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EPIDEMIOLOGY AND PATHOPHYSIOLOGY (RA ADLER, SECTION EDITOR)

Idiopathic Osteoporosis in Men

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Abstract Over the last decade, the increasingly significant problem of osteoporosis in men has begun to receive much more attention than in the past. In particular, recent observations from large scale population studies in males led to an advance in the understanding of morphologic basis of growth, maintenance and loss of bone in men, as well as new insights about the pathophysiology and treatment of this disorder. While fracture risk consistently increases after age 65 in men (with up to 50 % of cases due to secondary etiologies), osteoporosis and fractures may also occur in young or middle aged males in the absence of an identifiable etiology. For this category (so called idiopathic osteoporosis), there are still major gaps in knowledge, particularly concerning the etiology and the clinical management. This article provides a summary of recent developments in the acquisition and maintenance of bone strength in men, as well as new insights about the pathogenesis, diagnosis, and treatment of idiopathic osteoporosis.

Keywords Male osteoporosis · Idiopathic osteoporosis · Pathogenesis of male osteoporosis · Diagnosis of osteoporosis in men · Treatment of osteoporosis in men

Introduction

While osteoporosis has been traditionally considered to be a disease of aging women, it is becoming an increasingly important health problem in men. The increased longevity of the population is in part responsible for this observation but enhanced awareness of this problem in men is also noteworthy. Different population-based studies clearly demonstrate that aging in men, similar to aging in women, is associated with dramatic increases in fracture risk [1, 2]. It has been estimated that the lifetime risk of a man suffering an osteoporotic fracture is actually greater than his likelihood of developing prostate cancer [3].

As in women, osteoporosis in men could be due to secondary etiologies requiring careful clinical evaluation (Table 1) [2, 4–7]. The 3 major secondary causes of osteoporosis in men (accounting for up to 40 % of all men with osteoporosis) are alcohol abuse, glucocorticoid excess (most commonly, chronic glucocorticoid therapy and rarely Cushing's syndrome), and hypogonadism [4, 5]. Other important etiologies to rule out include excessive thyroid hormone exposure (either hyperthyroidism or overtreatment with thyroid hormone), gastrointestinal disorders (particularly celiac disease), chronic obstructive pulmonary disease, neuromuscular disorders, multiple myeloma or other malignancies, hyperparathyroidism, rheumatic disorders (eg, rheumatoid arthritis), diabetes mellitus, renal insufficiency, HIV infection, and other drugs (anticonvulsants, high-dose chemotherapeutics, selective serotonin reuptake inhibitors) [2, 4–7]. Overall, the prevalence of these secondary causes of osteoporosis is higher in men than in women, exceeding 50 % in many series. In the absence of an identifiable etiology, male osteoporosis is referred to as "idiopathic osteoporosis," particularly in individuals less than 65–70 years of age. Of course, there are men over 70 with bone fragility whose cause is not known. The older the patient, however, the more likely attribution of cause will be related to age-related bone loss and not to a specific or unknown condition. Moreover, as in women, other factors, such as smoking, physical inactivity, excessive leanness, and chronically low calcium intake may accelerate age-related bone loss or other etiologic cause in men [5].

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This article reviews what is known about the factors in men that lead to acquisition, maintenance and loss of bone, as well as new insights about the pathogenesis, diagnosis, and treatment of idiopathic osteoporosis in men.

Epidemiology

Prevalence of Fractures

The lifetime risk of any clinical osteoporotic fracture of the hip, vertebrae, or wrist in white men is 13 % compared with 40 % in women [8]. It has been estimated that worldwide in the year 2000 about 30 % of hip, 20 % of forearm, and 42 % of clinical vertebral fractures occurred in men [1]. These figures are likely to vary according to the country studied. For example, in Australia 1 in 3 men over 60 will suffer a fracture due to osteoporosis [9]. Moreover, a 0.3 % increase in the 10-year probability of hip fracture has been described in men for each 10° increment in latitude, thus, supporting a protective role of sunlight exposure, or other latitude-dependent effect, on hip fracture risk [10]. Differences in ethnicity are also relevant, with lower fractures rates described in African and African American men than Caucasian men [11].

As in women, the absolute risk of a subsequent fracture in men increases substantially after the first fracture [12]. From the Australian Dubbo Osteoporosis Study Cohort of community-dwelling men aged 60 years or older, the relative risk of subsequent fractures following a low-trauma fracture was higher in men (relative risk [RR] 3.47; 95 % confidence intervals [CI] 2.68–4.48) than in women (RR 1.95; 95 % CI 1.70–2.25) [12]. Importantly and consistent with other observations in the same cohort, higher mortality rates following all osteoporotic fractures were also observed in more men than women [13–15]. Regarding hip-fractures, a population-based Canadian study showed that after the fracture, either in-hospital mortality rates or 1-year mortality is higher in men than in women (10.2 % vs 4.7 % and 30.8 % vs 37.5 %, respectively) [16]. Moreover, men are less likely to return to independent living than women 1 year after the hip fracture [17].

Generally in men more than in women, fracture incidence follows a bimodal distribution with 2 major peaks [2, 6]. The first peak occurs between 15 and 45 years and is related mainly to traumatic fractures (ie, due to working activities, sports, or traffic accidents) particularly affecting the long bones. In this age range, not surprisingly, men are up to 3 times more likely to sustain a fracture than women [2]. Even though traumatic fractures are not considered as typical osteoporosis-related fractures, the analysis of 2 large US prospective studies provided evidence that high-trauma fractures are associated with low BMD and increased risk of subsequent fracture in older adults of both genders [18]. Moreover, a more recent observation by Amin et al. [19•] demonstrated that in boys, the occurrence of a distal forearm fracture during childhood is associated with an increased risk of subsequent fragility fractures at both major osteoporotic sites (RR 2.6; 95 % CI 2.1–3.3) and remaining sites (RR 1.7; 95 % CI 1.3–2.0). The second peak in fracture incidence occurs in older men and is similar to that observed in women. The age-related peak in fracture incidence, though, starts after age 70, about a decade older that the age-related peak in women. Most fragility fractures in men involve the hip, vertebrae, forearm, and humerus, although fragility fractures at other sites may also occur. Typical low-trauma fractures are also seen in younger men, 40 to 60 years old with idiopathic osteoporosis [20]. With

Table 1 Major causes of osteoporosis in men

Primary osteoporosis
• Idiopathic osteoporosis (<65–70 y)
With low bone turnover
With high bone turnover and hypercalciuria (less frequent)
• Age-related osteoporosis (>70 y)
Secondary osteoporosis
• Alcoholism [a]
• Endocrine disorders [a]
Hypogonadism
Cushing's syndrome
Diabetes (type 1 and 2)
Hyperthyroidism
Hyperparathyroidism (primary or secondary)
• Gastrointestinal disorders [a]
Malabsorption Syndromes (ie, inflammatory bowel diseases, gluten enteropathy)
Primary biliary cirrhosis
Post gastrectomy syndromes
• Chronic obstructive pulmonary disease
• Organ transplantation osteoporosis [a]
• Immobilization
• Neuromuscular disorders
• Systemic illnesses
Mastocytosis
Rheumatoid arthritis
Multiple myeloma
HIV disease [a]
Various other malignancies
• Medication/drug-related
Glucocorticoids [a]
Androgen deprivation therapy
Selective serotonin reuptake inhibitors
Anticonvulsants [a]
Chemotherapeutics
Thiazolidinediones [a]
Thyroid hormone (when used in excess) [a]

[a] These secondary causes of osteoporosis are more likely to present in young men with osteoporosis

greater longevity of men and the increasing growth of the population, the number of men with hip fracture worldwide is estimated to increase markedly in the years to come [21].

Prevalence of Osteoporosis Based on Bone Densitometry

Despite recent progresses in this field, the use of bone mineral density (BMD) to determine the presence of osteoporosis and assess fracture risk in men is not as well standardized as it is in women. According to the WHO criteria, in women the diagnosis of osteoporosis is established when the BMD T-score is −2.5 or less (ie, 2.5 standard deviations below average peak BMD of young healthy women) [22]. Two different diagnostic cut points for osteoporosis have been used in men, based either on the young normal male or young female reference groups. Prevalence rates differ consistently in relation to these cut-points. For example, the prevalence of osteopenia and osteoporosis in men over age 50 from the third National Health and Nutrition Survey (NHANES III) were 28 %–47 % and 3 %–6 %, respectively, using male cut-points while it was lower, 15 %–33 % and 1 %–4 % , respectively, using female cut-points [23]. Prevalence rates are highest for Non-Hispanic whites, compared with Mexican-American and Non-Hispanic black men. Despite the ongoing controversy over which normative database to use in men, it seems intuitively more attractive to use sex-specific reference ranges. Certainly, if one bases the argument on relative risk, the male reference will be preferable. The increase in RR as a function of reduced T-scores is similar for men and women. However, if one uses absolute bone density in g/cm^2 to determine fracture risk fracture risk between men and women for a given absolute bone density in g/cm^2 is the same. Since fracture risk is a function of absolute bone density, not changes relative to baseline, support has been gained to use a universal female database for men and women [2]. Whatever reference database is to be used, it is clear that many more men who sustain a fragility fracture have osteopenic T-scores than osteoporotic ones [24]. This is similar to the work of Siris et al. who showed the "osteopenic" women, perhaps by their sheer greater numbers, had a greater risk of fracture than "osteoporotic" women.

Pathophysiology

Patterns of Bone Growth and Bone Loss in Men

Major differences exist concerning bone accrual and bone loss among men and women, which account for the lower fracture incidence observed in men [25, 26•]. In both genders, bone growth occurs gradually during childhood and accelerates dramatically with puberty. However, men achieve 8 %–10 % greater peak bone mass than women. This increase in bone mass has been detected by convention dual energy X-ray absorptiometry (DXA), a technology that measures areal BMD (grams/cm^2). Larger areal density confers a mechanical advantage because forces are distributed more widely over a surface. It is important to note, however, that true bone density (that is a volumetric index, vBMD, expressed as g/cm^3) at peak bone age is very similar among the sexes. Thus, the increase in peak BMD observed by DXA in males is related to the development of larger bones because of greater periosteal apposition, a process likely to be dependent on the effect of androgens at periosteal bone (a mechanism that becomes operative at puberty and continues throughout life). Consistent with this hypothesis, cross-sectional, and longitudinal studies using peripheral quantitative computed tomography (pQCT) showed up to 40 % larger bone area in young adult men than women [27, 28]. Indeed, during pubertal growth, bone area increases equally in both sexes at central sites but more so in men at peripheral sites, consistent with the view that the degree of periosteal apposition is likely to be site specific. Moreover, more recent evidence from high-resolution pQCT (HRpQCT) shows significant differences in trabecular and cortical bone development at the ultradistal radius between girls and boys during the pubertal growth spurt [29]. While trabecular parameters did not change significantly during puberty in girls, trabecular bone volume fraction and thickness were increased throughout puberty in boys, and these changes were driven mainly by testosterone and IGF-1 levels. There were no differences in cortical thickness or cortical vBMD between boys and girls at the end of puberty. Periosteal and endosteal circumferences increased in both sexes but were higher in boys than in girls.

Of interest, these pQCT studies also indicate that in both genders, the decline in bone mass begins soon, around the third decade at trabecular bone sites, and accelerates in women after menopause. Therefore, in the middle aged man, bone loss proceeds at slower rates, unless a disorder (ie, hypogonadism) or therapeutic castration for a disease like prostate cancer intervenes. Moreover, with aging, bone in men is characterized by trabecular thinning, due to reduced bone formation, rather than increased resorption and trabecular perforation, a characteristic of the postmenopausal woman [30–32]. With thinning, and not loss, of bone trabeculae, bone strength in the vertebral body is maintained to a greater extent than the scenario in the postmenopausal woman. Conversely, cortical bone loss occurs after midlife in both sexes, around 65–70 years [28]. However, periosteal bone formation remains greater in aging men than in postmenopausal women, further contributing to lower fracture risk, which is particularly evident at cortical bone sites [25].

Pathogenesis of Idiopathic Osteoporosis in Men

Aging is the major determinant of osteoporosis and fracture incidence in men either in the presence or in the absence of

comorbidities and secondary causes [25]. However, there is a subset of men with so-called idiopathic osteoporosis who present with 1 or more fractures (generally symptomatic vertebral fractures) and low BMD before the age of 65–70 years. Of interest, a positive family history of osteoporosis has been often described in men with idiopathic osteoporosis, suggesting a major role of genetic factors [33, 34]. Indeed, twin and family studies have shown a predominant genetic effect on peak bone mineral mass acquisition rather than on age-related bone loss in both genders [35]. As in women, male offspring of subjects with osteoporosis show reduced bone mass well before age-related bone loss [33], suggesting the expression of inherited determinants of osteoporotic risk from an early age. Consistent with this postulate, a previous study on male twin-pairs of different ages revealed that intra-pair differences in radial bone mass and width increased with age both in monozygotic and dizygotic pairs [36]. Moreover, a more recent 3-generation study in men demonstrated that sons of men with osteoporosis have reduced bone size and reduced volumetric BMD, despite normal markers of bone remodeling, further reinforcing the view that in men the effect of genetics on bone is mainly growth-related rather than age-related [37]. Following the discovery of mutations in aromatase (*CYP119A1*), estrogen receptor alpha (*ESR1*), and *LRP5* genes in rare syndromes associated with the presence of osteoporosis and fractures in young male individuals [33, 35], polymorphisms in the same genes have been associated with osteoporotic risk in men and particularly in men with idiopathic osteoporosis [38–45]. However, the overall contribution of these genetic variants on BMD variation and fractures risk remains limited.

Although the category is clearly a heterogeneous one (with many different clinical phenotypes having been described) [46], most men with idiopathic osteoporosis present a rather typical clinical and histomorphometric phenotype that differs from age-related osteoporosis. In fact, they often show normal or slightly increased bone resorption but decreased bone formation, due likely to osteoblast dysfunction [47]. This hypothesis has been supported by several histomorphometric and in vitro studies [48–54]. In fact osteoblast cultures from men with idiopathic osteoporosis showed a slower proliferation rate as well as a decreased functional activity with a reduction in the expression of genes related to matrix formation, such as collagen type 1 and osteocalcin [48, 49]. This was consistent with most of the evidence from bone biopsies and HRpQCT analysis of these patients, showing a decrease in bone turnover, bone volume, osteoblast surface, osteoblast number, cortical thickness, and cortical porosity [50–54]. The latter was more severely impaired in osteoporotic patients with a vertebral fracture than in those without fractures [52, 55]. Despite this evidence that suggests osteoblast dysfunction as a major pathogenetic mechanism; circulating levels of sclerostin (an osteocyte product and major inhibitor of wnt/beta-catenin system and osteoblast activity) were surprisingly decreased rather than increased in a single report of 116 men with idiopathic osteoporosis [56].

Most of the structural abnormalities in trabecular and cortical bone of men with osteoporosis have been related to alterations in the endocrine system and particularly to impaired IGF-1 and sex hormone action [2, 5, 6, 57] (Fig. 1). Indeed, even though men do not undergo an equivalent of the menopause, both estrogen and androgen levels, and particularly their free bioavailable fractions, decline slowly but progressively after 50–60 years of age, apparently as a result of complex alterations in reproductive physiology, lifestyle factors, or increases in the levels of sex hormone binding globulin (SHBG) [58–60, 61, 62, 63]. Although direct androgen effects in the adult male skeleton help prevent osteoporosis by stimulation of periosteal cortical bone apposition and muscular strength, there is ample direct and indirect evidence indicating a major role for androgen aromatization into estrogens in the regulation of bone homeostasis in adult men [64–66]. It has been also suggested that threshold concentrations of estradiol may be required to limit age-related bone loss and that up to 40 %–50 % of middle-aged or elderly men might fall below that threshold [64, 66]. Subjects with estradiol levels below that threshold (around 16 pg/mL) exhibit a marked increase in fracture risk [67]. Interestingly, a population-based cross-sectional study using HRpQCT further characterized the age effects on bone microstructure in men as well as its relationship with hormonal variables [57]. In young men (20–39 years), the conversion of thick trabeculae into more numerous, thinner trabeculae observed from young adult to midlife was most closely associated with declining IGF-1 levels. Conversely, sex steroids, and particularly bioavailable estradiol, appeared as the major hormonal determinants of trabecular microstructure in elderly men. However, reduced IGF-1 and estradiol levels have both been often described in different series of men with idiopathic osteoporosis [68–75]. Variation in either SHBG or IGFBPs levels were also reported, which may reduce the amount of free available concentrations of sex hormones and IGF-1 within the bone, respectively [75, 76]. In most of these studies, these hormonal alterations were correlated with the observed impairment of histomorphometric parameters of bone formation. Moreover, a decrease in estrogen receptor alpha protein expression was described in osteoblast and osteocytes from middle-aged men with idiopathic osteoporosis [77]. Thus, in men with idiopathic osteoporosis, an impairment in either IGF-1 or estradiol action on bone (or both) might occur well before the physiological age-related decrease in endocrine function, thus, explaining the presence of low bone mass and fractures at a younger age. To this end, observations in men with idiopathic osteoporosis and their first-degree relatives suggest that these estrogen-related perturbations are at least in part genetically determined and occur mainly during growth [37, 73]. In particular, Lapuevy et al. showed, in a cross-sectional analysis of a large series of cases,

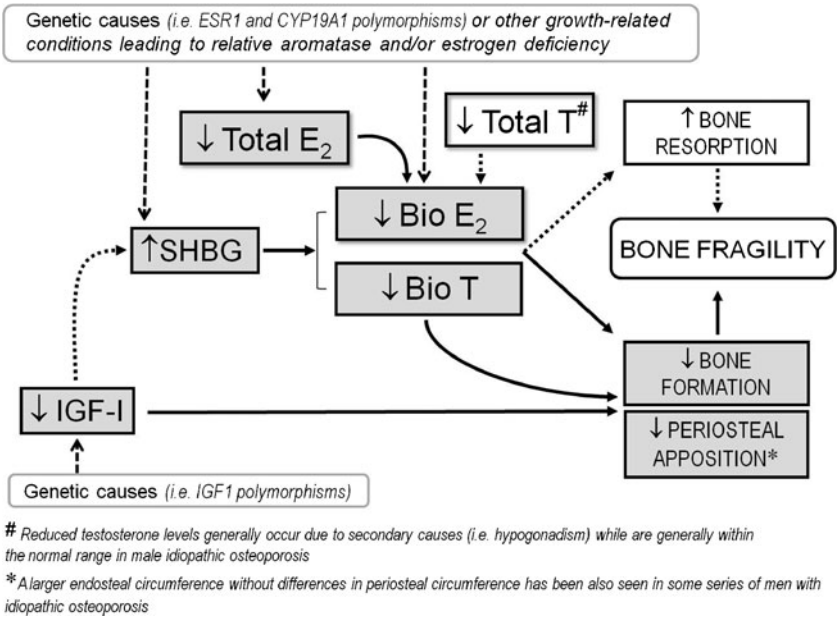

Fig. 1 Major pathogenetic mechanisms of idiopathic osteoporosis in men

that men with idiopathic osteoporosis, compared with age-matched controls with normal bone mass, have lower weight, truncal height, and upper/lower body segment ratio. In addition, they have lower trabecular and cortical vBMD (at the radius and tibia) and smaller cortical areas and thickness due to larger endosteal circumferences [73]. Higher serum SHBG and lower total estradiol, free estradiol, and free testosterone levels, without differences in total testosterone were also demonstrated. Moreover, a similar bone phenotype was present in the sons of these affected men with lower trabecular BMD and a thinner cortex at the radius. These observations suggest a genetic component related to inadequate skeletal maturation and acquisition of peak bone mass in idiopathic osteoporosis which is, at least in part, related to relative estrogen deficiency. This is consistent with some evidence from genetic-association studies in the general population, which reported an association between estrogen levels and polymorphic variation of the aromatase gene in young men before the attainment of peak bone mass [44, 78]. In addition, osteopenia and reduced cortical thickness due to greater endocortical circumference have been described in case reports of young men with aromatase deficiency or loss-of-function mutations of the ESR1 gene [5, 34, 64, 65]. Similarly, the reduction in IGF-1 levels, which can be often observed in men with idiopathic osteoporosis seems to be associated with a particular allelic configuration of the polymorphic microsatellite region of the IGF-1 gene composed of variable cytosine-adenosine repeats 1 kb upstream from the transcription start site. In fact, the frequency of homozygosity for the allele in question, designated 192, in a group of men with idiopathic osteoporosis was twice as high as that in a number of control populations [79].

Other hormonal factors, such as vitamin D insufficiency and increases in serum PTH levels, have been more strictly associated with age-related bone loss and fracture risk in elderly men rather than in men with idiopathic osteoporosis [80, 81]. Finally, it should be noted that certain heterogeneity also exists, since a subset of men with idiopathic osteoporosis shows hypercalciuria together with normal or increased bone turnover, thus, suggesting that different pathogenetic mechanisms might be related to idiopathic bone fragility in middle-aged men [4, 5].

Diagnosis

Since BMD measurement is not a routine test in men (even in the presence of clear risk factors), clinical features such as height loss, kyphosis, fracture, or symptomatic back pain are the most characteristic initial clinical presentations of male osteoporosis. About 40 %–50 % of men diagnosed with osteoporosis will be shown, upon further evaluation, to have a secondary cause of bone fragility. Thus, a detailed screening for secondary causes should be mandatory in the presence of a man with low BMD and/or a fragility fracture. Moreover, in the setting of a fragility fracture, it is necessary to rule out the possibility of a pathologic fracture due, for instance, to a skeletal metastasis or multiple myeloma. After the exclusion of secondary causes, the hypothesis of primary idiopathic or age-related osteoporosis can be considered in subjects aged below or above 65–70 years, respectively.

At present there is no universally validated strategy for therapeutic decision making in men. Decisions regarding treatment should be based on the absolute risk of fracture. Even though the majority of fractures occur in men whose BMD measurements are in the osteopenic rather than osteoporotic range, BMD actually remains a key factor in decision

making. Based on current recommendations, measurement of bone mass by dual energy X-ray absorptiometry (DXA) is generally recommended in men 70 years of age or older, in younger subjects when major risk factors for osteoporosis are evident or in subjects with a previous fragility fracture [7, 82]. The guidelines of The Endocrine Society and the International Society of Clinical Densitometry [83, 84] both recommend the male-specific reference range (−2.5 SD below average peak bone mass for 25-to 30-year-old young men) as a diagnostic threshold. In contrast, the International Osteoporosis Foundation (IOF) recommends the female database for diagnosis and, thus, a T-score −2.5 SD below the peak bone mass of young women, which corresponds to a T-score of approximately −2.75 in the male database [85, 86]. The uncertainty over which referent database to use is a result of a differing opinion as to whether absolute fracture risk or relative fracture risk should be used. Moreover in men younger than age 50, Z-score should be used when reporting BMD results [83], and a standard X-ray of the spine should be considered in case of low BMD levels, particularly when height loss has been reported, in order to assess the presence of asymptomatic vertebral fractures. More recent evidence suggested that the use of pQCT, HRpQCT, and finite element analysis (FEA) could improve fracture prediction in men, allowing a better analysis of bone microarchitecture and strength of trabecular and cortical compartments than densitometry [87–90]. However, these techniques require further validation in prospective studies and are not currently available in clinical practice.

Even though higher levels of bone turnover markers have been associated with greater bone loss in older men [91, 92], a prospective analysis in men aged above 65 years from the Osteoporotic Fractures in Men (MrOS) study did not reveal evidence for an independent association with the risk of hip or nonspine fracture after adjustment for hip BMD [92]. Likewise, the use of these markers for the follow-up of the anti-osteoporotic treatment in men remains controversial and requires more studies. Moreover, in the setting of primary osteoporosis in young or middle-aged men, fractures generally occur with a low bone turnover rate and the assessment of bone markers could be indicated to detect a condition of low bone formation rather than increased bone resorption. The measurement of sex hormone levels and their free bioavailable fractions is of limited clinical relevance in idiopathic osteoporosis and their use should be restricted to exclude the presence of secondary osteoporosis due to hypogonadism.

In order to improve diagnostic accuracy, specific risk-assessment tools such as FRAX (a fracture assessment tool from the WHO) incorporating major clinical risk factors (height, weight, family history of hip fracture, glucocorticoid use, rheumatoid arthritis, alcohol intake, smoking, secondary causes of osteoporosis) with age and eventually hip BMD have been developed for the prediction of fracture risk in postmenopausal women and men 50 years of age or older [93]. The use of this algorithm (with and without BMD) provides a country-specific estimate of 10-year probability of hip fracture and major osteoporotic fractures (clinical vertebral, hip, forearm, or humerus). Based on cost-effectiveness analysis, the NOF in the USA identified a 10-year fracture probability equal or greater than 3 % and 20 %, respectively, for hip and major osteoporotic fractures as being sufficient to justify treatment [94]. However, these guidelines are not universally accepted and recent validation studies from Australia and Canada reported that FRAX algorithm underestimates fracture risk in men [95, 96]. Indeed, in the Australian study the Garvan nomogram (which includes age, sex, number of non-major-trauma fractures since age 50, number of falls in last 12 months, and femoral BMD) was superior to FRAX in identifying fracture patients [95], but it is not known whether this is true for other populations. Conversely, a more recent analysis of the MrOS cohort reported that FRAX risk calculator without BMD was well calibrated to hip fracture but overestimated major osteoporotic fractures in elderly men [97].

Treatment

Therapeutic approaches to osteoporosis in men are less well defined than in women. Most of the pharmacologic agents that are currently available for men with osteoporosis have been previously tested and approved for women. The studies in men, in general, have not had adequate numbers of patients to ascertain a change in fracture incidence. Rather, other surrogate endpoints such as increases in BMD and changes in bone turnover markers have been used. On the whole, however, even without hard fracture endpoints, it seems that the efficacy of these drugs in men is similar to that in women [98, 99•]. While this approach could be reasonable at this stage for the treatment of secondary or age-related osteoporosis in men (conditions which share at least in part similar pathogenetic mechanisms in both genders), major uncertainty remains concerning the treatment of idiopathic osteoporosis in men, which is mainly characterized by a decrease rather than an increase in bone turnover and, which might relate to abnormalities in bone accrual.

Preventive interventions in males are similar to the approach used for women, and apply to all men. They include adequate calcium (1200–1500 mg/d) and vitamin D (400–600 IU/d) intake, avoidance of smoking or excessive alcohol consumption, weight-bearing exercise, and use of fall-prevention programs. However, drug therapy should be initiated in all men at high risk for fracture. Despite the current limitations in defining men at higher fracture risk and the lack of universally validated criteria the use of antiresorptive or anabolic compounds should be indicated in the following conditions: (a) the presence of a fragility fracture (clinical or morphometric vertebral or hip or other major osteoporotic

Table 2 Overview of currently approved medications for osteoporosis in men

Medication	Dosage	Main efficacy outcomes		Approved by		Major adverse events
		BMD	Fractures	FDA	EMA	
Alendronate [c]	Oral : 10 mg/d or 70 mg/w	+		+	+	Gastric, esophageal irritation, musculoskeletal pain (rare)
Risedronate [c]	Oral: 5 mg/d, 35 mg/w, 75 mg twice/m	+		+	+	Gastric, esophageal irritation, musculoskeletal pain (rare)
Zoledronic acid [c]	Intravenously: 5 mg/y	+	+	+	+	Flu-like symptoms (acute phase reaction), hypocalcemia,
Teriparatide	Subcutaneously: 20 mcg/d for 2 y	+		+	+	Headache, dizziness, hypercalcemia, nausea, diarrhea
Denosumab [c]	Subcutaneously: 60 mg/every 6 m	+	(+)[a]	+	(+)[b]	Eczema, cellulitis, hypocalcemia (rare)
Strontium Ranelate[d]	Oral: 2 g/d	+			+	Abdominal discomfort, severe skin eruption (with eosinophilia systemic syndrome, rare), thromboembolism

[a] Antifracture efficacy (vertebral fractures) restricted to a trial in men receiving androgen deprivation therapy for non-metastatic prostate cancer

[b] Approved for the treatment of men at high risk of fracture receiving androgen deprivation therapy for non-metastatic prostate cancer

[c] Rarely reported severe adverse events of osteonecrosis of the jaw and atypical femur fractures have been reported

[d] Recently, strontium ranelate has been associated with cardiovascular events such as myocardial infarction, based on a benefit-risk assessment analysis of pooled data from randomized studies

fractures); (b) presence of a T-score at the lumbar spine, femoral neck and/or total hip that is<−2.5; (c) in the USA for those who have a T-score between −1.0 and −2.5 but in whom FRAX calculates a risk for any type of fragility fracture in the next 10 years >20 %, and for hip fracture >3 %; and (d) long term glucocorticoid therapy [83, 94].

Pharmacologic agents approved by the FDA and/or European Medical Agency (EMA) for the treatment of both primary and secondary osteoporosis in men include different bisphosphonates (alendronate, risedronate, and zoledronic acid), teriparatide and strontium ranelate (Table 2). Alternative beneficial therapies in the presence of idiopathic osteoporosis might also include the use of recombinant human growth hormone, given that abnormalities in IGF-1 system have been associated with the suppression of bone formation in most patients [68–70, 76]. However, this hypothesis has been investigated in a single study in a limited sample (n =29) of men with idiopathic osteoporosis [100].

Antiresorptive Compounds

Bisphosphonate therapy is the mainstay of therapy for male osteoporosis. Alendronate and risedronate are oral amino substituted bisphosphonates that have been shown to increase BMD and to reduce bone turnover markers in men with osteoporosis [101–106]. The randomized placebo-controlled trials for both compounds were not designed or powered to determine anti-fracture efficacy. Indeed, a meta-analysis evaluating cumulative anti-fracture efficacy of randomized controlled trials indicated that alendronate treatment efficiently reduces the risk of vertebral fractures in men with low bone mass or fractures (odds ratio 0.44; 95 % CI 0.23–0.83), but there was insufficient evidence to prove a significant effect on non-vertebral fractures [107]. Similarly, in an open label clinical trial daily treatment with risedronate 5 mg for 2 years reduced the incidence of a new vertebral fracture by 60 % and of nonvertebral fractures by 47 % compared with placebo [106]. Consistent with this observation, risedronate has also been shown to be effective in the treatment of bone loss and the prevention of hip fractures in men >65 years of age who have sustained a cerebrovascular accident [108]. More recently, consistent results with the use of the most potent bisphosphonate, zoledronic acid (administered intravenously at a dose of 5 mg once yearly), were observed in osteoporotic men. This drug was as effective as alendronate in increasing BMD and in reducing bone turnover markers in men with idiopathic osteoporosis or osteoporosis due to hypogonadism [109], while it was superior to risedronate in increasing BMD and reducing bone turnover markers in the treatment and prevention of glucocorticoid-induced osteoporosis [110]. Moreover, in a post-hip-fracture trial performed in a mixed male and female population, zoledronic acid lowered the subsequent clinical fracture rate and decrease mortality compared with placebo [111]. A subsequent gender specific analysis of the same trial confirmed that the BMD increases were of a similar magnitude in men to those observed in women [112]. However, the subset of males was too small to allow a gender specific analysis on fracture and mortality. Of interest, a more recent placebo-controlled trial was specifically designed to determine a difference in fracture endpoints in men and was performed in a sufficiently large sample of 1199 men, 50–85 years old, with primary or hypogonadism-associated osteoporosis [113••]. Overall, patients treated with zoledronic acid had a 67 % reduction in RR of one or more new morphometric vertebral fractures and a 3.3 % risk reduction in absolute risk

(4.9 % vs 1.6 %; $P=0.0016$) after 2 years in comparison to the placebo group. Furthermore, the active treatment group experienced fewer moderate to severe vertebral fractures and less height loss in comparison with placebo. Results were similar in men with osteoporosis due to hypogonadism and in men with normal testosterone levels. No difference was seen in serious adverse events between the zoledronic acid and placebo groups. Although the power of the study to detect a reduction in the risk of nonvertebral fracture was modest, rates of nonvertebral fracture were consistently lower with zoledronic acid than placebo, and with similar point estimates to that reported in larger studies involving women. Moreover, since a similar efficacy was also observed concerning the effects of zoledronic acid on BMD and bone turnover markers between this trial in men and previous trials in postmenopausal women, this data provided further support for the precept that antiresorptive treatments are indeed effective in both genders.

A antiresorptive class, represented by Denosumab (a monoclonal antibody against RANKL, the major activator of osteoclast recruitment and activity) has been recently approved by the FDA and EMA to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer, following the positive outcomes of a large randomized controlled trial [114]. Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (relative risk, 0.38; 95 % confidence interval, 0.19 to 0.78; $P=0.006$). Moreover, following the efficacy results in increasing BMD and suppressing bone resorption reported by a recent 12 months placebo-controlled, phase 3 study in men with low BMD [115], in September, 2012 denosumab has received an indication in the USA for men with osteoporosis at high risk for fracture.

Despite the positive results on BMD of testosterone supplementation in eugonadal man with osteoporosis [116], evidence for fracture efficacy is weak even in the presence of hypogonadism [117]. Thus, the recent recommendations of The Endocrine Society emphasize the use of bisphosphonates or other approved therapies even for hypogonadal men [83]. Interestingly, in eugonadal osteoporotic men, the observed increase in BMD and the reduction in bone turnover following testosterone supplementation positively correlated with change in estradiol, but not in testosterone levels, further indicating that the skeletal effects of androgens in men are mainly due to their conversion to estrogens [116]. These data also provide a rationale for the use of selective estrogen receptor modulators (SERMs). However, available data with raloxifene in normal men is restricted to bone turnover with variable results depending on circulating estrogen concentrations (bone resorption markers were reduced if baseline estradiol levels were low) [118, 119]. Conversely, in men receiving androgen deprivation therapy for prostate cancer, treatment with either raloxifene or toremifene prevented bone loss in comparison to placebo [120, 121] and, in case of toremifene, also decreased vertebral fracture risk by 50 % [122]. Despite this evidence, further information is required and, thus, at this stage, the use of SERMs for male osteoporosis is not recommended.

Drugs with Osteoanabolic Activity on Bone

The development of drugs with osteoanabolic action on bone has extended our therapeutic options for osteoporosis in women as well as in men. These medications can stimulate bone formation and in some instances they may restore bone quality and quantity to a greater extent that can be obtained with inhibitors of bone resorption. To date, parathyroid hormone and its 1–34 analog represent the only osteoanabolic agents available in many countries (with a maximum overall duration of 24 months) for the treatment of osteoporosis in both genders. The full length, native molecule (PTH 1–84) and its 1–34 fragment (Teriparatide which is the only anabolic compound approved by the FDA) are administered as daily subcutaneous injection. Evidence for therapeutic efficacy in male osteoporosis with PTH analogs was obtained in at least 3 different trials [122–124]. In the largest of these studies by Orwoll et al. treatment with teriparatide for 11 months in a mixed sample of men with idiopathic osteoporosis, age-related osteoporosis or osteoporosis due to hypogonadism increased BMD to virtually the same extent as in women [124]. Consistent with the anabolic activity of this agent, markers of bone formation increased significantly during treatment. Moreover, response to treatment was similar regardless of gonadal status, age, baseline bone mineral density, and body mass index. Importantly, one of these studies was specifically designed to address the efficacy of treatment in middle-aged men with idiopathic osteoporosis (age range 30–68 years, mean 50 years) of whom 78 % had sustained fractures [123]. These men were previously characterized from the clinical point of view showing low bone turnover and markedly reduced indexes of bone formation on histomorphometry [69, 70]. After 18 months, active treatment with PTH1-34 was associated with substantial increases in lumbar spine and hip BMD, as well as with increases in bone turnover markers. However, while antifracture efficacy at vertebral and nonvertebral sites has been demonstrated with PTH analogs in postmenopausal women, all the trials in men were not designed nor powered to detect differences in fracture incidence. Some indication of decreased vertebral fracture incidence in men was provided by a follow-up study of men with previous teriparatide treatment [125], as well as in a clinical trial for glucocorticoid-induced osteoporosis in which women and men were included [126, 127]. Indeed, in the latter trial, teriparatide treatment was superior to alendronate in terms of increases in BMD and prevention of fractures. Concurrent therapies with antiresorptive compounds such as bisphosphonates are not recommended, since little or no benefits were observed in combination trials

with alendronate or risedronate, respectively [128, 129]. Conversely, sequential therapy with bisphosphonates has been recently shown to maintain or further enhance bone mass after PTH is stopped [130]. Moreover, in individuals who have been treated previously with an antiresorptive agent, the subsequent actions of PTH on bone density may be delayed, but only transiently, if bone turnover is markedly suppressed [130].

A monoclonal antibody against sclerostin (an osteocyte product inhibiting wnt/beta-catenin pathway and bone formation) has been developed and is currently being tested as a new osteoanabolic compound. Although this drug is not available yet, reports of a single-dose, placebo-controlled, randomized study, which enrolled both men and women, showed that bone formation markers increased markedly along with a substantial reduction in bone resorption markers [131].

Compounds with a Mechanism of Action That is Not Known

Additional studies in men have been performed with strontium ranelate (2 g/day) given orally, a compound that demonstrated vertebral and non-vertebral anti-fracture efficacy in women with postmenopausal osteoporosis through an uncoupling action on bone metabolism (with mild stimulation of bone formation combined with a mild antiresorptive effect) [132], even though its exact mechanisms of action in bone remain unclear. In a preliminary comparative, open-label, 1-year study male patients treated with strontium ranelate experienced a greater increase in BMD than those who took alendronate, even though this increment was partly dependent to the actual incorporation of the strontium element into the bone crystal [133]. More recent results from a 2-year placebo-controlled trial in older men with primary osteoporosis (mean age 73 years) demonstrated greater increases in lumbar and femoral BMD with strontium ranelate compared with placebo [134]. Moreover, a significant increase in bone alkaline phosphatase (a marker of bone formation) was observed in patients treated with strontium ranelate. Based on these results, the EMA has extended the indication for this compound to include the treatment of osteoporosis in men at increased risk of fracture. More recently, safety issues have surfaced with this drug and it is now recommended only in situations of severe osteoporosis [135].

Conclusions

The increasingly important problem of osteoporosis in men has begun to receive much-needed attention. In particular, over the last decade, large scale population studies in men have led to advances in understanding bone fragility and its treatment in men. These mainly include important new knowledge about the morphologic basis of bone growth and bone loss at trabecular and cortical sites, as well as in the pathophysiology and the diagnosis of the disorder, especially concerning age-related and secondary causes osteoporosis in men. However, osteoporosis and fractures may also occur in young or middle aged males in the absence of an identifiable etiology. For this category (so called idiopathic osteoporosis) there are still major gaps in knowledge, particularly concerning the pathogenesis, diagnosis, prediction of fracture risk, and clinical management. In fact, current diagnostic approaches either based on BMD or fracture algorithms (ie, FRAX) are less validated in men than in women and can be generally applied only in subjects aged 50 years or above. Importantly, both clinical and experimental evidence suggests that idiopathic osteoporosis in men has different microstructural abnormalities than age-related bone loss and is mainly characterized by impaired osteoblast activity and reduced bone formation. While most of the current treatment options for the treatment of osteoporosis in men are based on antiresorptive agents, which suppress bone turnover, osteoanabolic agents (ie, PTH analogs or the monoclonal antibody against sclerostin) or strontium ranelate, an agent with an unknown mechanism, should be conceptually a more attractive therapy for men with idiopathic osteoporosis and impaired osteoblast activity. However, only few and small-scale studies were specifically performed in men with idiopathic osteoporosis and despite the positive outcomes on BMD, evidence for a true benefit on fracture risk is generally considered to be weak [121]. It is also likely that at least in a subset of these males bone fragility is growth-related and mainly dependent on genetic mechanisms.

Compliance with Ethics Guidelines

Conflict of Interest L. Gennari declares that he has no conflicts of interest. JP Bilezikian is on the advisory board for Amgen.

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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