Male Osteoporosis

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ABSTRACT

Osteoporosis is a chronic condition characterized by impaired bone remodelling that results in reduced bone mineral density, excessive bone loss and increased fracture risk. Osteoporosis in men is a fairly common condition, affecting 2-8% of men worldwide and more than 30% by the age of 85. Despite these compelling figures, the condition is under-estimated, under-diagnosed and under-treated. As a result and since the condition is almost always a "silent disease", the first presentation is often a fragility fracture. Although the mechanisms and conditions that cause osteoporosis in men are similar to those in women, male osteoporosis has some unique features. Risk factors in men are very heterogenous and hypogonadism represents a common underlying cause. Other common aetiological factors are poor vitamin D and calcium levels, chronic underlying haematological, gastroenterological and rheumatological conditions and use of offending drugs or substances. The evidence for diagnosis, screening and treatment of male osteoporosis is quite poor and most of the current knowledge is extrapolated from the female counterpart. Identification and prompt therapy of underlying conditions leading to osteoporosis is essential before additional anti-resorptive or anabolic treatment is considered. This review discusses the current evidence on pathophysiology, aetiology, diagnosis, screening and treatment of osteoporosis in men.

KEYWORDS: Male osteoporosis, osteoporosis, fracture risk, hypogonadism, pharmacological treatment

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Introduction

Osteoporosis is a common disease characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture. It is a leading cause of morbidity and mortality in older people as well as a significant financial burden to health systems worldwide.

Although the mechanisms and conditions that cause osteoporosis in men are similar to those in women, male osteoporosis has some unique features. Furthermore, epidemiological data and clinical experience suggest that osteoporosis in men is overlooked and often diagnosed late when an osteoporotic fracture has already occurred. Epidemiological surveys show that causes or contributing factors for osteoporosis can be identified in a significant percentage of men who have sustained an osteoporotic fracture, a finding illustrating the importance and value of early diagnosis and treatment in order to prevent the fracture.

The epidemiology, aetiology, clinical evaluation and treatment of osteoporosis in men will be reviewed in this chapter.

Epidemiology

In the developed world, 2% to 8% of males are affected by osteoporosis (1, 2). By the age of 85 years, over 30 percent of men will have a femoral neck T-score at or below -2.5 (3).

Although the fracture risk for men is lower compared to women, it remains significant: A 60-year-old man has a 25% risk of fracture (compared to 44% for a woman of the same age) (4). Furthermore, 1 in 5 men over the age of 50 will sustain an osteoporotic fracture (5).

Pathophysiology

The underlying mechanism in all cases of osteoporosis is an imbalance between bone formation and bone resorption. Low bone mass density can occur either when pubertal bone accretion is reduced resulting in suboptimal peak bone mass or when the rate of bone resorption is accelerated after peak bone mass is achieved: that takes place when osteoclasts are degrading the bone matrix faster than the osteoblasts are rebuilding the bone (6).

Pubertal bone accretion – achievement of peak bone mass

Peak bone mass is defined as the amount of bony tissue present at the end of the skeletal maturation and represents the maximum amount of bone an individual can attain during his life. The exact age of peak bone mass is unclear and can be affected by a number of factors (genetic, ethnic, hormonal, environmental). However, it probably occurs around the mid-thirties in most people.

In men, there is a dramatic increase of bone mass during puberty and the peak bone mass seems to be skeletal site-specific: it occurs around the age of 20 in the spine but later on in life in femur and radius (7).

One major factor is the *timing of onset of puberty*. The evidence suggests that there is a critical time window during which adequate concentrations of sex steroids is essential in order to achieve the optimal bone mass. Adult men with a history of constitutionally delayed puberty have decreased radial and spinal bone mineral density (8) as well as femoral bone density (9). Furthermore, this bone deficit does not seem to be corrected with age even when the steroids' levels are restored (8, 9).

Another major determinant of peak bone mass is intact production of *gonadal steroids*. The findings suggest that men with idiopathic hypogonadotrophic hypogonadism have lower cortical and trabecular bone mass (10) which is improved after correction of the hormonal deficit (11). Interestingly, *both androgens and oestrogens* have profound effect on peak bone mass in men.

Age-related bone loss

The imbalance between bone resorption and bone formation is responsible for bone loss after the peak bone mass is achieved. In men, trabecular bone loss appears to start prior to cortical bone loss and typically soon after the peak bone mass is achieved (12).

Aetiology

Male osteoporosis has historically been classified into two main categories, primary and secondary. Furthermore, primary osteoporosis can be further

TABLE 1. Causes of osteoporosis in men

Endocrine conditions	Haematological conditions	Other conditions	Drugs and substances
Hypogonadism - delayed puberty	Multiple myeloma	Rheumatoid arhritis	Alcohol Tobacco
Diabetes mellitus (type 1, 2)	Mastocytosis	Renal and hepatic disease	Overreplacement with levothyroxine
Estrogen deficiency	Chronic anemia	Immobilisation	Glucocorticoids
Hypercortisolism (Cushing's)	**Gastrointestinal conditions**	Osteogenesis imperfecta	Heparin
Hyperthyroidism	Coeliac disease	Homocystinuria	Anticonvulsants
Hyperparathyroidism	Inflammatory bowel disease	Ehlers-Danlos syndrome	Chemotherapy Immunotherapy
Vitamin D deficiency	Malabsorption	Marfan syndrome	Protein pump inhibitors
Growth hormone deficiency	Cirrhosis	Eating disorders (anorexia nervosa)	Cyclosporine Anti-retrovirals Lithium

divided into i) involutional (or senile) osteoporosis, which occurs in men older than 70 years old with no other risk factor present, and ii) idiopathic osteoporosis, which occurs in patients younger than 70 years old without risk factors (13).

It should be noted however that, even though the underlying conditions that cause osteoporosis in men are similar to those in women, diagnostic search is often less vigorous and active in men, especially when no apparent risk factors are presents. Epidemiological surveys suggest that secondary causes can be identified in 40-60% of men who have severe osteoporosis or have sustained osteoporotic fractures (14, 15).

The medical conditions and risk factors for osteoporosis are summarised in Table 1. Some of these conditions and risk factors have been shown to be most predictive of osteoporotic fractures in men (16, 17, 18):

- Hypogonadism
- Low calcium and vitamin D levels
- Alcohol and tobacco use
- Low bone mineral density (BMD)
- Advancing age
- Prior history of fragility fracture
- Chronic glucocorticoid use and
- Parental history of hip fracture

Hypogonadism, both primary and secondary, is a common of osteoporosis in men. As previously discussed in this chapter, sex steroids play a key role in attainment of peak bone mass. Testosterone levels are also pivotal for maintenance of bone mass: the balance between bone formation and disruption is affected when testosterone levels fall < 200ng/dL as it seems that bone turnover increases at this point probably due to a parallel fall of serum oestrogen <15 pg/mL (19). It is well documented that low levels of oestradiol can increase the risk of fractures in men (20, 21) and this is probably be due to a deficit of testosterone transformation into oestradiol secondary to an aromatase enzyme dysfunction. Furthermore, hypogonadism lead to muscular atrophy, muscle mass loss and sarcopenia, factors further contributing to the risk of fractures.

Low serum vitamin D levels and poor calcium intake. The negative impact of low vitamin D levels on skeletal health is well-documented (22, 23). It is estimated that around 15% of male osteoporosis is caused by vitamin D deficiency (24). Suboptimal calcium intake (less than 1.200mg) is fairly common in elderly men. There is some evidence from trials supporting the role of calcium and vitamin D correction in men (25, 26) in terms of bone mass. However, the evidence is less clear for risk of fractures (27).

Cigarette smoking and excessive *alcohol consumption* are associated with accelerated bone loss and fracture risk (28, 29, 30) although the underlying mechanism is not entirely clear.

Glucocorticoid excess, either endogenous or iatrogenic has a negative impact on male skeletal health. This is primarily due to the direct impact on the bone, but also due to the secondary hypogonadism and sarcopenia the steroids' excess can induce.

Clinical manifestations

Osteoporosis is a silent disease. It doesn't give any symptoms until a fracture occurs. Even then, some of these fractures are incidental findings on imaging done for other purposes as they can be asymptomatic. However, it should be noted that these men often have symptoms of the underlying condition (endocrine, gastrointestinal, connective tissue) that predisposes to osteoporosis therefore there should be a high degree of clinical suspicion.

Typical fragility fractures occur in the vertebral column, the ribs, the hip and the wrist. Men sustain fewer fragility fractures than women but their mortality is higher than women following a fragility fracture (31).

Diagnosis

In all men, irrespective of age, a clinical diagnosis of osteoporosis can be made in the presence of a fragility fracture. In all other cases, bone mineral density (BMD) assessment by dual-energy x-ray absorptiometry (DXA) should be performed. DXA is considered the gold standard test to diagnose osteoporosis in men ≥50 years even though it is not as well standardised as in postmenopausal women. There has been some controversy regarding the reference database for the calculation of T-scores in men. This is because it is documented that at any

TABLE 2. Diagnostic criteria for osteoporosis and osteopenia in men ≥ 50 years based upon DXA measurements (33, 34)

Category	Bone mass
Normal	BMD value within 1.0 SD of the young adult female reference mean (T-score ≥ -1.0)
Osteopenia	BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (−2.5 < T-score < −1.0)
Osteoporosis	BMD value 2.5 or more SD below the young adult female reference mean (T-score ≤ −2.5)
Severe osteoporosis	T-score ≤ −2.5 and one or more fragility fractures

TABLE 3. Laboratory work-up

In all cases	In most cases
Full blood count	Testosterone
Calcium (corrected for albumin too)	Parathyroid hormone
Phosphorus	Serum/urine protein electrophoresis
Erythrocyte sedimentation rate	Thoracic-lumbar spine X-ray (Face/Profile)
Creatinine	**In selected cases**
Alkaline phosphatase	24hour urinary free cortisol
25 (OH) Vitamin D	Serum tryptase
TSH	Anti-Tissue Transglutaminase antibodies
24hour urinary calcium	Bone turnover markers (P1NP or CTx)

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skeletal site T-score men have a lower absolute risk for fracture than women (32). Nonetheless, both the World Health Organisation and the International Society for Clinical Densitometry (ISCD) recommend the use of a female reference database for men over the age of 50, rather than using healthy young males as reference (33, 34). The diagnostic cut-offs are summarised in Table 2.

For younger men, aged <50 years, the diagnosis should not be made on BMD measurements alone (34). In these individuals, a low Z-score ≤-2.0 alone is not necessarily suggestive of osteoporosis, unless there is a history of a fragility fracture or a secondary cause for osteoporosis is present.

Value of screening – who should be tested for osteoporosis

Routine male population screening for osteoporosis based solely on age has been a controversial issue. However, an increasing number of groups, institutions and societies such as the National Osteoporosis Foundation (NOF), International Society for Clinical Densitometry (ISCD), and the Endocrine Society recommend BMD testing for all men older than 65 or 70 as it is probably a cost-effective approach. This approach is reflected on the guidelines for diagnosis and treatment of osteoporosis in Greece (35), which recommend routine DXA measurement in all men above the age of 65. In younger men, under the age of 65, BMD testing should be performed when i) there is clinical evidence of possible low bone mass (fragility fracture, evidence of osteopenia in other forms of radiography) and/or ii) there are underlying conditions that predispose to osteoporosis (as summarised in Table 1).

Fracture Risk Assessment Tool (FRAX)

The FRAX score represents a diagnostic tool used to evaluate the 10-year probability of fracture. It integrates clinical risk factors and BMD at the femoral neck to calculate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture and can be used in men as an aid to the clinician, although its intervention thresholds increase the proportion of older men who are candidates for therapy compared to the WHO criteria (36).

Diagnostic approach to the man with osteoporosis for secondary causes

Detailed history should be obtained and thorough clinical examination should be performed in any man diagnosed with osteoporosis as they can potentially point towards a possible underlying diagnosis. The laboratory work-up is summarised in Table 3. It should be noted, that, if a rarer underlying condition is suspected, the relevant investigations should be performed.

Treatment

The treatment of osteoporosis in men consists of a) non-pharmacological measures, b) calcium and vitamin D correction, c) treatment of potential underlying causes and d) pharmacological measures.

Non-pharmacological measures

Lifestyle measures and modifications should be encouraged for men with osteoporosis. Weight bearing exercise has been shown to be beneficial by a) increasing muscular strength, b) potentially increasing bone mass, c) improving co-ordination thus preventing falls (37, 38, 39).

Calcium and vitamin D

The estimated daily calcium requirements are 1000mg for men aged 19-70 and 1200mg for men over the age of 70. Suboptimal serum calcium concentrations is a fairly common problem in elderly men, predominantly due to poor intestinal absorption (mainly due to polypharmacy) and reduced glomerular filtration therefore oral supplementation of 500-1000 mg/day of calcium carbonate is typically suggested.

Poor serum vitamin D concentrations is another common problem, especially amongst older men residing in institutions. Various dosing regimens have been proven to treat vitamin D deficiency in men. Most groups and societies suggest a daily vitamin D supplementation of 600-800 I.U.

Treatment of underlying conditions

Secondary causes can be identified in 40-60% of men who have severe osteoporosis or have sustained osteoporotic fractures (14, 15). This underlines the importance of prompt and appropriate management of the underlying cause for osteoporosis (see Table 1 for the various causes). Offending medications should be discontinued if that's possible or have their dose reduced. There are some special considerations for some of these underlying conditions:

Hypogonadism is a common cause for osteoporosis in men. Proper assessment of the hypogonadism, calculation of the bioavailable/active testosterone and the decision to treat with testosterone balancing the cardiovascular risk is an important aspect of treatment of osteoporosis in hypogonadal men. There are quite convincing data that correction of the hormonal deficit in younger men with clear aetiology for the hypogonadism (e.g. pituitary tumour, Klinefelter syndrome) increases bone mass (40, 41, 42, 43). The evidence is less clear for older men as only a few small trials (44, 45, 46) and the "Testosterone Trials" (47) have examined the efficacy of testosterone on bone mass. The improvement on bone mass following administration of testosterone in older men is similar to the one observed in the placebo groups. It is probably recommended that the decision to treat with testosterone in older men should be taken on an individualised basis taking into account the cardiovascular risk as well.

An area of debate is whether testosterone replacement therapy is adequate in a man with osteoporosis due to hypogonadism or whether additional anti-osteoporotic treatment is necessary. In the absence of any strong clinical data, the recommendation of the Endocrine Society is to add an anti-osteoporotic pharmacological agent to the hypogonadal men with high fracture risk alone (48). Risk factors include a previous fragility fracture, severe osteoporosis (defined as T-score ≤-3.0), treatment with high dose glucocorticoids and persistent osteoporosis despite successful correction of the hypogonadism for at least 2 years.

Osteoporosis due to gastrointestinal diseases (commonly celiac disease or inflammatory bowel disease) is characterised by the low, and often very low, calcium and vitamin D concentrations and secondary hyperparathyroidism therefore these patients often require higher doses of calcium and vitamin D.

Glucocorticoid-induced osteoporosis is a relatively common cause of osteoporosis in men and is observed even with relatively low doses of exogenous steroids (equivalent to prednisolone 5-7.5 mg). The bone loss is more aggressive in the first months of treatment with steroids therefore it should be treated aggressively, particularly in those already at high risk for fracture.

Pharmacological measures

With regards to the pharmacological approach to osteoporosis in men, there are two questions: which patient to treat and what the treatment options are.

Whom to treat?

For hypogonadal men, the indications for additional to testosterone treatment have been discussed earlier in this chapter (see "Treatment of underlying conditions" section).

For eugonadal men, the indication for pharmacological treatment are: a) history of fragility fracture, b) established osteoporosis, c) osteopenia (48, 49).

Treatment options

Bisphosphonates is the first line treatment for most men with osteoporosis. Most groups suggest oral alendronate or risendronate as initial therapy (48, 50, 51) since randomized trials (52, 53, 54, 55, 56) have proven the efficacy and safety of these medications (down to eGFR 30-35 ml/min). When oral bisphosphonate is contraindicated or not tolerated, zolendronate can be used (57, 58).

Denosumab is a potent anti-resorptive agent and has a role for treatment of osteoporosis in men especially when a) bisphosphonates are not tolerated or not effective and b) the patient's renal function is poor (eGFR < 30-35 ml/min). It should be noted that denosumab has been shown to improve bone mass in men (59), but there are no data about fracture risk reduction.

Teriparatide has been shown to be effective in improving the spinal and femoral BMD in men (60).

Similar results have been shown for *abaloparatide* (61), but none of these trials assessed fractures. In most guidelines, these agents are reserved for men with severe osteoporosis or men with osteoporosis and a new fracture or men who did not respond to previous treatment. It is crucial that treatment with these agents is always followed by an antiresorptive agent.

Romosozumab, an agent with mixed anabolic and antiresorptive action, has shown an improvement in spinal and total hip BMD in men (62). A

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