Curr Treat Options in Rheum (2018) 4:355–366
DOI 10.1007/s40674-018-0107-1

Osteoporosis (A Lau, Section Editor)

Management of Male Osteoporosis: an Update

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Published online: 2 October 2018

This article is part of the Topical Collection on *Osteoporosis*

Keywords Male osteoporosis · Fracture · Pathophysiology · Testosterone · Secondary osteoporosis · Osteoporosis therapy

Abstract

Purpose of review Osteoporosis is a major health concern for men in our aging population. The incidence of osteoporotic fractures in men is expected to rise as life expectancy increases. When adjusted for age, one half of all hip fractures occur in men and of all osteoporotic fractures; hip fractures account for the highest morbidity and mortality. Several factors contribute to bone loss in men. Sex steroid deficiency plays an important role in male age-related bone loss. Careful evaluation for secondary causes of bone loss (including lifestyle factors, comorbidities, and risk medications) is warranted.
Recent findings Osteoporosis guidelines recommend bone mineral density (BMD) testing in men over age 70, earlier in men with other risk factors. As in women, adequate calcium and vitamin D intake, regular weight-bearing exercise, smoking cessation, limiting excessive alcohol, and fall prevention strategies are recommended. Available clinical data support efficacy of bisphosphonates (alendronate, risedronate, zoledronic acid), denosumab, and anabolic therapy (teriparatide) in men with osteoporosis as well as in women. Abaloparatide, a parathyroid hormone-related peptide analog with demonstrated anti-fracture efficacy in women, awaits the conclusion of clinical trials in men. Romosozumab shows similar BMD and bone turnover marker effects in osteoporotic men compared to women; evaluation of safety concerns is ongoing.
Summary Recent insights into osteoporosis pathophysiology and bone cell biology provide promising direction for effective therapeutic strategies for the management of male osteoporosis.

Introduction

Although osteoporosis is most commonly identified in women, it remains a significant health burden for men. Osteoporotic fractures in the elderly are responsible for deterioration in quality of life as well as increasing healthcare costs with our aging population [1]. Approximately 50% of hip fractures in those over age 50 years are in men and the mortality after hip fractures in men approaches 40%, which is more than double that of women [2–6]. Notably, the exponential rise in the incidence of hip fractures occurs about one decade after that in women.

Increases in longevity predicts an increased incidence of hip fractures, especially in Western societies with aging populations [7]. In addition, there are multiple secondary causes of osteoporosis in men related to comorbidities, lifestyle, and medications (Table 1). Despite these compelling arguments, there remains a low awareness of male osteoporosis and consequently a large care gap.

Diagnosis and screening, risk factors, and FRAX

Estimates of the lifetime risk of fragility fracture in men over the age of 50 range from 13% to 30% [5, 9]. Similar to women, in men, the most common osteoporotic fractures are at hip, vertebra, and humerus; forearm fractures occur less frequently in men than in women. A densitometric diagnosis of male osteoporosis will be less common than in females due to the higher peak bone mass in men and the lack of a postmenopausal acute decline in BMD. In addition, *T* scores by convention (International Osteoporosis Foundation [10], International Society for Clinical Densitometry [11]) are compared to young Caucasian female reference databases for both men and women. This convention is based on more recent data suggesting that both men and women fracture at similar absolute BMD [12]. When BMD is measured by DXA, the size artifact of larger bones makes areal BMD appear greater in men, who have larger bones, than women, who have smaller bones. For both men and women, the volumetric BMD at peak bone mass is similar. Postmenopausal bone loss in women related to abrupt lowering of estrogen results in trabecular perforation and cortical porosity weakening both trabecular and cortical bone. In men, less harmful trabecular thinning may occur and cortical porosity-induced decreases in bone strength is partially offset by periosteal bone apposition, leading to greater bone size in men with resultant greater bone strength [13, 14]. There is evidence that estradiol produced from the aromatization of testosterone in men provides the majority of antiresorptive benefit in elderly men rather than direct effects of testosterone on bone. Testosterone may modulate periosteal bone growth with consequent effects on bone size. Although testosterone levels decline gradually with age, the skeletal impact of decreasing sex steroid levels in men is much less than that in women. Nonetheless, some men will achieve estradiol levels sufficiently low to predispose to high bone turnover and bone loss, as in women, with consequent increased fracture risk [15, 16]. IGF-1 likely impacts on long bone growth and periosteal bone apposition in men and a positive correlation of IGF-1 levels and BMD has been observed in adult men [17].

A recent meta-analysis of secondary causes of osteoporosis in men suggests these may be more frequent in men than in women with up to 50% of men having secondary osteoporosis [18–20]. The major secondary causes of osteoporosis in men include glucocorticoid-induced

Table 1. Factors contribute to bone loss in men. Adapted from [8]s

General	Age > 70 years
	Low BMI < 19
	History of prior fracture at age of > 50 years
	History of recurrent falls
Lifestyle	Sedentary lifestyle or lack of exercise
	Current smoking
	Excess alcohol intake > 3 servings per day
Dietary	Low calcium intake
	Vitamin D deficiency
Diseases	Hypogonadism
	Chronic liver or kidney disease
	Stroke
	Diabetes (Type 1 and 2)
	Hyperparathyroidism
	Hyperthyroidism
	Cushing's disease
	Chronic obstructive pulmonary disease (COPD)
	Hypercalciuria
	Rheumatoid arthritis
	Gastrointestinal disorders (e.g., Celiac disease, inflammatory bowel diseases, liver disease)
	Hematological disorders (e.g. Multiple myeloma or other monoclonal gammopathies)
	HIV
	Organ transplantation
Medications	Chronic corticosteroid use
	GnRH agonists
	Androgen deprivation therapy
	Anticonvulsants

osteoporosis, alcohol abuse, cigarette smoking, hypogonadism (including androgen deprivation therapy for prostate cancer), and type II diabetes (Table 1). As in women, there are significant genetic factors in men influencing peak bone mass and declines in bone strength with age [21]. Most of the genetic predisposition to osteoporosis and fractures remains unclear at this time.

Although clinical risk factors may predict fracture risk and to a lesser degree BMD in men, most often, elderly men are not evaluated for osteoporosis, even after a fracture has occurred. There are numerous guidelines proposing that both primary identification of fracture risk (BMD, clinical risk factors) and secondary diagnosis of osteoporosis (subsequent to fragility fracture) is appropriate in older males. The

prospective osteoporosis MrOS cohort of over 5000 men suggested hip BMD was a stronger predictor of hip fracture in men than in women. Finite element analysis of hip strength is an even stronger predictor of hip fracture [22]. Based on the increased fracture incidence with age, clinical practice guidelines such as from the Endocrine Society 2012 suggest all men over the age of 70 should have BMD testing and risk assessment. In addition, men between age 50 and 70 with additional risk factors may also warrant BMD testing with risk assessment [23]. Men with progressive kyphosis especially when associated with significant height loss (greater than 6 cm) should have lateral spine imaging to detect atraumatic morphometric vertebral fractures which on their own would be diagnostic of osteoporosis regardless of BMD [24].

It is important in men to complete the evaluation of osteoporosis with a screen for secondary causes. This should include CBC, calcium, creatinine/eGFR, TSH, 25 hydroxy-vitamin D, ALP, and serum protein electrophoresis. In selected individuals, it may be reasonable to measure anti-TTG (celiac disease) as well as urinary calcium (hypercalciuria) and PTH. In men symptomatic of hypogonadism, a measurement of morning bioavailable testosterone may influence the selection of therapy. Although bone turnover markers could be measured, assay and biologic variability limit their usefulness in men as in women. Bone turnover markers are not useful in diagnosing osteoporosis and do not aid greatly in the selection of osteoporosis therapies [25, 26].

Treatment

The treatment of male osteoporosis varies considerably between countries; due to care gaps in fracture risk assessment and osteoporosis awareness in men, treatment is much less common in men than in women. Nevertheless, treatment guidelines from the National Osteoporosis Foundation [27] and the Endocrine Society [23] recommend the cost-effective treatment of men with osteoporosis as defined by a hip or a spine fracture, a BMD *T* score at spine or hip of less than or equal to – 2.5, or patients on greater than 3 months glucocorticoid at a prednisone equivalent dose of 7.5 mg per day. Published guidelines for men on androgen deprivation therapy or long-term glucocorticoid therapy suggest intervention at *T* scores somewhat higher such as – 1.5 or less [28•, 29].

Because there are fewer epidemiologic studies of osteoporosis in men as compared to women, the FRAX tool to estimate 10-year osteoporotic fracture and hip fracture risk is less well validated for males. Nonetheless, FRAX (or other equivalent tools) can be used to integrate clinical risk factors with femoral neck BMD to determine if an individual patient meets a treatment threshold. In many countries, a treatment threshold for major osteoporotic fracture is greater than 20% and for hip fracture is greater than 3% for both men and women. In other jurisdictions, there is a variable FRAX treatment threshold to accommodate treating younger patients with lower 10-year fracture risk than in older patients. There is widespread agreement that men with a prior fragility fracture require osteoporosis pharmacotherapy [27, 30, 31].

Lifestyle measures

The management of male osteoporosis, as in women, starts with diet and lifestyle recommendations. Limiting alcohol intake to less than 3 units per day, discontinuing smoking, and initiating regular weight-bearing exercise are recommendations in most treatment guidelines. One thousand- to 1200-mg elemental calcium could be achieved optimally from diet or from combination diet and supplement. Vitamin D supplements of 800 to 2000 IU daily may be required to achieve recommended 25 hydroxy-vitamin D serum levels of 20 to 50 ng/mL (50 to 125 nmol per liter). The Endocrine Society recommends supplement Vitamin D to achieve serum 25 hydroxy-vitamin D levels of 30 ng/mL [23].

Pharmacological therapy

Pharmacologic management of male osteoporosis is less well validated than in women. This is due to the regulatory requirement only to show parallel changes in BMD and bone turnover markers to that seen in women without the need to demonstrate anti-fracture efficacy. Consequently, the trials in men are usually much smaller, with only some showing significant reductions in fragility fractures. As with women, we have options of antiresorptive or bone anabolic therapy for the management of male osteoporosis (Table 2). Approved therapies include the oral bisphosphonates alendronate and risedronate, the intravenous bisphosphonate zoledronic acid, the RANK ligand monoclonal antibody denosumab, and the bone anabolic teriparatide.

Bisphosphonates

Oral bisphosphonates (alendronate and risedronate) and intravenous zoledronic acid are effective at increasing BMD and lowering markers of bone turnover in men as in women [32, 34, 45–47]. These bisphosphonate studies demonstrated equivalent BMD effects in both hypogonadal and eugonadal males. Subsequent meta-analyses of oral bisphosphonates demonstrate vertebral fracture efficacy in men with scant data on nonvertebral and hip fractures [48].

The zoledronic acid male study showed a 67% reduction in new morphometric vertebral fractures after 2 years of annual zoledronic acid 5 mg infusion, as compared to placebo [35]. The mixed male and female population of patients after recent hip fracture (the recurrent fracture trial) demonstrated a 35% reduction in the risk of subsequent fracture in patients treated with annual zoledronic acid infusion compared to placebo [36]. In this study, similar BMD increases were seen in males and females [49]. There is no evidence that the adverse events of bisphosphonates vary between both genders. Adverse events may include upper gastrointestinal symptoms with oral bisphosphonates and flu-like symptoms following zoledronic acid infusion. As in women, serious but rare adverse events such as osteonecrosis of the jaw and atypical femoral fracture have been reported in men.

Denosumab

Denosumab is a fully human monoclonal antibody directed against receptor activator of nuclear factor kappa B ligand (RANKL), effectively inhibiting the formation and activity of osteoclasts. The 3-year registration study for

Table 2. Clinical outcomes of pharmacological therapies for male osteoporosis

Treatment	Route of administration/ dosage	BMD improvement	BTM	VF risk reduction	Non-VF reduction	References
Alendronate	Oral, 10 mg/d	Yes	reduced	Yes	NS	Orwoll et al. 2000 [32]
Risedronate	Oral, 5 mg/d	Yes	reduced	Yes	Yes	Ringe et al. 2009 [33], Boonen et al. 2009 [34]
Zoledronic acid	IV, 5 mg/year	Yes	reduced	Yes	NS	Boonen et al. 2012 [35], Lyles et al. 2007 [36]
Denosumab	SC, 60 mg/6 months	Yes	reduced	Yes*	NS	Orwoll et al. 2012 [37], Smith 2009 [38]
Teriparatide	SC, 20 mcg/d for 18–24 months	Yes	increased	NS**	NS	Orwoll et al. 2003 [39], Kaufman et al. 2005 [40]
Testosterone replacement therapy (in hypogonadal men) ***	IM, Testosterone enanthate 200 mg every 2 week	Moderate increase at lumbar spine only	reduced	NS	NS	Amory et al. 2004 [41], Tracz et al. 2006 [42]
Strontium ranelate***	Oral, 2 g/d	Yes	BsALP increased, CTX decreased	Yes	Yes	Meunier et al. 2004 [43], Reginster et al. 2005 [44]

BTM bone turnover markers, *BsALP* bone-specific alkaline phosphatase, *CTX* serum C-telopeptide cross-links, *VF* vertebral fracture
*Three-year reduction in incidence of new vertebral fractures seen in men receiving ADT for prostate cancer given denosumab versus placebo (RR 0.38, 0.19–0.78) [38]
**Fifty-one percent relative risk reduction in risk of vertebral fractures, p value = 0.07 [40]
***Not FDA-approved for treatment of osteoporosis. Strontium ranelate withdrawn from market in most countries due increased cardiovascular risk

denosumab in postmenopausal women with osteoporosis showed significant reductions in vertebral, nonvertebral, and hip fractures. The much smaller trial of denosumab in men with osteoporosis demonstrated 1-year improvements in BMD and suppression of bone turnover markers versus placebo similar to that seen in women [37]. Although in this study there was no significant reduction in fractures, in a larger study of men with prostate cancer on androgen deprivation therapy, there was a reduction in new vertebral fractures in men given denosumab for 3 years versus placebo (RR 0.38, 0.19–0.78) [38]. Adverse events were rare in the studies of men on denosumab, the nature and frequency of which were similar to the studies in women.

Teriparatide

At present, teriparatide, as a parathyroid hormone analogue, is the only approved bone anabolic therapy for men. Abaloparatide is a PTHrP analogue licensed in the US for the treatment of postmenopausal osteoporotic women with trials now initiated in men (NCT03512262). Both treatments are given for a maximum of 2 years by daily subcutaneous injections due to animal carcinogenicity (osteosarcoma) observed with long-term high-dose treatment. Transient stimulation of the PTH receptor leads to greater osteoblast stimulation than osteoclast-induced bone resorption with consequent new bone formation. As with antiresorptive therapies, trials of teriparatide in men were powered to demonstrate BMD and bone turnover marker effects similar to those in women. In men as in women, BMD increased to a greater degree at spine than hip on teriparatide versus placebo. PINP, as a marker of bone formation, increased rapidly and maintained increases to the end of the 11-month trial. CTX as a marker of bone resorption increased initially with a return to baseline by the end of the study [39]. Both teriparatide and abaloparatide have demonstrated vertebral and nonvertebral anti-fracture efficacy in women; with both agents, too few hip fractures were observed to determine hip fracture efficacy in women. The trials of teriparatide in men were too small to demonstrate significant anti-fracture efficacy. Teriparatide has also been trialed in men and women with glucocorticoid -induced osteoporosis and in this mixed population, compared to alendronate, there was significantly greater improvement in BMD with significantly fewer vertebral fractures in patients treated with teriparatide [50, 51]. A male-specific subanalysis of this study did not show significant differences from women in the study. Subsequent to bone anabolic therapy with teriparatide or abaloparatide, antiresorptive therapy is required in order to maintain the bone anabolic benefit. Switches to bisphosphonate or denosumab are effective in preventing declines in bone density in women and presumably would also be effective in men. Adverse events among individuals treated with teriparatide or abaloparatide include nausea, headache, and dizziness. The incidence of hypercalcemia was significantly lower with abaloparatide than with teriparatide (3.4% vs 6.4% respectively). Safety and efficacy of a transdermal patch delivering abaloparatide is currently being evaluated in postmenopausal women with osteoporosis (NCT01674621).

Strontium ranelate

Strontium salts have a high affinity for bone and can replace calcium in bone leading to artifactual elevations in BMD. Trials of strontium ranelate 2 g daily in

women have shown vertebral and nonvertebral anti-fracture efficacy versus placebo [43, 44]. Strontium ranelate has been approved in many countries in Europe and Asia for the treatment of both male and female osteoporosis. The 2-year study in men with osteoporosis showed similar increases in BMD as were seen in women. In 2014, post-marketing data indicating increased cardiovascular risk, increased risk of venous thromboembolic events, and increased toxic skin reactions have led to its withdrawal or marked restriction in most countries.

Testosterone

Testosterone therapy has physiologic relevance in men with osteoporosis who often have low serum testosterone or estradiol levels. Although in hypogonadal men with osteoporosis, increases in BMD can be seen with testosterone supplementation, no anti-fracture efficacy has been demonstrated [42, 52]. Furthermore, there remains controversy as to the long-term adverse effects of testosterone supplementation on the prostate and cardiovascular system [53]. This unfavorable balance of risk and benefit, as well as the demonstrated efficacy of bone specific therapies in both eugonadal and hypogonadal men has led the Endocrine Society to not recommend testosterone for the treatment of male osteoporosis [23]. Testosterone remains recommended for the symptomatic management of men with hypogonadism. There is no contraindication to its combination with the indicated bone-specific osteoporosis therapies.

Emerging therapies

Recent advances in the understanding of bone cells biology and genetics have led to the development of new therapeutic strategies to treat osteoporosis. Interaction with the Wnt signaling pathways with monoclonal antibodies directed against sclerostin and Dkk-1 may be effective strategies to achieve a bone anabolic response. Novel therapies which target the RANK/receptor activator for nuclear factor-κB ligand/osteoprotegerin signaling pathways, including cathepsin K inhibitors, effectively reduce bone resorption in men and women.

Sclerostin inhibitors

Osteocytes produce a glycoprotein, sclerostin, which inhibits bone formation through inhibition of Wnt/β-catenin signaling and consequent activation of osteoblasts. In contrast to other anabolic therapies, romosozumab, as a sclerostin monoclonal antibody, appears to have a transient effect increasing bone formation markers and decreasing bone resorption markers with effects largely resolving after a year of therapy [54, 55]. In the FRAME study, romosozumab (210 mg subcutaneously per month) significantly decreased the risk of vertebral fractures (63%) and all clinical fractures (36%) at 1 year compared to placebo in postmenopausal women with osteoporosis [56••]. A study in osteoporotic men demonstrated similar BMD and bone turnover marker effects as compared to women (BRIDGE) [57]. In another trial (ARCH), romosozumab showed a significant reduction in vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis and prior fragility fracture compared to alendronate [58••]. Unexpectedly, a cardiovascular risk was found in older patients with severe osteoporosis

when compared to alendronate and this is currently under further investigation.

Cathepsin K inhibitors

Cathepsin K is an enzyme released from osteoclasts that degrades the bone matrix proteins. Odanacatib, as a cathepsin K inhibitor, decreases bone resorption with little effect on inhibiting bone formation. The long-term odanacatib fracture trial (LOFT) was a randomized, blinded, placebo-controlled trial that included 16,713 postmenopausal women with osteoporosis. Treatment with oral odanacatib for 3 years was associated with relative risk reductions of 72% for clinical vertebral fractures, 47% for clinical hip fractures and 23% for clinical nonvertebral fractures compared to placebo [59••]. However, the phase 3 clinical development was terminated when an increase in the risk of stroke was found [60•].

Conclusions

Male osteoporosis is a significant health concern with major health, quality of life, and economic burden to our aging male population. The awareness and appropriate management of male osteoporosis has lagged behind that of female counterparts in part because of less attention to males in epidemiologic and clinical trials. Recent initiatives for secondary prevention of osteoporotic fractures such as fracture liaison services may help to bridge the gap in awareness of male osteoporosis. The lifestyle and dietary management of male osteoporosis is perhaps more important than with female osteoporosis due to the more widespread prevalence of secondary causes of osteoporosis in men.

Nonetheless, we have guidelines for the management of male osteoporosis which should be effective in reducing the burden of fragility fractures in men if applied more universally. Therapies for male osteoporosis, although with less proven anti-fracture efficacy, will likely benefit men with osteoporosis to at least an equal extent as women.

Compliance with Ethical Standards

Conflict of interest

Dr. Kendler reports grants and personal fees from Amgen, grants and personal fees from Eli Lilly, grants from Astrazenica, personal fees from Pfizer, outside the submitted work.
Mohammed Almohaya declares that there is no conflict of interest.
Ahmad Alobedollah declares that there is no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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