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Osteoporosis in men

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Male osteoporosis is an increasingly important public health problem: from age 50 onward, one in three osteoporotic fractures occurs in men and fracture-related morbidity and mortality are even higher than in women. In 50% of osteoporotic men, an underlying cause can be identified (secondary osteoporosis). In the absence of an identifiable etiology, male osteoporosis is referred to as 'idiopathic osteoporosis' in men aged 30–70 years and as 'age-related osteoporosis' in older men. As in women, estrogen, not testosterone, appears the most important sex steroid regulating male skeletal status. Diagnosis and treatment recommendations are still largely based on bone mineral density (BMD), with osteoporosis defined as a T-score of 2.5 standard deviations below young adult values. However, there is ongoing discussion as to whether male or female reference ranges should be used and, like in women, treatment decisions are increasingly based on absolute fracture risk estimations rather than on BMD alone. In men, evidence-based data on the efficacy of pharmacologic interventions in reducing fracture risk are convincing but not conclusive. In particular, bisphosphonates and teriparatide seem to be as effective in men as in women.

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Introduction: basic bone biology

Bone is composed of support cells (osteoblasts and osteocytes), remodeling cells (osteoclasts), osteoid (nonmineral matrix of collagen and glycosaminoglycans) and inorganic mineral salts (hydroxyapatite, a complex of calcium and phosphate). Osteoblasts are responsible for the synthesis of the osteoid and its mineralization, which makes bone rigid and hard. Resorption of mineralized bone is done by osteoclasts.

Bone remodeling is the coupled process of bone formation and bone resorption to maintain bone mass in adults (Fig. 1). This process consists of five phases. In the activation phase the resting bone surface becomes a remodeling surface. Precursors of osteoclasts differentiate into functional osteoclasts due to stimulation by cytokines and growth factors. In the next phase (resorption phase), osteoclasts digest mineralized bone, making scalloped erosions in the bone surface. After the resorption phase there is a reversal phase, coupling formation to resorption. This requires proliferation and differentiation of osteoblast precursor cells and accumulation of the new osteoblasts in the resorption cavity. This phase is followed by the synthesis of osteoid and its subsequent mineralization (formation phase) by osteoblasts. Finally, most of the osteoblasts become inactive bone lining cells on the bone surface (quiescence phase). Some osteoblasts however become incorporated in the mineralized bone. These cells, then called osteocytes, are thought to communicate with the osteoblasts and to initiate in this way resorption or formation.¹

Epidemiology

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and increased fracture risk.² Osteoporosis has largely been thought of as a problem affecting women, while the disease and its consequences in men are often under recognized. Although less frequent than in women, male osteoporosis is associated with a significant burden in terms of economic cost, morbidity and even mortality. The significance of osteoporosis in men can be quantified in assessing the incidence of osteoporotic fractures and the prevalence of low bone mineral density (BMD).

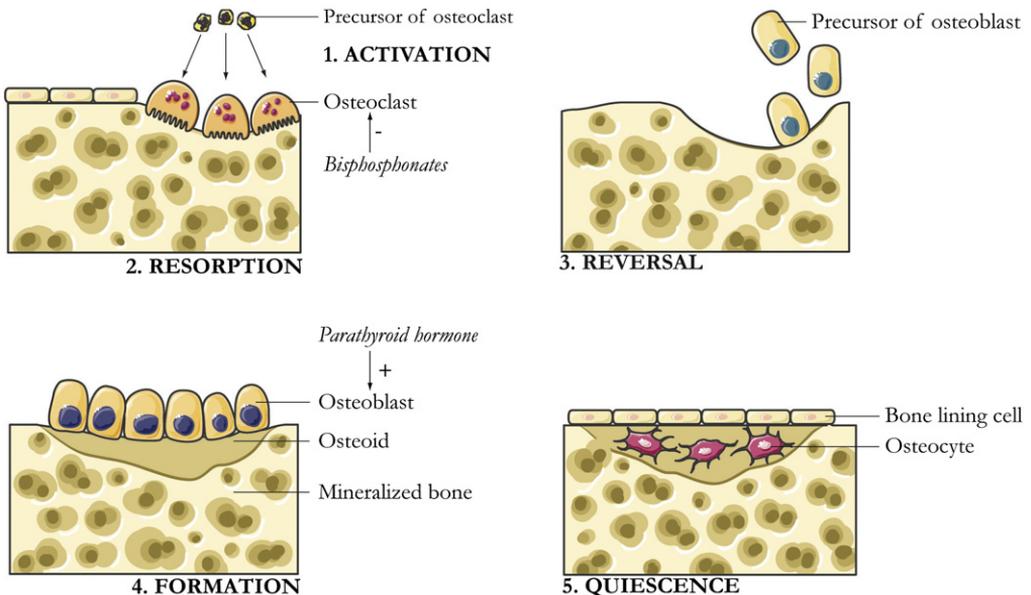


Fig. 1. Five phases of bone remodeling with target of action of bisphosphonates and parathyroid hormone. Figure produced (adapted from) using Servier Medical Art.

Incidence of osteoporotic fractures in men

Fracture incidence in men follows a bimodal distribution: a peak between 15 and 45 years affecting mainly long bones, as the result of greater exposure to high-energy trauma at work, in traffic and in sports, followed by an exponential increase in osteoporotic fracture incidence with advancing age. The age-associated increase is similar to that in women, but starts later, after approximately 70–75 years of age, while in women the rise in incidence starts after 55 years of age.^{3,4} The combination of this delay and the shorter life span in men explains the increased risk of fracture in women compared to men.⁵

Nevertheless, fracture risk in men is substantial: from age 50 onward, one in three osteoporotic fractures occurs in men with a lifetime risk of any osteoporosis-related fracture close to 15% (versus 40% in women).^{6,7} Moreover, in older men, fracture-related morbidity and mortality appear to be even higher than in women and because of the ageing of the population, the number of osteoporotic fractures in men is expected to increase dramatically in the future. The higher rate of fracture-related mortality in men may be the result of more comorbidities in men at the time of fracture, suggesting men with osteoporotic fractures are more frail than women.⁸

Hip fractures

Although age-specific incidence rates of hip fracture in men are about half those in women, only approximately 30% of all hip fractures occur in men, because of the higher life expectancy in women.⁹ In both genders, the incidence of these fractures rises exponentially with ageing, with the majority in men occurring over the age of 80 years.⁵ The epidemiologic pattern of hip fracture occurrence in men is influenced by race and geography, with particularly high incidences in Caucasian men in Northern Europe and North America and lower incidences in Asian and African men as well as black men in North America.^{10,11}

Of all osteoporotic fractures in men, hip fracture contributes most to the burden of osteoporosis in terms of morbidity and mortality. Within one year after hip fracture, 50% of men require institutionalization and only 20% return to their pre-fracture level functional independence.¹² Mortality in male hip fracture patients is about three times higher than in age- and sex-matched controls and is two- to four-fold higher than in women.^{13–15} A recent meta-analysis of prospective cohort studies that assessed mortality in women (22 cohorts) or men (17 cohorts) aged 50 years or older with hip fracture showed that the relative hazard for all-cause mortality in the first three months after hip fracture was 5.75 (95% CI, 4.94–6.67) in women and even 7.95 (95% CI, 6.13–10.30) in men. Excess mortality decreased substantially over time, but did never return to rates seen in age- and sex-matched controls, and, at any given age, excess mortality after hip fracture was higher in men than in women.¹⁶ This excess mortality among male patients may reflect more comorbidities in men at the time of fracture, but persists even when controlling for age and comorbidities, which means male gender in itself is an additional and independent risk factor for hip-fracture-associated mortality.^{17,18}

Vertebral fractures

Of all clinical vertebral fractures, characterized by sudden back pain and confirmed on thoracic or lumbar spine radiographic examinations, approximately 20% occur in men.¹⁹ A significant proportion of these fractures occur in middle-aged men, often as a result of severe trauma, while moderate or no trauma is more often reported in women.¹⁹ Silent vertebral deformities, only revealed by radiological screening, are more prevalent in men than in women, at least up to the age of 65 years. From 65 years of age on, this trend is reversed since the age-standardized incidence of silent vertebral deformities in men increases less than in women.²⁰ Osteoporosis is the main cause of vertebral deformities in men, although the relatively high prevalence in the younger age group suggests physical trauma as another important factor.²⁰ Geographic variations as observed in the incidence of hip fractures also exist in vertebral fractures, but differences are smaller and not statistically significant.²¹

Compared with hip fractures, vertebral fractures in men are less disabling, but, as they can cause back pain, height loss, kyphosis and impaired mobility, they can have a substantial negative impact on function and quality of life.^{22,23} Vertebral fractures also predict the occurrence of other osteoporotic fractures²⁴ and are associated with a significantly higher mortality in men than in women. In a 5-year

prospective study in Australia, age-standardized mortality ratios were 2.38 (95% CI 2.17–2.59) in men and 1.66 (95% CI 2.03–2.32) in women, respectively.⁸ Radiographic vertebral deformities have also been associated with excess death, although the risk is lower than in men with clinical vertebral fractures. For example, a 10-year population-based study of 598 individuals found the risk of mortality in men with prevalent vertebral deformities to be significantly higher than in age- and sex-matched controls (hazard ratio 2.4; 95% CI 1.6–3.9).²⁵

Other osteoporotic fractures

The incidence of osteoporotic fractures of the proximal humerus, humeral shaft, clavicle, scapula, sternum, rib, pelvis and ankle increases with age in men as it does in women. These fractures are predictive for the occurrence of fractures at hip and vertebrae and some (like fractures of proximal humerus, pelvis and multiple ribs) have been associated with excess mortality.⁸ The incidence of distal forearm fractures is also characterized by an age-related increase, but remains six times lower than in women.²⁶ Distal forearm fractures are not associated with excess mortality, but the association with other osteoporotic fractures is even stronger than in women.²⁷

Prevalence of osteoporosis in men based on bone mineral density

The diagnosis of osteoporosis continues to be largely based on BMD measurement by dual-energy X-ray absorptiometry (DXA). The 1994 World Health Organization (WHO) classification system—although, in principle, only intended for Caucasian postmenopausal women—defines osteopenia and osteoporosis as bone densities at the lumbar spine or the proximal femur of at least -1 or -2.5 SD below the peak bone mass of a young healthy woman, respectively.²⁸ These thresholds have been validated as markers for fracture risk in postmenopausal white women, but not for use in men. There is some ongoing controversy whether gender-specific T-scores should be used, as will be discussed below. Prevalence of osteoporosis in men aged >50 years is 3–6% when using a male normative database compared to only 1–4% when based on a female reference base. In women aged >50 years, the prevalence of osteoporosis is 13–18%.²⁹

Pathophysiology

Bone accrual occurs gradually during childhood, but accelerates during puberty. In men, this rapid increase starts later, but is greater and takes longer than in women. Eventually, at skeletal maturity, men will reach a greater peak bone mass.³⁰ This greater peak bone mass in men is due to the development of larger bones because of greater periosteal bone expansion. The larger bone size of men leads to biomechanically stronger bones and reduces fracture risk.³¹ Larger bones in men explain their greater areal bone mineral density (aBMD, in g/cm^2) as measured by DXA, but volumetric bone mineral density (vBMD, in g/cm^3), measured by quantitative computed tomography (qCT), is similar in men and women.³² Most recent evidence also showed that trabecular bone parameters (trabecular bone volume fraction, number and thickness) do not change in girls during puberty, but trabecular bone volume fraction and thickness significantly increase in boys from late puberty onward, resulting in a higher trabecular bone mass in boys compared to girls.³³ Trabecular bone density, however, does not differ between sexes.³⁴

The decline in bone quality with advancing age starts with trabecular bone loss, beginning in the third decade in women and men. After menopause, the trabecular bone loss accelerates, while after midlife in men trabecular bone loss attenuates at the distal radius and tibia, but not at the spine.³² Trabecular bone loss consists of loss of individual trabeculae in women, and of trabecular thinning in men due to the gradual decline of bioavailable testosterone. Trabecular thinning has less impact on bone strength than loss of individual trabeculae, partly explaining lower fracture risk in men.³⁵ In both sexes, cortical bone loss begins after midlife, around 65–70 years. In men, the slope of the decrease of cortical BMD is less than in women, due to the progressive decline of sex steroids in ageing men instead of an equivalent of menopause with abrupt deficiency of sex steroids.³² A concurrent increase in periosteal bone expansion with outward cortical displacement partly compensates for cortical thinning. This periosteal bone formation is greater in ageing men than in women and further contributes to

the lower fracture risk in men.³⁶ Overall, differences in bone fragility and osteoporotic fracture risk between women and men are explained by differences in bone geometry (smaller bones in women) and differences in bone loss (more age-related decreases in trabecular and cortical vBMD with less compensatory periosteal expansion in women).

Estrogens and androgens have traditionally been thought to regulate bone turnover in women and men, respectively. At menopause, abrupt estrogen deficiency leads to increased bone resorption and loss of trabeculae, with a dramatic increase in fracture risk. In contrast, levels of bioavailable testosterone decline more gradually in ageing men, with no phase of rapid bone loss in mid-life, but slow trabecular thinning. Only in the context of abrupt decline of androgens, as with androgen depletion therapy in prostate cancer, accelerated bone loss with a sharp increase in fracture risk occurs in men.³⁷ As a result, androgens have long been considered key determinants of bone turnover regulation in men. However, the case report of a man with absent estrogen receptor and the observation that estrogen treatment reduces bone turnover and increases bone density in men with deficiency of the aromatase enzyme (which converts testosterone to estradiol), suggested that estrogens might be essential and even more important than androgens in maintaining male skeletal integrity.^{38–40} In line with this concept, several reports found bioavailable estradiol to be more strongly associated with BMD and to be a better predictor of bone loss and fracture incidence than bioavailable testosterone [for review, see Ref. ⁴¹]. This was recently illustrated in 3141 men participating in the European Male Ageing Study (EMAS), a large multicenter population-based study: higher free and total estradiol but not testosterone were independently associated with bone health, as assessed by calcaneal quantitative ultrasound (QUS) or DXA.⁴² Growing evidence suggests a potential threshold for estradiol to prevent bone loss and fractures in men. With ageing, an increasing proportion of men have estradiol levels below this threshold, with a consequent increase in bone loss and fracture risk.⁴¹ While these findings suggest that estrogen may play a dominant role in regulating bone resorption in ageing men, androgens might still be important in male skeletal homeostasis. As Leder et al. demonstrated in an experiment of alternating blockade and replacement of estrogens and androgens in men, both androgens and estrogens contribute to inhibiting bone resorption.⁴³ In orchidectomized male rodents, stimulation of estrogen receptor- α preserves trabecular and cortical bone, whereas stimulation of the androgen receptor maintains trabecular bone mass [for review, see Ref. ⁴⁴]. However, any impact of androgens on fracture risk is likely to be (at least partly) independent of BMD. Along other effects, testosterone may reduce fall risk in men by enhancing muscle mass and muscle strength. Further studies are required to clarify the impact of testosterone levels on fracture risk and to better understand the role of sex steroids in the regulation of bone turnover and bone loss (including the potential for threshold levels of sex steroids and their association with increased rates of bone turnover, bone loss and fractures).

Further research is also needed to assess the role of sex hormone binding globuline (SHBG) in male skeletal homeostasis. A number of studies found that SHBG, of which the concentrations rise during ageing, is inversely associated with BMD.⁴⁵ It is generally accepted that the increasing levels of SHBG in ageing men contribute to bone loss by limiting the biological availability of the active fractions of sex steroids. In a recent study by Leblanc et al. free estradiol and SHBG but not free testosterone were independently associated with fracture risk. Although low free testosterone was not associated with increased fracture risk, men with low free testosterone and high SHBG did have an increased fracture risk.⁴⁶ Overall, these findings suggest that the impact of SHBG on BMD might not be fully explained by reduced exposure to the biologically active fractions of sex steroids. Consistent with the inverse relationship between SHBG and DXA-assessed bone density, SHBG was found to be negatively associated with calcaneal QUS parameters as well.⁴²

Etiology of osteoporosis in men

In some studies, in more than 50% of men with osteoporosis, the disease is the result of an identifiable cause that results in bone loss and bone fragility. In postmenopausal women with osteoporosis, this is the case in merely 20–30%.⁴⁷ When, after careful screening, no underlying cause can be identified, male osteoporosis is referred to as ‘age-related osteoporosis’ in men older than 70 years and as ‘idiopathic osteoporosis’ before the age of 70.

Secondary osteoporosis

The most common causes of secondary osteoporosis are glucocorticoid excess, hypogonadism and excessive alcohol consumption. Other etiologies are gastro-intestinal malabsorption syndromes, renal insufficiency, chronic respiratory disorders, rheumatoid arthritis, malignancy, anemia, hyperthyroidism or excess thyroxine, hyperparathyroidism, anticonvulsants, smoking and immobilization.

Endogenous or exogenous glucocorticoid excess can be revealed in almost 20% of osteoporotic men.⁴⁷ It leads to muscular atrophy, secondary hypogonadism and osteoblast insufficiency by increased apoptosis of osteoblasts and osteocytes.⁴⁸ Van Staa et al. demonstrated that daily intake of prednisolone 5 mg/day (or equivalent) reduces BMD and increases the risk of vertebral and non-vertebral fractures. Fracture risk starts to increase within 3–6 months after initiating oral corticosteroid therapy and gradually declines after discontinuation.⁴⁹

Hypogonadism as induced by chemical or surgical castration is a well established cause of osteoporosis in men.³⁷ Some degree of—mostly less severe—male hypogonadism is also found in about 15% of osteoporotic men, although this prevalence may vary according to the cut-off point to define hypogonadism.⁴⁷ Increased fracture risk in men on androgen depletion therapy indicates the critical role of androgens for maintenance of skeletal status in men.³⁷ However, as discussed, increased bone turnover and reduced bone density in men with deficiency of the aromatase enzyme suggest that at least part of the androgen action is mediated by estrogens.⁴⁰

Excessive alcohol consumption is responsible for 15% of cases of osteoporosis in men as well.⁴⁷ The effect on fracture risk and BMD depend on daily intake. Drinking no more than two units a day may decrease the risk of falls and may (slightly) improve BMD.⁵⁰ The underlying mechanism of this effect of alcohol remains to be clarified, but it is possible that certain nutrients in alcoholic drinks have a beneficial effect upon bone.⁵¹ Three or more units of alcohol a day is associated with an increase in fracture risk, probably potentiated by an increased risk of falls. Excessive alcohol consumption is also associated with lower BMD levels due to nutritional deficiency in alcoholics and due to a direct toxic effect of alcohol on osteoblasts.⁵²

About 8% of osteoporotic men have *idiopathic hypercalciuria* (≥ 3 –4 mg/kg/day or 300 mg/24 h).⁵³ This increase in calcium excretion can be due to an increase in intestinal absorption of calcium resulting from an alteration in vitamin D metabolism, an increase in bone resorption or reduced renal reabsorption of calcium, but the underlying mechanisms are not elucidated.^{47,54}

Smoking is associated with elevated bone resorption resulting in decreased BMD. In smokers, low 25-hydroxyvitamin D with secondary hyperparathyroidism may partly explain the effect of tobacco on bone turnover. However, the mechanism responsible for the low 25-hydroxyvitamin D in smokers remains to be clarified, but this could be a lower vitamin D dietary intake, a reduced exposure to sunlight because of sedentary lifestyle of smokers or, which has never been studied, an effect of tobacco smoking on cutaneous vitamin D synthesis or its intestinal absorption.⁵⁵

Adults with type 1 *diabetes mellitus* have a decreased bone mass and an increased fracture risk compared with adults without diabetes. These patients have a low bone turnover with reduced bone formation due to low levels of insulin and insulin-like growth factor-1 (IGF-1) which impairs osteoblastic maturation and function.⁵⁶ Patients with type 2 diabetes mellitus usually have a normal or increased bone mass. The obesity-induced relative insulin resistance in these patients leads to increased levels of insulin and IGF-1 which increases proliferation and function of osteoblasts. However, despite their normal or even high bone mass, patients with type 2 diabetes mellitus are at risk of fractures, due to other factors such as diabetic neuropathy, sarcopenia, visual impairment and an increased bone fragility due to the accumulation of advanced glycation end products (AGE) in collagen as a result of hyperglycemia.⁵⁷

Age-associated osteoporosis

Ageing is the major determinant of fracture incidence in men and women. In ageing men, the composite effects of reduced activity, lower muscle mass and several age-related endocrine events contribute, to varying degrees, to the development of osteoporosis. These age-related endocrine

changes include declining levels of sex steroids, changes in the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis and changes in the vitamin D-parathyroid hormone system (PTH).

As already discussed, recent findings suggest that estrogens play a major role in regulating bone turnover in ageing men, but it is likely that both androgens and estrogens contribute to fracture occurrence.

The age-related decrease in levels of GH and IGF-1 is associated with reduced bone density.⁵⁸ It is possible that estrogen action on bone is, at least in part, related to these changes in the GH-IGF-1 axis. Reduced secretory capacity of the pituitary gland in ageing men blunts GH pulsatile secretion. This in turn decreases also the hepatic production of IGF-1 and IGF-binding protein 3, which results in an increased SHBG secretion and increased binding of SHBG to sex steroids with reduced bioavailability of sex steroids.⁵⁹ At least in rodents, the effects of estrogen on bone are often associated with reduced levels of IGF-1.^{60,61} However, the extent to which estrogen action on bone in humans is related in changes in the GH-IGF-1 axis requires more research.⁴⁴

In elderly men, low dietary calcium intake and reduced vitamin D synthesis due to impaired renal function and decreased sunlight exposure lead to a negative calcium balance. This stimulates the secretion of PTH and induces age-related secondary hyperparathyroidism with increased bone loss.⁶² Together with an increased risk of falling due to vitamin D insufficiency, this results in an increased fracture risk. Vitamin D has indeed been linked with muscular strength and falls. Receptors for vitamin D are expressed in human skeletal muscles, with expression decreasing significantly with age.^{63,64} This results in loss of muscular strength in older people with an increased risk of falling, as several clinical studies have demonstrated.⁶⁵

Idiopathic osteoporosis

Idiopathic osteoporosis usually presents as one or more symptomatic vertebral fractures in young men (aged 30–70 years), but also cortical fractures (stress fractures of lower extremities or hip fractures) may occur. Idiopathic osteoporosis is due to osteoblast dysfunction, which decreases osteocalcin production and increases production of factors stimulating osteoclast activation. This leads to a negative bone balance at the level of the individual bone remodeling units, resulting in osteoporosis.⁶⁶ Histomorphometry in idiopathic osteoporosis is characterized by reductions in bone volume, trabecular thickness, wall thickness and osteoid thickness.⁶⁷

Hormonal (low estradiol levels and low IGF-1 concentration) and genetic factors (LRP5 gene mutations) may contribute to idiopathic osteoporosis.^{67–69} Indeed, in patients with idiopathic osteoporosis, a family history of osteoporosis is not uncommon.⁷⁰ Genetic determinants account for 50 to 80% of the inter-individual differences in peak bone mass in men and women. Although most of the studies on the genetics of osteoporosis have been performed on women, there is strong evidence of an important genetic component in osteoporosis in men as well.⁷¹ Among others, a single nucleotide polymorphism (SNP) affecting an Sp1 binding site in the type 1 collagen gene and polymorphisms within the vitamin D receptor, aromatase or IGF-1 genes have been described to be associated with low peak bone mass in men.⁷²

Diagnostic evaluation of men suspected of osteoporosis

Guidelines for the diagnostic evaluation of male osteoporosis are not as well validated as in postmenopausal osteoporosis.

Clinical assessment

Clinical assessment consists of a careful medical history and clinical examination to identify underlying causes of bone loss. The medical history should address family and fracture history, (im) mobility, calcium and vitamin D intake, medications, alcohol intake and tobacco use. Clinical examination focuses on height and dorsal kyphosis as a marker of the degree of spinal osteoporosis, body mass index as a risk factor for osteoporosis, and signs of hypogonadism, alcohol abuse and glucocorticoid excess. In case of a history of falls, an evaluation of gait and balance is needed as well.

Laboratory evaluation

Laboratory evaluation is important for the evaluation of secondary causes of osteoporosis in men. Initial biochemical evaluation should include a complete blood count, serum calcium (corrected for albumin), phosphorus, creatinine, liver transaminase, thyroid-stimulating hormone (TSH), 25-hydroxyvitamin D and total and free testosterone to exclude hypogonadism. Although several recent reports suggest that serum estradiol levels are more closely associated with BMD than testosterone, the clinical value of measuring estradiol concentrations remains uncertain in men. Current immunoassays are indeed not able to measure low male estradiol concentrations accurately. More sensitive techniques such as mass spectrometry however are promising in this respect.

Depending on the clinical context, additional laboratory tests may include a 24-h urine calcium and creatinine excretion to exclude idiopathic hypercalciuria, as well as serum and urine electrophoresis in case of suspicion of multiple myeloma, prostate specific antigen (PSA), intact serum PTH and celiac antibody testing. A 24-h cortisoluria and/or low dexamethasone suppression test may be needed when there is clinical suspicion for Cushing's disease.

More specialized are the markers of bone turnover, such as serum osteocalcin, serum CTX (C-telopeptide of type 1 collagen) and urinary collagen cross-links. Elevated bone turnover may be associated with increased bone loss and fracture risk independent of BMD, but since the additional value of these tests in the individual patients remains unclear, routine measurement is not recommended.⁷³

BMD measurements

The 1994 World Health Organization (WHO) classification system, intended for Caucasian postmenopausal women, defines osteoporosis as a BMD value at the lumbar spine or the proximal femur of at least -1 or -2.5 SD below the peak bone mass of a young normal woman.²⁸ Key question is whether osteoporosis in men needs to be defined as a bone density of -2.5 SD below male or female peak bone density. Since some data suggest that men and women with similar absolute bone density are at similar risk for fracture, many experts recommend the use of a female normative database. Others have argued that, since bone size in men is larger than in women, men have a higher peak bone density and the use of female reference ranges (i.e., comparing males to female normal values) may result in under diagnosis of osteoporosis in men.⁷⁴ Moreover, some data suggest that men fracture at higher BMD than women.⁷⁵ As a result, the International Society for Clinical Densitometry (ISCD) has recommended the use of reference ranges of young men to diagnose osteoporosis in men age 50 and older.^{74,76} In men younger than age 50, Z-scores should be used when reporting BMD results.^{76,77}

Less controversial is the fact that BMD should be measured at both the spine and hip in all patients. Spinal degenerative changes, found in 60% of women over 70 years and in an even higher proportion of men, artefactually increase spine BMD, whereas the hip is much less affected.⁷⁸ In men over the age of 65–70 years, BMD assessment should therefore systematically include a measurement taken at the hip. Some authors have suggested including a forearm BMD in older men, but the ISCD does not share this recommendation.⁷⁹

However, even when using male database, DXA has low sensitivity for fracture and, as in women, the majority of fractures occur in men with a bone density value above the -2.5 SD threshold. For example, in a prospective population-based cohort study of 7806 men and women aged 55 years and older, 79% of all non-vertebral fractures occurred in men with a T-score above -2.5 .⁸⁰ This shows that factors other than BMD contribute to absolute fracture risk.⁸¹ In particular, an existing osteoporotic fracture is the most significant predictor of future fracture risk, doubling fracture risk compared to persons with no previous fractures.^{25,82} The FRAX[®] algorithm, developed by the WHO Collaborating Centre for Metabolic Bone Disease at Sheffield, UK, integrates the weight of various clinical risk factors for fracture risk, with or without information on BMD at the femoral neck. The FRAX[®] algorithms estimate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) based on age, sex, weight, height, previous fragility fracture, parent history of hip fracture, secondary osteoporosis, rheumatoid arthritis, use of glucocorticoids, current smoking and alcohol intake of three drinks per day or more. The FRAX[®] models have been developed from studying nine population-based cohorts from different regions of the world,

since clinical risk factors as well as fracture probability varies geographically. At present, FRAX[®] algorithms are available for Argentina, Austria, Belgium, China, Finland, France, Germany, Hong Kong, Italy, Japan, Lebanon, New Zealand, Spain, Sweden, Switzerland, Turkey, UK and US.⁸³

The 2010 NOF (National osteoporosis foundation) Clinician's Guide recommends DXA in men with specific conditions (e.g., rheumatoid arthritis) or on specific medications (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for \geq three months) that may predispose to bone loss, in men age 70 and older regardless of clinical risk factors (because of the risk of hip fracture in this age group) as well as in men age 50–70 when they have a prior fragility fracture or because of clinical risk factors.²

Currently, T-score based criteria remain the basis for most therapeutic decisions in men and women. Nevertheless, consensus is increasingly building that treatment decisions should be based on assessments of absolute fracture risk instead of BMD alone. Recent recommendations of the NOF suggest treatment in postmenopausal women and men aged 50 years and older, who have a hip or vertebral fracture, a T-score ≤ 2.5 at the femoral neck or spine without secondary causes, or a T-score between -1.0 and -2.5 with a 10-year probability of a hip fracture $\geq 3\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$, based on the US-adapted WHO algorithm.²

Treatment

The key objective of osteoporosis treatment, in men as in women, is to reduce fracture risk. This is achieved not only by therapies that improve bone quality, but also by dealing with the secondary causes of osteoporosis, as when discouraging smoking or excessive alcohol intake. Moreover, since sarcopenia (the age-related decline in muscle mass and muscle strength) contributes to falls and fracture risk in ageing men, physical activity should be recommended as well. Supplementation of calcium and vitamin D is essential in ageing men who develop an age-related secondary hyperparathyroidism due to a negative calcium balance. Calcium and vitamin D suppress PTH and reduce bone loss. A recent meta-analysis in 63 897 men and women aged 50 years and older confirmed that treatment with calcium and vitamin D significantly reduces the risk of fractures of all types by 10–15%.⁸⁴ Dietary calcium intake should be around 1500 mg and a vitamin D intake of 800 IU daily is required.

Although several trials of osteoporosis therapies in men have shown improvements in BMD, conclusive evidence-based data on the anti-fracture efficacy of pharmacologic interventions in men is not available. However, from the mechanism of bone loss and from the available evidence, there is no reason to assume that men would respond differently from women to pharmaceutical interventions and most common pharmacological therapies (bisphosphonates and PTH) seem to be as effective in men and women.

Bisphosphonates

Bisphosphonates bind to calcium-containing crystals (hydroxyapatite). During bone resorption phase bisphosphonates are released from the bone mineral. They are taken up by osteoclasts and inhibit their activity by incorporating into ATP and generating metabolites which induce apoptosis of osteoclasts (bisphosphonates without nitrogen) or by inducing changes in the cytoskeleton, leading to inactivation of osteoclasts (nitrogen-containing bisphosphonates) (Fig. 1).

Several trials in men with osteoporosis found bisphosphonates to increase BMD and some also provided evidence for a reduction in fracture incidence. In a two-year, randomized, double-blind, placebo-controlled trial in 241 eugonadal or hypogonadal men aged 31–87 years with osteoporosis, 10 mg of *alendronate* per day significantly increased BMD at all sites (lumbar spine, femoral neck and total body) and reduced the number of radiographic vertebral fractures.⁸⁵ In a similar two-year, randomized, double-blind, placebo-controlled trial in 284 osteoporotic men, the administration of 35 mg once-a-week *risedronate* resulted in a significant increase in BMD of the lumbar spine and proximal femur and in significant reductions in bone turnover markers.⁸⁶ Since this trial had been powered for a BMD endpoint, very few vertebral and non-vertebral fractures and no differences in fracture rates between the risedronate and treatment group were reported. However, another two-year open-label study of 316 men with osteoporosis again showed that treatment with risedronate significantly increased BMD at lumbar spine, femoral neck and total hip, and significantly reduced the

risk of new vertebral fractures. A 60% risk reduction was observed at one year and a consistent 61% risk reduction at two years, but because of the open-label nature of the study, these findings have to be interpreted with caution.^{87,88} A randomized, double-blind, placebo-controlled trial in 2127 men and women with surgical repair of a hip fracture, showed that the annual infusion of *zoledronic acid* within 90 days after repair, was associated with a significant risk reduction of new clinical fractures and with an improved survival.⁸⁹ While the subset of men was too small to allow separate fracture (or mortality) analyses, changes in surrogate endpoints (bone density or bone remodeling) were similar in women and men. In fact, in all bisphosphonate trials, the changes in bone density and bone remodeling in men were in line with those previously documented in women, supporting the concept that treatment efficacy with bisphosphonates is not affected by gender.

Parathyroid hormone

The continuous production of PTH, as is the case in primary or secondary hyperparathyroidism, leads to increased bone loss, but the intermittent administration of PTH increases the number and activity of osteoblasts (Fig. 1).

Teriparatide [rhPTH(1–34)] is known to increase BMD and to reduce the risk of fractures in women with osteoporosis. An 11-month randomized trial in 437 men with osteoporosis showed that daily injection of 20 µg or 40 µg teriparatide similarly increased spine and femoral neck BMD compared with placebo.⁹⁰ Compared with alendronate, lumbar spine BMD increased more in patients receiving teriparatide.⁹¹ A follow-up trial in 355 men who were treated with teriparatide or placebo showed that 18 months after discontinuation of teriparatide, the teriparatide group had a significantly lower risk of moderate and severe vertebral fractures. After discontinuation of teriparatide, BMD gradually decreased but remained significantly higher than baseline and administration of an antiresorptive treatment after discontinuation of teriparatide prevented this decline and even increased BMD.⁹² These findings support the use of sequential therapy of teriparatide followed by an antiresorptive treatment. Combined therapy of PTH with bisphosphonates, on the other hand, appears to blunt the effect of PTH and is not recommended.⁹³

Testosterone therapy

In hypogonadal men, testosterone replacement improves BMD, as was demonstrated in a 36-month trial in 18 hypogonadal men. In this trial, transdermally administered testosterone significantly increased BMD at the spine and hip. Both BMD values reached maximum levels after 24 months of testosterone replacement.⁹⁴

However, in eugonadal ageing men, who represent the vast majority of men with osteoporosis, the use of testosterone is more controversial. In a randomized controlled trial in which 108 men over 65 years of age were randomized to either a testosterone or placebo patch for 36 months, no significant gain in lumbar BMD was observed despite increased concentrations of serum testosterone. Only in patients with low pretreatment testosterone levels (100–300 ng/dL or 3.5–10.4 nmol/l) replacement therapy was associated with a significant increase in lumbar spine BMD.⁹⁵ Similarly, in a small open-labeled trial in twenty-one eugonadal men with idiopathic osteoporosis Anderson et al. observed some increase in lumbar BMD after intramuscular administration of testosterone.⁹⁶ However, since all these trials have been small and of short duration, no firm conclusion on fracture risk reduction is possible at this stage. Moreover, concern persists regarding the long-term side-effects of testosterone replacement, in particular cardiovascular side-effects and the risk of prostate carcinoma. Further studies are required to assess the role and safety of sex steroid replacement. Until then, testosterone replacement cannot be recommended in ageing men with osteoporosis, unless they have significantly lower total testosterone (below 250 ng/dL or 9 nmol/l) as well as symptoms of hypogonadism.⁹⁷

Selective estrogen receptor modulators (SERMs)–selective androgen receptor modulators (SARMs)

With estrogen likely to be the dominant sex steroid in regulating bone turnover in ageing men, low doses of estrogens or SERMs may be considered as osteoporosis therapy. SERMs like raloxifene increase

BMD and reduce vertebral fracture risk in men with prostate cancer on androgen deprivation therapy.⁹⁸ SERMs also decrease bone turnover in healthy middle-aged men with low baseline estradiol levels, which is frequently observed in male osteoporosis.⁹⁹ However, the efficacy of SERMs in eugonadal ageing men remains uncertain and requires further study.

In a preclinical study in orchidectomized rats, Gao et al. demonstrated that a SARM significantly increased total BMD as well as skeletal muscle strength of orchidectomized rats, which was associated with a less pronounced pharmacologic effect in the prostate in comparison with dihydrotestosterone (DHT). In this study a nonaromatizable androgen (DHT) was used to avoid the indirect action of androgens through conversion to estrogen. The used SARM was also nonaromatizable, thus mediating its effect on bone by direct action on the androgen receptor and making comparison with DHT possible.¹⁰⁰

SARMs may reduce fracture risk via a skeletal effect (increasing BMD) and a nonskeletal effect (improving muscle strength) with minimal adverse effect on the prostate.¹⁰¹ However, since further clinical research is needed to assess the skeletal and nonskeletal effects of SARMs and since clinical trials of SARMs are just beginning, their use cannot yet be recommended in men.

Summary

With the ageing of the population, male osteoporosis is an increasingly important health problem: from age 50 onward, one in three osteoporotic fractures occurs in men and fracture-related morbidity and mortality is higher than in women. In men with low BMD, 50% have an underlying cause, most often glucocorticoid excess, hypogonadism or alcohol abuse. Age-related osteoporosis is due to declining levels of sex steroids, changes in the growth hormone-insulin-like growth factor-1 axis as well as in the vitamin D-parathyroid hormone system. Idiopathic osteoporosis (in men aged 30–70 years) is characterized by low bone turnover. Recent findings suggest that estrogen is also the dominant sex steroid in regulating male bone turnover. Low testosterone may be associated with increased fracture risk, but this effect is probably mediated primarily by its nonskeletal action on maintenance of muscle mass and strength. Diagnosis and treatment are based on measurement of BMD, with osteoporosis defined as a T-score of 2.5 standard deviations below average density of the young adult. There is ongoing discussion whether to use male or female reference values and increasing consensus that treatment decisions should be based on absolute fracture risk estimations rather than on BMD alone. The aim of treatment is to reduce fracture risk: by dealing with the secondary causes of osteoporosis, adequate exercise, supplementation of calcium and vitamin D, and, potentially adding osteoporosis medication. Evidence-based data on the efficacy of bisphosphonates and PTH in reducing fracture risk is not conclusive, but convincing. No recommendations can be given on testosterone replacement or the efficacy of SERMs in eugonadal men.

Practice points

- DXA is recommended in all men from 70 years of age on and in men age 50–70 with a prior fragility fracture or clinical risk factors.
- Treatment decisions should be based on assessments of absolute fracture risk and not on BMD alone.
- Supplementation of calcium and vitamin D is essential in ageing men to prevent age-related secondary hyperparathyroidism.
- Bisphosphonates and PTH seem to be as effective in men as in women and should be given to men with DXA-documented osteoporosis, a prior fragility fracture or high absolute fracture risk as assessed by FRAX[®].
- Testosterone replacement can only be recommended in older men with osteoporosis who have symptoms of hypogonadism as well as total testosterone values below 250 ng/dL (9 nmol/l).

Research agenda

- To establish whether to use male or female normative database in defining osteoporosis in men.
- To gain further insight in the causes of idiopathic osteoporosis.
- To better understand the role of sex steroids and SHBG in the regulation of bone turnover and bone loss, including the potential for threshold levels of sex steroids and their association with increased rates of bone turnover, bone loss and fractures.
- To clarify the role of sex steroids in the maintenance of muscle mass and the potential impact of sarcopenia on the development of osteoporosis in men.
- To formally establish anti-fracture efficacy of pharmacological intervention in a well-designed fracture-endpoint trial.
- To assess long-term efficacy and safety of androgen replacement therapy in ageing men.

Conflict of interest

The authors have no conflict of interest.

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