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REVIEW ARTICLE

Osteoporosis in men: a review

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Osteoporosis and consequent fracture are not limited to postmenopausal women. There is increasing attention being paid to osteoporosis in older men. Men suffer osteoporotic fractures about 10 years later in life than women, but life expectancy is increasing faster in men than women. Thus, men are living long enough to fracture, and when they do the consequences are greater than in women, with men having about twice the 1-year fatality rate after hip fracture, compared to women. Men at high risk for fracture include those men who have already had a fragility fracture, men on oral glucocorticoids or those men being treated for prostate cancer with androgen deprivation therapy. Beyond these high risk men, there are many other risk factors and secondary causes of osteoporosis in men. Evaluation includes careful history and physical examination to reveal potential secondary causes, including many medications, a short list of laboratory tests, and bone mineral density testing by dual energy X-ray absorptiometry (DXA) of spine and hip. Recently, international organizations have advocated a single normative database for interpreting DXA testing in men and women. The consequences of this change need to be determined. There are several choices of therapy for osteoporosis in men, with most fracture reduction estimation based on studies in women.

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INTRODUCTION

Despite some recent increased attention in men, osteoporosis is still considered a disorder of postmenopausal women. While some organizations have recommended screening older men for osteoporosis,[1–2] the United States Preventive Services Task Force concluded that there was insufficient information to justify screening older men with dual energy X-ray absorptiometry (DXA) at this time.[3] While there is no current evidence that screening men for osteoporosis leads to fewer fractures, recent therapeutic studies showing fracture risk reduction provide a rationale for reconsideration of screening recommendations (see below). There is continuing evidence that men at clear risk for osteoporotic fracture, such as those who have already suffered a fragility fracture, those who are on oral glucocorticoids, and those on androgen deprivation therapy for prostate cancer are not evaluated and/or treated for osteoporosis. Specifically, in studies of secondary fracture prevention, men are less likely than women to have evaluation or treatment of osteoporosis.[4] Men at risk for glucocorticoid-induced osteoporosis are also less likely to be evaluated and/or treated.[5] Most men on androgen deprivation therapy for prostate cancer have little attention paid to their osteoporosis risk, despite the fact that the fracture rate may be as high as 20% in the first 5 years of androgen deprivation therapy.[6–7] There is a study comparing fracture risk in Caucasian women in the United States compared to Chinese women in the United States,[8] but no similar study of men of these ethnic groups. In the United States, direct pharmaceutical advertising to patients is legal, and there are many advertisements for medications for erectile dysfunction or hypogonadism. In contrast, all osteoporosis medication advertisements are directed to postmenopausal women. Thus, both patients and clinicians have less concern about osteoporosis in men, compared to women, even though the mortality after hip fracture is twice as high in men as it is in women.[9–10] Hence, even in 2014, there is a significant disparity in care of men versus women, but in this case, men are those less likely to be evaluated or treated for osteoporosis, despite worse outcomes after fracture.

EPIDEMIOLOGY OF OSTEOPOROSIS IN MEN

Early in adult life there are more fractures in men than women, but the great majority of these fractures are traumatic in origin and not related to osteoporosis, although

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there is some evidence[11] that even traumatic fracture history may be a risk for later osteoporotic (low trauma) fracture. With aging, the incidence of osteoporotic fracture increases in both men and women, with men having hip fractures about 10 years later in life than women.[12] The lifetime risk of osteoporotic fracture in men has been estimated to be between 10% and 25%, depending on the population studied.[13–14] In the United States, as well as much of the rest of the world, life expectancy is increasing for men more than for women,[15] which suggests that men will be living long enough to fracture. In some populations, women are having fewer hip fractures,[16] but the change in hip fracture incidence in men is much more modest, with men continuing to have about half as many fractures as women, at any given age. The prevalence of osteoporosis by the usual bone mineral density (BMD) testing of spine and hip by DXA, will be changing, based on new standards for the measurement (see below).

CLASSIFICATION AND PATHOPHYSIOLOGY OF OSTEOPOROSIS IN MEN

A classification method for osteoporosis[17] devised in 1986 is still helpful in 2014 (Table 1). Osteoporosis has been divided into primary and secondary causes, with primary subdivided by age. The earlier age primary osteoporosis (Table 1) is called postmenopausal osteoporosis because mostly women develop this type of osteoporosis soon after menopause. Trabecular more than cortical bone is affected by Type 1 osteoporosis, as manifested by vertebral and distal radius fractures. Men may have Type 1 primary osteoporosis, presenting in middle age with vertebral fractures or low BMD by DXA. Genetic causes of Type 1 osteoporosis in men may involve genes for IGF-I[18] or estrogen metabolism;[19] and secondary osteoporosis may also be manifest at this age (see below). Type 2 primary osteoporosis is found in men and women over age 70. Both trabecular and cortical bone are affected, leading to fractures of the proximal femur, in addition to vertebrae and radii. It is important to note differences in aging-associated changes in bone between men and women. Using high-resolution quantitative computed tomography of the distal forearm, Khosla *et al.*[20] demonstrated that, as they age, women lose trabeculae and have greater spacing between trabeculae. Men, on the other hand, only have thinning of trabeculae as they age. Studies using quantitative computed tomography with finite element analysis[21] have shown that women lose more cortical bone in vertebrae than men. Men have larger bones at peak bone mass; and with aging, more periosteal bone is deposited in long bones, compared to women.[22] These differences may explain why men fracture later in life than women.

It has been generally accepted that sex hormones play an important role in primary osteoporosis. Indeed, the abrupt loss of estrogen at the menopause is considered the major reason for Type 1 primary osteoporosis in women. Men do not have a dramatic loss of androgens with aging, but most reports have shown that serum testosterone levels decline with aging.[23] Sex hormone binding globulin increases with aging, lowering bioavailable or free testosterone even further. However, in a recent report[24] from Australia, successfully aging men did not show a decline in serum testosterone levels until the eighth or ninth decade. The authors postulated that chronic conditions found commonly in older men lead to lower serum testosterone levels, not aging *per se*. It will be necessary to study this further in many larger populations. Nonetheless, it has been difficult to demonstrate that the decrease in testosterone found empirically with aging in many men is the proximate cause of aging-associated bone loss. Studies[25] have shown that serum estradiol levels are more robustly associated with BMD in aging men. In this context, testosterone acts as a pro-hormone because the major source of circulating estradiol in men is aromatization of testosterone. There are androgen receptors on bone cells,[26] and androgen deficiency-induced loss of muscle mass likely leads to decreased lower body strength and increased propensity to falling and thus more fractures.

Table 1. Classification of osteoporosis in men

Primary Osteoporosis		Secondary Osteoporosis	
Type 1	Type 2	Disorders	Medications
Age < 70	Age > 70	Hypogonadism	Oral glucocorticoids
Vertebral fractures	Vertebral and hip fractures	Hypercalciuria	Androgen deprivation therapy
Specific genetic syndromes	Relation with muscle, sarcopenia	Hyperparathyroidism	Proton pump inhibitors
Cryptic secondary osteoporosis	Known risk factors	Hyperthyroidism	Selective serotonin reuptake inhibitors
		Cushing's syndrome	Dopamine antagonists
		Celiac disease	Thiazolidinediones
		Inflammatory bowel disease	Enyzme-inducing anti-epileptics
		Rheumatoid arthritis	Chronic opiate analgesics
		Chronic obstructive pulmonary disease	Cancer chemotherapy (cyclophosphamide)
		Alcohol abuse	
		Chronic kidney disease	
		Bariatric surgery	

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Androgens may play a role in the sarcopenia associated with aging. In a recent study,[27] older men with sarcopenia (defined by relative appendicular skeletal muscle mass) were more likely to have osteoporosis by DXA than men with normal relative appendicular skeletal muscle mass. As interactions between muscle and bone are investigated, new understanding of osteoporosis pathophysiology and potentially new therapeutic approaches may be forthcoming.

Secondary osteoporosis is common in both men and women and is the reason that patients need a thorough evaluation consisting of medical history, physical examination and laboratory testing. In some[28] but not all[29] studies, secondary causes of osteoporosis[30] are more common in men than women. Two causes of secondary osteoporosis that relate to medical therapy are of particular concern because of their heightened fracture risk and prevalence. Glucocorticoid-induced osteoporosis is the most common iatrogenic cause of secondary osteoporosis and is especially important because increased fracture risk can be demonstrated as early as 3 months after starting oral glucocorticoid therapy.[31] Men are less likely than women to have attention paid to the increased fracture risk associated with glucocorticoid therapy.[5,32] The American College of Rheumatology has published guidelines[33] for management of glucocorticoid-induced osteoporosis, and recommendations for men are included. The most important aspect of glucocorticoid-induced osteoporosis is the realization that the patient is at risk soon after starting oral glucocorticoids. Also deserving increased attention to bone are those men undergoing androgen deprivation therapy (ADT) for prostate cancer. Such men may have a generally good prognosis,[34] but fracture risk[6] is elevated (as high as 20% fracture risk in 5 years) because of their very low serum levels of both testosterone and estradiol.[35] The severity of the bone loss and dramatically increased fracture risk are underappreciated, and only a minority of men are evaluated and/or treated for ADT-induced osteoporosis. There are many other secondary causes of osteoporosis in men, and a full listing is beyond the scope of this review. Important causes include hypercalciuria, hyperparathyroidism, inflammatory bowel disease, bariatric surgery and causes of hypogonadism in addition to ADT. Reviews of secondary causes of osteoporosis[30] and laboratory evaluation for secondary osteoporosis[36] are available. Medications that are associated with increased osteoporosis risk and examples of how laboratory testing can identify causes of secondary osteoporosis are given below.

IDENTIFYING MEN AT THE HIGHEST RISK FOR FRACTURE

In the United States and many other parts of the world, it is well established that people who suffer fragility fractures are unlikely to have evaluation and/or treatment for underlying osteoporosis, but men are actually less likely to get evaluated and/or treated than women.[4] After one osteoporotic fracture, men and women have about the same, highly increased risk of another fracture.[37] Thus, programs[38] aimed at identifying patients who have fractured are important means of finding men who need osteoporosis management.

For older men without specific causes of osteoporosis, many of the risk factors found in women also are important in older men. The risk factors used in the FRAX calculator[39] or the Garvan nomogram[40] are used in men and women: age, weight or body mass index, current smoking, excess alcohol intake (>3 units daily), oral glucocorticoid use, rheumatoid arthritis, previous fracture, parental history of fracture and recent fall history (Table 2). Many experts would add low serum levels of 25-hydroxyvitamin D,[41] general frailty, diabetes mellitus, mobility disorders (e.g., Parkinson's disease, multiple sclerosis, cerebrovascular accidents, spinal cord injury) and many medications. In addition to glucocorticoids and androgen deprivation therapy, the following drugs may be associated with increased fracture risk: proton pump inhibitors, anti-depressants, dopamine antagonists, thiazolidinediones, immunosuppressives (e.g., cyclosporine), enzyme-inducing antiseizure medications (e.g., phenytoin), opiate analgesics and some cancer chemotherapy (e.g., cyclophosphamide). Hence, the evaluation of men at risk for osteoporosis includes a careful history, including medication use.

EVALUATION OF THE MAN AT RISK FOR OSTEOPOROSIS

As mentioned above, there is controversy over whether all older men should be screened for osteoporosis, but there is little disagreement that in 2014 the 'gold standard' test for defining osteoporosis is DXA of spine and hip. This method is widely available, although bone densitometers are not evenly distributed around the world. While less expensive

Table 2. Comparison of FRAX and Garvan fracture risk calculators

Risk factor	FRAX	Garvan
Age	Yes	Yes
Gender	Yes	Yes
Height	Yes	No
Weight	Yes	No
Previous fracture	Yes	Since age 50
Parental hip fracture	Yes	No
Current smoking	Yes	No
Glucocorticoid use	Yes	No
Rheumatoid arthritis	Yes	No
Secondary osteoporosis	Yes	No
EtOH> 3 units daily	Yes	No
Femoral neck BMD	Yes	Yes
Falls in last 12 months	No	Yes
URL	http://Shef.ac.uk/FRAX/	http://Fractureriskcalculator.com

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tests of bone mass, such as quantitative heel ultrasound predict fracture well,[42] they cannot be used to follow patients on therapy and no therapeutic trials have been based on osteoporosis defined by heel ultrasound.

Standard evaluation of osteoporosis risk includes measurement of BMD by DXA of spine and hip. There has been a long standing controversy as to the normative database to use for men. DXA machines in the United States and most other parts of the world use a male normative database for calculating the *T*-score for men. The *T*-score is the number of standard deviations from the normal young mean bone density. Men have larger bones than women, which makes the bone density look greater on DXA, and the standard deviation of DXA is different from that of women. Studies of osteoporosis treatment in men have all included men diagnosed with osteoporosis based on the male normative database.[43–44] In some studies, men fractured at a higher absolute BMD than women,[45] but other studies suggest that men and women fracture at the same absolute BMD.[46] The FRAX calculation, which predicts 10-year fracture risk uses the absolute femoral neck bone density for men and women, which means that the same standard is used for both sexes. The International Society for Bone Densitometry and the International Osteoporosis Foundation now support the use of the white female database for the diagnosis of osteoporosis in men and women of various ethnic groups.[47–48] Using the female database means that fewer men will have osteoporosis, which is not congruent with the epidemiology of osteoporosis,[49] but if DXA and the FRAX are both used, a large proportion of older men will be candidates for osteoporosis treatment.[50] The rationale for using the white female database for all has been reported.[48] While it is encouraging that the combined use of both DXA and FRAX will identify many men at risk for fracture, there are no studies demonstrating that a man without osteoporosis by DXA but with a high fracture risk by FRAX will respond to treatment.

The International Society for Bone Densitometry recommends that if the spine or hip BMD cannot be obtained or cannot be interpreted because of artifacts, forearm BMD should be measured by DXA (usually distal 1/3 radius). Because of the change from a male to a female normative database for DXA interpretation, one aspect of DXA evaluation in men on ADT requires re-examination. In studies from several institutions, including our own,[51–53] about 15% of men on ADT have osteoporosis only in the forearm (usually the distal 1/3 radius) with osteopenia or normal bone density in spine and hip. In many older men, arthritic changes in the spine (with osteophytes and facet sclerosis) or hip[54] may spuriously increase the apparent bone density. However, a new study[55] shows that densitometers may over-read osteoporosis in the forearm based on a male normative database. The difference between the male and female databases is particularly dramatic here, leading to apparently very low *T*-scores in the radius or forearm, compared to spine or hip. Thus, it will be important to re-analyze forearm BMD in populations of men on ADT, using the much larger female normative database.

As stated above, switching to a white female normative database for interpretation of DXA will result in fewer men having osteoporosis, but calculating FRAX in the same men will identify a large proportion of older men eligible for osteoporosis treatment.[50] It is likely that the men with high fracture risk by FRAX will respond to therapy, but an early study of some older women with risk factors for osteoporosis but without DXA-diagnosed osteoporosis did not have fewer fractures when treated with risedronate, whereas those with DXA-diagnosed osteoporosis did respond.[56] Even in women, the relationship between FRAX risk and response to therapy is quite limited.[57]

Nonetheless, International Society for Bone Densitometry and International Osteoporosis Foundation now advocate one normative database, but clearly a country-specific database calibrated to local fracture data in a given country would likely be superior for identifying people at risk for fracture.[58] For men, using the white female normative database will result in fewer men having a *T*-score <-2.5. Thus, the FRAX score should also be calculated, and many older men will be eligible for treatment by the criteria used in the United States: a 10-year hip fracture risk of $\geq$3% or a 10-year any major osteoporotic fracture risk of $\geq$20%.[50] In the UK, a case finding approach is used, combining risk factors from the medical history and physical examination with calculation of FRAX without BMD measurement.[59] Men at intermediate risk by this method then undergo DXA and FRAX is re-calculated. Men at low risk are reassured, and men at high-risk commence treatment. In the last mentioned group, DXA may be used to follow treatment response. A similar case-finding method is used by the United States Department of Veterans Affairs,[60] although DXA is used in the initial clinical evaluation. In addition to history and physical examination, which will provide information on risk factors for osteoporosis and potential secondary causes, there is a modest amount of laboratory information that is needed for both diagnosis and to assure safety of therapy. There is no specific blood or urine test for osteoporosis. Nonetheless, a few blood tests should be done routinely, including serum chemistries such as calcium, albumin (to calculate the corrected serum calcium), phosphate, alkaline phosphatase, 25-hydroxyvitamin D and a measure of renal function such as serum creatinine or estimated glomerular filtration rate. The tests may signal the diagnosis of hyperparathyroidism, hypophosphatasia, certain types of osteomalacia and other disorders as well as demonstrating that the patient has renal function good

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enough for certain osteoporosis medications. A 24-h urine calcium is also recommended because it may identify hypercalciuria or hypocalciuria (which may signal malabsorption or vitamin D deficiency). Multiple myeloma can cause spine changes on X-ray that look like osteoporotic vertebral fractures. Screening for this can start with a complete blood count because about three-fourths of such patients have anemia, but many patients may need serum and/or urinary protein electrophoresis or measurement of serum light chains.[36] There is controversy about measurement of serum testosterone levels. If the patient is not a candidate for testosterone replacement (e.g., a man on ADT), knowing the serum testosterone level will not affect the choice of therapy. However, in an older man without prostate cancer, there is at least a small amount of evidence that testosterone will increase bone density,[61] but there is definite concern about potential side effects.[62] In middle-aged men, hypogonadism is an important cause of secondary osteoporosis. For men at risk (based on history and physical examination) for other secondary causes of osteoporosis, there may be specific laboratory tests that will help establish or confirm the diagnosis.[36]

Finally, it is clear that having a previous fracture is an important risk for another fracture.[37] Many vertebral fractures are not diagnosed; thus, images of the spine may reveal previously unrecognized spine fractures. This may be done by conventional X-rays of the thoracic and lumbar spine, but many bone densitometers are capable of vertebral fracture assessment, a method of imaging the lateral spine with considerably lower radiation dose than conventional X-ray. Finding an existing vertebral fracture increases future fracture risk markedly,[63] and some experts believe that a spine image should be part of routine osteoporosis evaluation.

CURRENT TREATMENT OF OSTEOPOROSIS IN MEN

In the United States, FDA-approved osteoporosis treatment for men includes the bisphosphonates (alendronate, risedronate and zoledronic acid), the anti-resorptive antibody denosumab and the anabolic agent teriparatide. Ibandronate is also available, and in some countries strontium ranelate is approved for osteoporosis in men. Alendronate,[43] risedronate,[64] ibandronate[65] and zoledronic acid[44] all increase BMD in men and have effects on bone turnover markers similar to the effects in women. From the similarity in changes in these surrogates for fracture, it is assumed that the clinical fracture reduction observed in clinical trials of these drugs in women will apply to men as well. In choosing therapy, there is little guidance based on improvements in fracture risk. While there are some head-to-head trials of various osteoporosis medications in women, these trials also use the same fracture surrogates as a means to compare the various therapies. In one head-to-head trial[66] of teriparatide versus alendronate in glucocorticoid-induced osteoporosis in men and women, teriparatide treatment resulted in fewer morphological and clinical vertebral fractures than did alendronate treatment. Zoledronic acid increased bone density to a greater extent in men on oral glucocorticoids than did risedronate.[67] Zoledronic acid and alendronate treatment led to equivalent increases in BMD in older men.[44] Thus, there is little information the clinician can use to determine which osteoporosis treatment is likely to result in fewer fractures in men. The clinician must therefore choose therapy based on studies in women, tailoring it for the specific male patient. For example, the man with osteoporosis and an esophageal motility disorder such as achalasia should be treated with an intravenous bisphosphonate such as zoledronic acid or a subcutaneous injection such as denosumab or teriparatide. As in women, adherence to treatment is a challenge in men because osteoporosis is a silent disorder without symptoms until there is a fracture.[68] Medications generally do not make patients feel different, which may be one reason for the poor adherence to therapy. Men with osteoporosis need longitudinal care for this chronic condition.

As previously stated, while there are good studies[43–44,64–67] that demonstrate that osteoporotic men respond to standard treatment with changes in BMD and bone turnover markers to a degree similar to that in women, there are few studies that demonstrate decreased fracture risk. However, in two recent studies,[69–70] agents shown to decrease clinical fractures in women were found to decrease morphological vertebral fractures on X-ray in men. Specifically, as reported by Boonen *et al*.[69] the incidence of new morphological vertebral fracture was the primary end point of a 2-year study comparing zoledronic acid with placebo in about 1 200 men. Zoledronic acid-treated men had fewer morphological vertebral fractures at the end of the 2-year study, compared to the men randomized to placebo infusion. Smith *et al.*[70] randomized over 1 400 men on androgen deprivation therapy for prostate cancer to either denosumab or placebo. Denosumab is a monoclonal antibody to RANK Ligand and is a potent anti-resorptive agent. At the end of 2 years, men receiving denosumab subcutaneously every 6 months had fewer morphological vertebral fractures than men receiving a placebo injection every 6 months. While neither study was large enough to demonstrate fewer clinical fractures in the active drug group, the changes in bone density and bone turnover markers and the reduction in morphological vertebral fractures provide further evidence that drugs that reduce clinical fractures in women are likely to also do so in men. In the ADT study,[70] men were eligible to participate if the spine or hip *T*-score was −1.0 or worse, based on a male normative database.

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Table 3. Some advantages and disadvantages of osteoporosis medications

Drug	Potential advantages	Potential disadvantages
Oral bisphosphonates	Inexpensive	Adherence and compliance
	Long experience	Side effects: GERD, ONJ, AFF
Intravenous bisphosphonates	Long intervals between infusions	More expensive
	Potential improved adherence	Side effects: ONJ, AFF
Denosumab	Convenient 6 month dosing	More expensive
	Appears to increase BMD up to 6 years	Side effects: ONJ, AFF
Teriparatide	Anabolic	Expensive
	No ONJ or AFF	Daily subcutaneous injection
Strontium ranelate	Improves BMD in men	Less long-term experience
	May have some anabolic effect	New concern about cardiovascular safety

Abbreviations: AFF, atypical femoral fracture; BMD, bone mineral density; ONJ, osteonecrosis of the jaw.

Thus, some men in the study would actually be in the normal range, based on a female normative database. In the United States, denosumab is now approved for men with osteoporosis, not necessarily due to ADT.[71]

Strontium ranelate is approved for osteoporosis treatment in some countries, not including the United States. In a randomized controlled trial,[72] strontium ranelate increased bone mineral density in men to an extent similar to that found in women, who also have fewer fractures if treated with this drug. However, strontium ranelate may have some adverse cardiovascular effects, and the European Medicines Agency states that the drug is contraindicated in patients with the following disorders: ischemic heart disease, peripheral vascular disease, cerebrovascular disease or uncontrolled hypertension. In a recent study from Denmark,[73] almost 30% of men treated with strontium ranelate had one or more of these conditions. This is not surprising because osteoporosis and various vascular diseases have increased prevalence as men age. Thus, it is not clear whether strontium ranelate will be an important addition to the list of potential osteoporosis treatments for older men.

Teriparatide is the only anabolic agent for osteoporosis available in the United States. It is a protein, the first 34 amino acids of parathyroid hormone. Unlike the chronic parathyroid hormone excess of hyperparathyroidism, which leads to bone loss, teriparatide is given as a once daily subcutaneous bolus injection. This intermittent administration activates osteoblasts[74] and leads to increased bone formation, and fewer fractures in women.[75] The changes in fracture surrogates (DXA and bone turnover markers) are similar in men and women.[74–76] In a follow-up observational study,[77] men who had received prior teriparatide therapy in a randomized controlled trial had fewer vertebral fractures. Teriparatide therapy is limited to 2 years of therapy and must be administered by a daily subcutaneous injection. As mentioned above, teriparatide treatment led to fewer vertebral fractures in men and women with glucocorticoid-induced osteoporosis,[66] compared to those treated with alendronate. Two recent reviews[78–79] provide further information on choosing osteoporosis treatment for men. Some potential advantages and disadvantages of the different osteoporosis medications are shown in Table 3.

CONCLUSIONS

While there has been some progress in the recognition of osteoporosis in men—particularly the fact that almost one-third of hip fractures occur in men and that men are twice as likely to die within a year after hip fracture—much more work needs to be done. The realization of the risk of fracture and fatality has led to some increases in evaluation and treatment in men, but it is clear that many men have no attention paid to their fracture risk, despite obvious risk factors. Evaluation by history, physical examination, FRAX calculation and BMD by DXA will help in diagnosis and treatment. The serious consequences of fracture in high risk men need to be appreciated by both patients and clinicians.

Conflict of Interest

The authors declare no conflict of interest.

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