Best Practice & Research Clinical Rheumatology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

Male osteoporosis-what are the causes, diagnostic challenges, and management

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Keywords:
Male
Fractures
Causes
Diagnostic
Management

A B S T R A C T

Osteoporosis is underrecognized and undertreated in men, even though up to 25% of fractures in patients over the age of 50 years occur in men. Men develop osteoporosis with normal aging and accumulation of comorbidities that cause bone loss. Secondary causes of bone loss may be found in up to 60% of men with osteoporosis. Mortality in men who experience major fragility fracture is greater than in women. Diagnosis of osteoporosis in men is similar to women, based on low-trauma or fragility fractures, and/or bone mineral density dual-energy X-ray absorptiometry (DXA) T-scores at or below −2.5. Because most clinical trials with osteoporosis drugs in men were based on bone density endpoints, not fracture reduction, the antifracture efficacy of approved treatments in men is not as well documented as that in women. Men at a high risk of fracture should be offered treatment to reduce future fractures.

Abbreviations: BMD, bone mineral density; ISCD, International Society for Clinical Densitometry; FRAX, fracture risk assessment tool.

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https://doi.org/10.1016/j.berh.2022.101766
1521-6942/

Introduction

Osteoporosis is a worldwide disease that causes more than nine million fragility fractures annually, one every 3 s [1].

Men have a lower risk of osteoporosis and fragility fractures than women. This is because women have bones with smaller diameters, lower peak bone mass, a menopause-related bone resorption process, and a higher risk of falls than men [2]. Despite osteoporosis and fragility fractures being less common in men than women, 39% of osteoporotic fractures worldwide occur in men [1]. Data from 2005 indicate that of the 2 million osteoporotic fractures that occur annually in the US, 29% occur in men. This percentage corresponds to an associated cost of 17 billion US dollars [3]. In men and women, the incidence of hip fractures increases exponentially with age, although in men, the increase begins approximately 10 years later [4]. Data from the U.S. 2008 Nationwide Emergency Department Sample showed the incidence of hip fracture in men ranging from 0.56 per 1000 per year at the age of 60 years to 13 per 1000 per year at age 85 years [5]. Similar results were reported in a Norwegian study covering the years 2004–2005, with an incidence of 0.49 per 1000 person-years of hip fractures in men at age 60 and 12.3 per 1000 person-years at age 85 [6]. A 60-year-old man has an approximately 25% risk of having an osteoporotic fracture during his remaining lifetime [7]. Men are less likely than women to be evaluated and receive antiresorptive treatment after a hip fracture [8,9]. The mortality rate associated with hip fractures [10,11] and vertebral and other fractures [12] is higher in men than in women. In a prospective study in community dwelling women and men aged 60 years and older in Australia, mortality after a low trauma fracture was 48% in women and 57% in men within 10 years [13]. The reason for this difference in mortality is not clear, but higher risk of infection in men than in women after a low trauma fracture could be one explanation [14].

Analysis of the literature shows that male osteoporosis is underdiagnosed and undertreated, both in primary and secondary prevention of fragility fractures [15,16].

Causes

After reaching peak bone mass in the third decade of life in most individuals, men lose approximately 30% of their trabecular bone and 20% of their cortical bone during their remaining lifetime [17]. Acceleration of age-related bone loss can occur either when bone resorption is increased or when bone formation is impaired during skeletal remodeling.

Causes of osteoporosis in men are similar to those in women (Table 1).

Table 1
Causes of osteoporosis in men.

Endocrine diseases	Connective tissue diseases	Gastrointestinal diseases	Hematologic disorders	Drugs	Miscellaneous causes
Hypogonadism	Osteogenesis imperfecta	Malabsorption syndromes	Multiple myeloma	Glucocorticoids	Eating disorders
Delayed puberty	Ehlers-Danlos syndrome	Inflammatory bowel disease	Chronic hemolytic anemia	Heparin	Immobilization
Estrogen deficiency	Marfan syndrome	Cirrhosis	Systemic mastocytosis	Thyroxine suppressive therapy	Rheumatoid arthritis
Hypercortisolism	Homocystinuria			Antiseizure medications	Renal disease
Hyperthyroidism				Gonadotropin-releasing hormone analogs	Cirrhosis
Hyperparathyroidism				Cyclosporine	Alcohol
Vitamin D deficiency				Chemotherapy	Tobacco
Growth hormone deficiency				HIV medications	
Diabetes mellitus (type 1 and 2)					

Epidemiologic studies suggest that secondary causes for osteoporosis can be identified in 40–60% of men who have osteoporotic fractures [18,19]. The most common ones were hypogonadism, glucocorticoid (GC) therapy, gastrointestinal disease, vitamin D deficiency, antiseizure medication therapy, hypercalciuria, and alcohol use.

Gonadal steroids play an important role in attainment and maintenance of bone mineral density (BMD) in men. Several cross-sectional and longitudinal studies indicate that levels of bioavailable estradiol rather than testosterone are strongly correlated with the BMD and fracture risk in men [20,21]. Bone density decreases in young men castrated for sexual delinquency [22] and older men with advanced prostate cancer who undergo androgen deprivation therapy (ADT) [23,24]. Reduction in BMD can be detected already after six to nine months of ADT [25]. In a study on 50,613 men with prostate cancer, 19% of 6650 men who received ADT and survived at least five years after diagnosis had a fracture compared with 12% of the 20,035 patients who did not receive ADT [26]. Both endogenous and exogenous GC excess cause osteoporosis in men. This is primarily due to deleterious GC effects on bone by increased bone resorption and reduced bone formation [27], but GC-induced hypogonadism may also be a contributory factor. Studies have shown that GC excess, which is nearly always caused by exogenous GC therapy, is responsible for approximately 15% of vertebral fractures in men [18,28]. The underlying disorders for which GCs are given can also contribute to fracture risk. Vitamin D deficiency is associated with low BMD, poor physical performance, and increased risk of fractures [29,30]. Although several trials have reported a beneficial effect of calcium and vitamin D on bone density in older men, the data on fracture risk are more variable [31].

Diagnostic challenges

While diagnostic testing for osteoporosis in men follows thresholds like postmenopausal women, several noteworthy differences exist. Men achieve peak bone mass around the same time as women (20–29 years); however, men have larger bones (~30% larger bone area) and higher peak bone mass (~20%) than women [32]. In addition, men do not have the accelerated bone loss that women experience around menopause. These two mechanisms are responsible for the fact that age-specific prevalence of osteoporosis and fracture rate in men lag women by about 10 years [33]. The older age of men who suffer fractures contributes to the higher mortality observed in men compared to women after a fracture. Osteoporosis in men is underdiagnosed and undertreated, even more so than in women. There are fewer studies on the diagnosis and treatment of osteoporosis in men compared to women.

In men $\geq$50 years old, osteoporosis is diagnosed either by the presence of a fragility fracture after the age of 50 or by low BMD; in some parts of the world, only hip and spine fractures would lead to the diagnosis of osteoporosis without a T-score $\leq$ -2.5. Fragility fractures are classically defined as a fracture of the spine, hip, humerus, or wrist that occurs spontaneously or after a fall from standing height. BMD measured by dual-energy X-ray absorptiometry (DXA) of the spine and hip remains the best test to predict future fracture risk. There is debate regarding whether to use a male or female reference database. Most published studies of osteoporosis in men used a male-specific reference database. The International Society for Clinical Densitometry (ISCD) recommends using a uniform Caucasian (nonrace adjusted) female reference for men and women because men and women fracture at similar absolute BMD [34]. A T-score of $\leq$2.5 defines osteoporosis in men [35]. A T-score between $-$1.0 and $-$2.5 is defined as osteopenia. For men <50 years old, the ISCD recommends using a Z-score of < -2.0 (below the expected range for age) combined with a history of fragility fractures or the presence of other risk factors for low bone density/fractures [36]. There is no consensus at what age bone density screening is recommended in men (Table 2). The National Osteoporosis Foundation, the Endocrine Society, and the ISCD recommend BMD screening in men at age $\geq$70; between ages 50 and 70, BMD is recommended if risk factors for osteoporosis are present. These risk factors include diseases and conditions such as fractures after the age of 50, loss of more than 1.5 inches (4 cm) of height, low body weight, hypogonadism, hyperthyroidism, Chronic obstructive pulmonary disease (COPD), nephrolithiasis, previous bariatric surgery, diabetes mellitus, drugs that affect bone metabolism (GCs, tricyclic antidepressants, Gonadotropin-releasing hormone (GnRH) agonists), or lifestyle factors (excessive alcohol or smoking).

Table 2
Simplified age recommendation for BMD screening in men of some select organizations. RF, risk factor for osteoporosis; USPSTF, US Preventive Services Task Force; ISCD, International Society for Clinical Densitometry.

	Endocrine Society (2012) [53]	National Osteoporosis Foundation (2014) [54]	USPSTF (2018) [55]	ISCD (2019)
Age for BMD screening	≥70 50-69 + RF	≥70 50-69 + RF	Insufficient evidence	≥70 50-69 + RF

Since DXA is typically performed at an older age in men, osteoarthritis or degenerative changes are particular problems in men that can falsely elevate BMD.

Fracture risk calculators, such as fracture risk assessment tool (FRAX), are commonly used in men and women with osteopenia to estimate the 10-year risk for major osteoporotic and hip fractures. FRAX incorporates age, sex, weight, height, previous fracture, parental fractured hip, current smoking, GCs, rheumatoid arthritis, secondary osteoporosis, alcohol 3 or more units/day, and femoral neck BMD. The risk calculations help determine a therapy recommendation (see below). The FRAX calculator does not capture the GC dose but treats GC as a dichotomous variable (yes/no). Yet, higher doses of GC carry a higher risk of fractures. Tables to adjust for the GC dose have been published [37].

In men with osteopenia or osteoporosis, spine X-ray or vertebral fracture assessment by DXA should be considered.

Risk factors can be identified in up to 60% of men with osteoporosis [38]. A careful history and physical examination are essential to determine such risk factors. Routine laboratory workup includes complete blood count, renal and liver function tests, albumin-adjusted calcium, phosphate, 25-hydroxy vitamin D, alkaline phosphatase, and 24-h urine calcium and creatinine. Morning testosterone and sex hormone binding globulin (SHBG) are checked up to three times in men with osteoporosis who have hypogonadism signs (testicular atrophy) or symptoms (low libido). Further testing that might be triggered by history, exam, or routine laboratory results include tests for thyroid diseases (TSH), hyperparathyroidism (PTH), Cushing's syndrome (24-h free urinary cortisol), systemic mastocytosis (tryptase), or celiac disease (tissue transglutaminase antibodies).

Management

Management of male osteoporosis should include patient education, lifestyle adjustments, and nonpharmacological and pharmacological treatment. The management plan should be individualized, considering age and ethnicity, comorbidities, severity of osteoporosis, BMD, fracture history, and recency of fractures.

Most research on all aspects of osteoporosis management has been performed in postmenopausal women, and therefore some parts of the management plan for male osteoporosis have been adopted from knowledge about management of postmenopausal osteoporosis. It has been shown that patient education improves the quality of life, adherence to treatment, and helps the patients implement changes to daily living activities that may decrease the risk of fractures [39]. Lifestyle adjustments include smoking cessation, moderate alcohol intake, and increased physical activity. In addition, the diet should be healthy and sufficient to avoid weight loss if the patient is nonobese. The recommended daily intake of calcium is 800–1200 mg. The recommended intake of vitamin D varies between guidelines, the most common recommendations being 20–40 μg cholecalciferol per day, aiming for a serum 25-hydroxy vitamin D3 above 50 nmol/l (20 ng/ml). These recommendations seek to avoid calcium and/or vitamin D deficiency that may lead to secondary PTH and bone loss. In addition, in the majority of clinical trials investigating the antifracture efficacy of approved treatments, the participants were supplemented with calcium and vitamin D. The majority of the clinical trials investigating medical treatments of male osteoporosis have been planned in accordance with the guidance from the medical agencies. They state that it is not necessary to demonstrate antifracture efficacy in men for drugs that already have shown antifracture efficacy in postmenopausal osteoporosis, if similar effects on BMD and bone turnover markers can be demonstrated in men. Currently, bisphosphonates, denosumab, and teriparatide are approved for the treatment of male osteoporosis.

The effect of alendronate was investigated in 241 men between 31 and 85 years with osteopenia or osteoporosis [40]. The men were randomized to alendronate 10 mg daily or placebo and followed for 2 years. After 2 years, BMD at the spine and hip had increased significantly in the alendronate-treated men and was higher at all sites compared with the placebo-treated men. The incidence of new morphometric vertebral fractures, but not of nonvertebral fractures, was significantly reduced in the alendronate-treated men. Thirty-six percent of the men had testosterone levels below the normal level for younger men. The increases in BMD in hypogonadal men were similar to the increases in eugonadal men.

The effect of 35 mg weekly risedronate was examined in a 2-year study including 284 men older than 30 years with osteoporosis or osteopenia [41]. Treatment with risedronate resulted in significant increases in BMD at the lumbar spine, total hip, and femoral neck. Few fractures occurred during the study with similar incidences in risedronate and placebo-treated men. No detailed information about the response in the hypogonadal men included in the study was provided, but it was mentioned that BMD of the lumbar spine increased more in risedronate-treated hypogonadal men than in hypogonadal men receiving placebo.

Zoledronate was investigated in a randomized, placebo-controlled trial comprising 1199 men between 50 and 85 years. The men were randomized to yearly infusions of zoledronate 5 mg or placebo for 2 years [42]. The risk of new morphometric vertebral fractures was significantly reduced by 67%. BMD of spine and hip was significantly increased, and bone turnover markers significantly decreased in the men receiving zoledronate. The response with respect to bone turnover markers, BMD and morphometric vertebral fracture risk was similar between the 25% of the men who were hypogonadal and the eugonadal men.

The effect of denosumab on male osteoporosis was investigated in the ADAMO trial comprising 242 men between 30 and 85 years. The men were randomized to denosumab 60 mg every 6 months or placebo for 1 year. During the second year, all men received denosumab 60 mg every 6 months [43]. After 12 months, BMD at the spine and hip had increased significantly, and bone turnover markers were reduced significantly in men treated with denosumab compared to placebo-treated men. Fifteen percent of the men were hypogonadal, and they responded similarly to the eugonadal men with respect to BMD and bone turnover markers. Very few fractures occurred in this study. During the second year, BMD continued to increase in the men continuing denosumab treatment [44]. A previous study comprising 1498 men with nonmetastatic prostate cancer and osteopenia who received ADT demonstrated that denosumab 60 mg every 6 months over 3 years significantly increased BMD compared with placebo [45]. In this study, denosumab significantly reduced the risk of new morphometric vertebral fractures.

The effect of teriparatide was investigated in a clinical trial enrolling 437 men between 30 and 85 years of age with BMD T-scores at the spine or hip less than −2.0 [46]. The men were randomized to teriparatide 20 or 40 μg daily or placebo for 2 years; however, the study was stopped after an average time on treatment of 11 months due to the findings of osteosarcomas during toxicology studies in rats treated with teriparatide for their near lifetime. In men treated with teriparatide, bone formation markers increased rapidly and subsequently also markers of bone resorption increased. BMD at the spine was increased significantly compared with placebo already after 3 months of therapy. At the end of study, BMD at the spine had increased by 5.9% in the men treated with 20 μg daily, and femoral neck BMD had increased by 1.5%. The response pertaining to bone turnover markers and BMD was similar in the 50% of men who had low serum testosterone as in the eugonadal men. Eighty-three men were enrolled in a study investigating the effect of teriparatide compared to alendronate in GC-treated patients [47]. In this study, the patients were treated with teriparatide for up to 3 years. Moreover, in this study, men responded similarly to teriparatide with respect to BMD as in postmenopausal women, and it is therefore assumed that the antifracture efficacy seen with teriparatide in postmenopausal women will also be seen in men. Abaloparatide has not been investigated in men. The effect of romosozumab in male osteoporosis has been investigated in the BRIDGE study (A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis) comprising 245 men between 55 and 90 years with BMD T-scores at spine or hip ≤ -2.5

or ≤1.5 in combination with a vertebral or nonvertebral fragility fracture [48]. The men were randomized to romosozumab 210 mg monthly for 1 year. BMD at the spine and total hip increased by 12.1% and 2.5%, respectively, significantly different from the small increases seen in the placebo-treated men. Adverse events were generally well balanced between the groups; however, a numeric imbalance in adjudicated serious cardiovascular adverse events was seen; 8/163 in the romosozumab-treated men versus 2/82 in the placebo-treated men. These findings have been interpreted differently by authorities across the world. Romosozumab is approved for the treatment of male osteoporosis in Japan, but not in many other countries, for example the EU and US.

The effect of testosterone on bone health in hypogonadal men has been investigated in a study comprising 211 men with hypogonadism but normal BMD [49]. The men were randomized to testosterone gel adjusted to maintain serum testosterone levels within the normal range for young men or placebo for 1 year. BMD at the lumbar spine and femoral neck increased by 3.3% and 1.5%, respectively, significantly different from the changes in the placebo-treated men. In addition, Quantitative computed tomography (QCT) of the spine and hip also showed increases in volumetric BMD and estimated bone strength. No fracture data are available in this study. The potential benefits of testosterone treatment in hypogonadal men with osteoporosis should be balanced against the potential risks associated with the treatment. Therefore, most guidelines do not recommend using testosterone for the treatment of osteoporosis in older men with hypogonadism, but instead using the approved treatments that have been demonstrated to improve BMD equally well in hypogonadal as in eugonadal men with osteoporosis.

Conclusion

Male osteoporosis occurs less frequently than osteoporosis in postmenopausal women but is still responsible for a substantial disease burden in the population. Approximately 25% of fractures in patients over 50 years occur in men. Osteoporosis in men increases with age as in women, and mortality after major fragility fractures is greater in men than women. Male osteoporosis is defined by the occurrence of fragility fractures, in some parts of the world, only hip and spine fractures or by DXA BMD T-scores of −2.5 or lower at the hip, lumbar spine, and/or forearm. Men having T-scores of −2.5 or lower and prior fragility fractures are at high risk of future fractures. Men with T-scores between −1.0 and −2.5 should be assessed by FRAX or similar tools to determine fracture risk. At least half of men with osteoporosis have secondary causes of bone loss, and identification and treatment of these causes may help prevent further bone loss and possibly improve bone density. Treatment trials of osteoporosis in men have led to the approval of multiple medications for use in men, although these trials were typically small, short in duration, and used bone density rather than fracture endpoints.

Practice points

- Male osteoporosis occurs less frequently than osteoporosis in postmenopausal women but is still responsible for a substantial disease burden in the population.
- Secondary causes for osteoporosis can be identified in 40–60% of men who have osteoporotic fractures.
- Osteoporosis in men is underdiagnosed and undertreated, even more so than in women.
- Greater awareness of osteoporosis in men by health practitioners is needed to prevent undertreatment and improve patient care.

Research agenda

- Clinical trials of osteoporosis treatments in larger, longer-term studies of men with fracture endpoints would be helpful in confirming the fracture benefit of these medications.
- More clinical trials of new osteoporosis treatments such as abaloparatide and romosozumab are needed in men so these can be reviewed for approval by regulatory agencies.
- The optimal treatment sequence in men has not been investigated. Analyses in post-menopausal women suggest that bone anabolic therapy is more effective in improving BMD when given before an antiresorptive treatment than in the reverse sequence [50]. If this is also the case in men is currently unknown.
- Another hot topic is a treatment target. The FNIH-ASBMR SABRE project has shown that increase in BMD is a predictor of the antifracture efficacy of treatment [51]; however, most studies included in this analysis were performed in postmenopausal women. The posthoc analysis of the FREEDOM trial which demonstrated that a possible BMD treatment target could be total hip BMD T-score in the range of −2.0 to −1.0 only included postmenopausal women [52]. Therefore, identifying a treatment target in men awaits further study.

Funding

No funding for this publication.

Declaration of competing interest

SB has received institutional research grants from Takeda/Shire and served as an advisory board member and consultant for UCB, Amgen, Gilead, and Astellas. BLC has received institutional research grants from Takeda/Shire, Ascendis, and Chugai Pharmaceuticals, and consulted for Takeda/Shire, Ascendis, Entera Bio, Extend Bio, ShouTi Pharma, Calcilytix, Amgen, and Radius Health. MM has served as an advisory board member, consultant, and research investigator for Takeda/Shire and consulted and research investigator for Chugai Pharmaceutical Co., Ltd. and Amolyt Pharma. BL has received research grants from Amgen, Novo Nordisk and served as an advisory board member and consultant for UCB, Amgen, Gedeon Richter, Gilead, Astellas, and AstraZeneca.

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