient first thing in the morning. Other medications, food, and other liquids must be postponed for at least half an hour. In addition, the patient must not lie down for half an hour after taking an oral bisphosphonate. Despite these precautions some patients have esophageal irritation or dyspepsia. In patients with esophageal motility disorders, gastroesophageal reflux not under control, or Barrett's esophagus, etc., oral bisphosphonates are contraindicated. For such patients, intravenous zoledronic acid is a reasonable alternative. All bisphosphonates are potentially nephrotoxic, although in osteoporosis studies with risedronate [Miller *et al.* 2005] and zoledronic acid [Boonen *et al.* 2008], there has been little evidence of such toxicity. Nonetheless, the package inserts of the various drugs limit the use of these drugs in

patients with decreased renal function.

Two potential side effects of bisphosphonates have been reported in both the medical and popular literature. Osteonecrosis of the jaw is an area of exposed bone found in the mouth, usually after a dental extraction, and some patients on bisphosphonates have experienced this. Reviews on the subject [Abrahamsen, 2010; Khosla *et al.* 2007] are recommended, but suffice it to say here that for the man at risk for fracture, the chance of fracturing if he does not take bisphosphonates far outweighs the chance of having osteonecrosis of the jaw, should he take the medication. The same can be said for some unusual subtrochanteric femoral fractures, mostly found in women on alendronate. Here again there are extensive reviews of the subject [Rizzoli *et al.* 2011; Shane *et al.* 2010], and while such fractures are of concern, there is good evidence [Vestergaard *et al.* 2011] that bisphosphonates prevent many more typical fractures than they cause atypical fractures. For both of these potential side effects, much more work is needed to determine whether there really is cause and effect and, if so, to determine whether patients at the greatest risk for the side effects can be identified.

There are no studies in men on the optimal length of bisphosphonate treatment. From studies in women [Black *et al.* 2006], it is likely that most men will need 5 years of bisphosphonate therapy before there is consideration of a 'drug holiday'. One approach, based on clinical experience rather than evidence, is to measure BMD by DXA after 5 years of bisphosphonate therapy. If there has been a statistically significant improvement in the BMD and the after-therapy DXA diagnosis is no longer osteoporosis, then a 1- to 2-year drug holiday makes clinical sense. If the response has not been vigorous or the DXA remains in the osteoporotic range, then continuation of therapy for another 2 years with a repeat DXA would be indicated. It is helpful to have the clinician ask the patient to describe exactly how he takes the oral bisphosphonate, in order to be sure that all of the instructions are being followed. Some [Ishijima *et al.* 2009], but not all [Antoniucci *et al.* 2009] studies suggest that 25-hydroxyvitamin D levels need to be optimized in order to have a strong BMD response to bisphosphonates. Adherence to bisphosphonates, because they generally do not make patients feel different, has been poor [Patrick *et al.* 2010]. There is only a little evidence in men [Hansen *et al.* 2008] that a repeat DXA at 2 years after starting therapy improves persistence with bisphosphonate therapy.

An alternative to bisphosphonate therapy is teriparatide, the first 34 amino acids of parathyroid hormone. This peptide is delivered as a subcutaneous injection once daily, and it is FDA approved for men for therapy for up to 2 years. While chronic oversecretion of parathyroid hormone as in hyperparathyroidism leads to bone loss, the intermittent bolus of the parathyroid hormone fragment has the opposite effect, resulting in a vigorous increase in BMD. In a study in men [Orwoll *et al.* 2003], bone density increased in the spine and hip (but not in the radius) in men treated with teriparatide. There were no differences in the incidence of clinical fracture between the teriparatide and placebo groups, but the study was too small to expect any differences. In a follow-up study [Kaufman *et al.* 2005] of some of the original participants, there was some evidence of decreased fracture risk on X-ray. Because teriparatide decreases fracture in women [Neer *et al.* 2001] and because the changes in surrogates for fracture (bone density and bone turnover markers) are similar in men and women on this drug, it is assumed that teriparatide will decrease the incidence of fractures in men. Side effects with teriparatide are different from those of bisphosphonates, with dizziness and leg cramps being the most common. A few patients have experienced transient hypercalcemia about 4–6 hours after injection with resolution at 24 hours. Only a few patients have had hypercalciuria after using this medication. Teriparatide has been usually reserved for those men with the highest risk for fracture because it is expensive and must be taken as a subcutaneous injection every day. In addition, because of concern about osteosarcoma in a strain of laboratory rats given teriparatide, the drug can only be used for 2 years. However, no increase in human osteosarcoma cases in patients on teriparatide has been reported. There is evidence [Kurland *et al.* 2004] that following the 2 years of teriparatide therapy with a bisphosphonate preserves and may increase the BMD accrual.

Denosumab is a potent antiresorptive medication, administered as a subcutaneous injection every 6 months. In the US, it is only FDA approved for women with postmenopausal osteoporosis. However, in Europe, it is approved for men on androgen deprivation therapy for prostate cancer, based on a large randomized, controlled trial [Smith *et al.* 2009]. In the trial, almost 1500 men with mildly low BMD were given either denosumab or placebo for 2 years. Those who

received denosumab had significant increases in BMD in the spine, hip, and interestingly, the distal one third radius. In addition, those men who received denosumab had fewer new vertebral fractures on X-ray. Thus, while this drug is not FDA approved for men, it holds great potential. The impact of the increase in radius BMD is not known, but this is the first modern agent that appears to do this. More studies will be needed to determine the long-term effectiveness and safety of denosumab and its place in the treatment of male osteoporosis. Another osteoporosis medication available in Europe but not the United States is strontium ranelate. In an open-label prospective study [Ringe *et al.* 2010] daily strontium ranelate increased bone density more than weekly alendronate. Other drugs that have been used in women are calcitonin and calcitriol, but there is little information on their usefulness in men, and the drugs are not approved by the FDA for osteoporosis in men.

Finally, testosterone has been used to increase BMD in younger men with specific causes of hypogonadism [Behre *et al.* 1997]. In a randomized, placebo-controlled trial in older men with mildly low serum testosterone levels, injections of testosterone increased BMD [Amory *et al.* 2004]. Testosterone might affect fracture risk by improving muscle mass and function, leading to fewer falls and/or by conversion to estradiol and affecting bone turnover. However, there are no studies of testosterone therapy large enough to demonstrate that testosterone reduces fracture risk, nor are the potential harms of chronic testosterone therapy adequately established.

Conclusions

Osteoporosis is still considered a disease of older white women, but it is clear that both sexes and all ethnic groups have some risk for fracture. Men do poorly after a hip fracture [Bass *et al.* 2007] with about one third of men aged 75–84 dying within a year of the fracture and many of the others never regaining independence. Thus, even though women fracture more often, those men who experience hip fracture are vulnerable. Primary prevention entails finding those men at the highest risk and getting them to evaluation and treatment. The US Preventive Services Task Force [US Preventive Services Task Force, 2011] has stated that the benefits and harms of general osteoporosis screening in men have not been adequately defined. Thus, identifying those men clearly at higher fracture risk should be the goal. Finding men with known fracture risks, such as those on androgen deprivation therapy, or on oral glucocorticoid therapy should lead to evaluation, treatment, and fewer fractures. Secondary prevention is important as well. If a man has survived one fracture, he is at high risk for another. It is not too late to evaluate and treat. One of the most important lessons from the zoledronic acid post-hip-fracture study [Lyles *et al.* 2007] was that treatment not only decreased the incidence of subsequent fracture, it also decreased mortality. In conclusion, the clinician needs to be vigilant for men who are likely to fracture and get them to treatment.

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