Aging Clinical and Experimental Research (2021) 33:1439–1452
https://doi.org/10.1007/s40520-021-01845-8

REVIEW ARTICLE

Management of osteoporosis in older men

Jean-Marc Kaufman[1]

Received: 11 February 2021 / Accepted: 19 March 2021 / Published online: 5 April 2021

Abstract
As many as one out of three fragility fractures occur in older men and the outcome of major osteoporotic fractures, in particular hip fractures, is worse in men than in women. Osteoporosis in older men is thus an important threat to the quality of life of individual patients and a considerable burden for society. However, only a small minority of older men with high or very high fracture risk are receiving therapy. This does not need to be so as tools for fracture risk assessment are available and several drugs have been approved for treatment. Nevertheless, the evidence base for the management of osteoporosis in older men remains limited. This narrative review summarises the evidence for older men on the burden of osteoporosis, the pathophysiology of fragility fractures, the clinical presentation, diagnosis and risk assessment, the patient evaluation, and the non-pharmacological and pharmacological management.

Keywords Osteoporosis · Fractures · Older men · Management

Introduction: the burden of osteoporosis in older men

In patients with osteoporosis, low bone mass and altered bone quality result in reduced bone strength with increased risk of fracture. Although this disorder affects most often postmenopausal women, as many as one out of three fragility fractures occur in older men and it has been estimated that about one out of five patients with osteoporosis or low bone mass is a man [1–3]. The lifetime risk of an osteoporotic fracture in a man aged 50 years has been estimated at 13 to 25% [4, 5]. About a quarter of hip fractures occur in men [6] and their outcome is worse than in women with substantially higher associated mortality [7–10]. A third of the health burden and a quarter to a third of the economic burden of osteoporosis-related fractures is from fractures in men [2, 3]. The major osteoporotic fractures in older men are the fractures of the hip and vertebrae with fractures of the proximal humerus, distal forearm, ribs, sternum, clavicle, pelvis, distal femur also contributing to the burden of osteoporosis [4]. In the European Union, the total health burden due to fractures in men in 2010 was estimated to be 384,000 lost quality-adjusted life years (QALYs) and projected to increase to 491,000 QALYs lost in 2025: the cost for health care was estimated at 11.6 billion for 2010 and projected to increase to 15.5 billion in 2025 [3].

The age-adjusted incidence rate of hip fracture in men is about half that in women, which reflects the greater bone strength with intrinsically lower fracture risk in men. Indeed, this 2:1 ratio appears rather constant in many regions of the world even though there are large geographical variations in absolute fracture rates with the highest incidence rates observed in Northern Europe and North America: incidence rates are lower and female to male ratio is blunted in Asia and parts of Latin America [11]. There are also race/ethnic differences with the lowest fracture risk in Blacks and Asians, but the relation between bone mineral density (BMD) and fracture risk appears rather homogenous across race/ethnic groups [12]. The incidence rate of most types of osteoporotic fractures increases exponentially with age in both women and men. However, men have a lower fracture risk and attain a similar incidence rate of osteoporotic fractures as in women at about 10 years older age, with marked increases of fracture incidence seen in men in their eighties [4, 5].

Osteoporosis thus represents a significant threat to the health of the growing number of older men and a considerable cost for the health care system. Yet, even more so than osteoporosis in women, osteoporosis in men is largely

✉ Jean-Marc Kaufman
jean.kaufman@ugent.be

[1] Department of Endocrinology, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium

underdiagnosed and undertreated, even in men who already sustained a fragility fracture and have a high risk of new fracture [6, 13–16]. Some progress has been made in recent years, but awareness of osteoporosis in men and its heavy burden on the elderly remains low. This narrative review focuses on the management of osteoporosis in older men. A search of the literature on this topic in PubMed, Web of Science and by screening reference lists of review articles performed in preparation of this review exposed the wide gap existing between the only limited data on osteoporosis in elderly men and a wealth of data on postmenopausal osteoporosis: the evidence base for the management of osteoporosis in older men is rather limited and much is based on extrapolations from the knowledge base on postmenopausal osteoporosis.

Pathophysiology of osteoporotic fractures in older men

The steep rise of fracture incidence in men after age 75 years is caused by the combined effects of decreased bone strength and increased incidence of falls.

Skeletal changes underlying bone fragility in older men

Lifelong bone loss, deterioration of trabecular bone microarchitecture, thinning and increased porosity of cortical bone, and altered bone material properties, all contribute to increased bone fragility [17, 18]. Bone loss results from remodelling imbalance with bone formation not matching resorption. Trabecular bone loss begins in men well before midlife, whereas cortical bone loss occurs mainly after age 65 years. Bone loss continues throughout life and tends to accelerate in older men [18–21]: in the US cohort of the Osteoporotic Fractures in Men (MrOS) Study, men 85 years of age had a 2.5 times greater estimated femoral neck bone loss compared to 65 years-old men [21]. Accelerated bone loss results from increased bone turnover rate as reflected in higher levels of serum bone turnover markers [22].

Trabecular bone loss in men occurs primarily by thinning of the trabeculae with less decrease in trabecular number and connectivity compared to women, which reflects milder increases in bone turnover in men. Nevertheless, there are between-subject variations in the rate of bone loss and those older men with higher bone turnover and accelerated bone loss also present with a more pronounced deterioration of trabecular architecture with fewer trabeculae and greater trabecular separation [23]. Accelerated bone loss has also been identified as an independent risk factor for hip and other non-spine fractures [24, 25].

Cortical bone loss results from increased bone remodelling at the endosteal and intracortical bone surfaces. Whereas some periosteal bone apposition continues throughout life, in aging men this no longer compensates for the increased endocortical and intracortical bone resorption. The latter are characterized by a phenomenon of trabecularization of the endosteal bone envelope and by increase of intracortical porosity. The whole of these changes with aging results in slightly larger bones with thinner, more porous cortex and wider bone marrow cavity [17, 18, 20, 23, 26].

Little is known on bone material properties in older men, but age-related changes such as decreased osteon size, resulting from the reduced bone formation, and relative increase of interstitial bone, might contribute to bone fragility [17].

Factors underlying increased incidence of falls

Falls occurs frequently [27]. In 2,741 community-dwelling men aged 78.8 ± 5 years from the MrOS US cohort, at least one incident fall occurred in 35% of the men during a 1 year observation and 23% of men reported two or more falls [28]. Causation of falls is complex with the involvement of multiple and interacting risk factors. Muscle weakness, disorders affecting mobility and balance, visual impairment, cognitive impairment and diseases, medications and sleep disorders affecting mental alertness, living arrangements and environmental factors can all contribute to an increased incidence of falls in older men [26, 28]. Many older men have several risk factors with a cumulative effect on fall incidence [27].

Age-related decline of physical capacity, often exacerbated by comorbidity, plays an important role. Different measures reflecting particular aspects of impaired physical performance have been associated with risk of incident falls in older men, including lower extremity disability and foot problems [27], balance and gait abnormalities [27], low activity level with poor physical performance [28], Parkinson's disease [29], low muscle mass [30], low muscle strength [31], sarcopenia [32], and frailty [33].

Another important cluster of risk factors is related to transient or more permanent decrease of mental alertness. Increased incidence of falls has been linked to cognitive impairment [27], sleep disturbances and hypoxia during sleep [29, 34], use of sedative hypnotics [27, 29].

Moderate to severe lower urinary tract symptoms have also been shown to carry a significant fall risk in elderly men [35, 36].

Role of hormonal and non-hormonal factors

Sex steroid hormones

Sex steroids play an important role in the regulation of bone homeostasis and the preservation of skeletal integrity

in adult men. Hypogonadism is a well-recognized secondary cause of osteoporosis in men [37]. Acquired profound hypogonadism such as in men receiving androgen deprivation therapy (ADT) for prostate cancer, induces high bone turnover, accelerated bone loss and increased fracture risk [38, 39]. This raises the question of how the more progressive and much more limited changes in sex steroid status in aging men affect bone metabolism [40]. Testosterone (T) and its 5α-reduced active metabolite dihydrotestosterone contribute to the maintenance of the adult skeleton through androgenic effects expressed via the androgen receptor and exerted either directly on the bone tissue or indirectly through effects on muscle. However, the main effects of sex steroids to help preserve bone health in aging men by limiting bone turnover, bone loss, deterioration of trabecular microarchitecture, and cortical porosity appear to be exerted by estradiol (E2), the aromatization product of testosterone, acting on bone via the estrogen receptor-α [40, 41]. Studies in older men found an inverse association between E2 or its non-SHBG-bound fractions (free or bioavailable E2) with prospectively assessed bone loss [42–46]. Conversely, observational studies in community-dwelling older men did not convincingly established an association of serum T or its non-SHBG-bound fractions with BMD changes independent from E2 levels [40, 41]. On the other hand, in some studies greater bone loss was found to be associated with higher serum SHBG levels independently of T and E2 levels [45, 47]. In the MrOS US study cohort, the highest rate of bone loss was observed in men presenting with the combined findings of low bioavailable E2, low bioavailable T and high SHBG levels [45].

There is substantial evidence linking low (non-SHBG-bound) E2 also with increased fracture risk, even though there are some discordant findings [40, 41]. Low serum E2 has been associated with increased risk of hip fractures in older men from the Framingham study [48], low E2 and calculated free E2 with clinical fractures in men from the EPIC study cohort [49], low calculated free E2 with clinical vertebral, nonvertebral and hip fractures in the MrOS Sweden cohort [50], the lowest quartile of bioavailable E2 with a higher risk of nonvertebral fractures in the MrOS US cohort [51], and low E2 and calculated bioavailable E2 with the risk of all fractures in the MrOS Hong Kong cohort [46]. The observed associations between E2 levels and fracture risk tend to be nonlinear with substantially higher fracture risk when serum total E2 is below a threshold situated around 16 pg/mL (59 pmol/L) [41]. However, evidence linking E2 levels with fracture risk is essentially limited to clinical and nonvertebral fractures and two studies with systematic radiographic assessment of vertebral fractures in the MrOS US cohort and the combined MrOS Sweden and Hong Kong cohorts, respectively, did not show an association with E2 levels [52, 53].

Consistent findings in several cohort studies in older men [50–56], even though not confirmed in all [48, 49], convincingly show that high serum SHBG is associated independently of T and E2 levels with increased risk not only of clinical and nonvertebral fractures, but also of radiographically assessed vertebral fractures [52, 53].

In most cohort studies [46, 48–52] serum (non-SHBG-bound) T was not independently associated with fracture incidence. Exceptions are a report of an association of low T with fracture in the Dubbo study cohort even though BMD was associated with E2 [55] and a U-shaped association of T with fracture risk in the Health In Men Study (HIMS) cohort [56]. In some studies low T levels, although not independently associated with fractures, did have some additive effect on fracture risk in presence of low E2 levels [46, 48, 51]. An effect of T on fracture risk in older men might be indirect through its androgenic, anabolic action on muscle: in the MrOS US and Sweden cohorts low (bioavailable)T was associated with decreased physical performance and increased incidence of falls [57, 58].

In summary, both low E2 and high SHBG are independently associated with a higher rate of bone loss and increased fracture risk, whereas low T can have an additive effect on fracture risk, possibly through increased fall risk. However, it is noteworthy that the effect size of these associations is only small and they explain only a small fraction of between-subject differences is bone loss and fracture risk. From an analysis of data from the MrOS cohorts, the authors concluded that there is limited clinical utility of serum T, E2 and SHBG measurements to evaluate fracture risk as they did not meaningfully contribute to fracture risk assessment in a model including clinical risk factors and BMD (FRAX algorithm) [59].

Other hormonal factors

Vitamin D insufficiency, as defined by a serum 25-hydroxy-vitamin D (25-OH-vitamin D) below 20 ng/mL (50 nmol/L) is a common finding in older men. Low vitamin D status in older men has been associated with a greater rate of hip bone loss [60], a higher risk of hip fractures and major osteoporotic fractures [61–63], and greater fall risk [64]. Moreover, in the MrOS cohort a low vitamin D status had an additive effect on the increased rate of hip bone loss and hip fracture incidence associated with a low bioavailable E2 and/or high SHBG [65]. Whereas the whole of these findings indicate that serum 25-OH-vitamin D measurement can contribute to detect men at higher risk of hip fracture, it has also been shown that additional measurement of 1,25-dihydroxy-vitamin D, the active vitamin D metabolite, does not offer added value in this regard [63].

Secondary hyperparathyroidism can adversely affect bone health by increasing bone resorption and cortical porosity [66, 67]. Several factors can contribute to the occurrence of secondary hyperparathyroidism in older men, including vitamin D deficiency, low dietary intake and less efficient intestinal absorption of calcium, and decreased renal function. Interestingly, serum parathyroid hormone (PTH) levels may increase with age independently of 25-hydroxyvitamin D, phosphate, renal function, and ionized calcium [68] and in the MrOS US cohort men with a serum PTH in the upper quartile (intact PTH ≥ 38 pg/mL) had an increased rate of hip bone loss independent of 25-OH-vitamin D levels and estimated glomerular filtration rate [69].

Another factor likely to contribute to altered bone metabolism in older men is the decreased activity of the somatotropic axis reflected in the age-related decline of plasma IGF1 levels, with possible adverse effects on osteoblastic function and indirect effects through increased muscle wasting with decreased mechanical stimulation of bone [70, 71]. Interestingly, the decreased growth hormone/IGF1 activity might underlie at least in part the age-related increase of SHBG with high SHBG reported to be an independent risk factor for bone loss and fracture in older men [40].

Finally, a series of fundamental processes affecting adversely bone cells, including among others oxidative stress, DNA damage, cellular senescence, and osteocyte apoptosis probably play an important role in the development of bone fragility in the elderly [72].

Clinical presentation, diagnose and risk assessment

Clinical presentation

Osteoporosis is asymptomatic until a fragility fracture occurs, which is only one of several reasons why osteoporosis is underdiagnosed and undertreated. Osteoporosis in older men can be primary, 'senile' osteoporosis or secondary, i.e. the consequence and epiphenomenon of another disease or its treatment. Some more common causes of secondary osteoporosis in men [73, 74] are shown in Table 1. It is generally believed that compared to women, osteoporosis in men is more often secondary osteoporosis [73, 74]. However, this observation applies mostly to younger men (< 70 years) and reflects to a large extent the strongly biased population of men seen at the osteoporosis consultation. Indeed, asymptomatic men and even men with a history of fracture are still infrequently screened for osteoporosis. In the MrOS study cohort, for a battery of laboratory tests proposed to detect possible secondary causes of osteoporosis, the prevalence of laboratory abnormalities was not greater in older men as compared to men without osteoporosis, except for 25-OH-vitamin D and alkaline phosphatase [75]. Nevertheless, there is a high prevalence of comorbidities in older men with osteoporosis. Although these may not be the cause of the osteoporosis they can still contribute to the fracture risk.

Table 1 Some more common secondary causes of osteoporosis in men [73, 74]

Glucocorticoid treatment
Chronic obstructive pulmonary disease
Hypogonadism
Androgen deprivation therapy for prostate cancer
Alcohol abuse
Primary renal hypercalciuria
Post-transplantation
Primary hyperparathyroidism
Hemochromatosis
Multiple Myeloma
Immobilisation (e.g. stroke, Parkinson's disease)

Diagnosis

A clinical diagnosis of osteoporosis can be made based on the occurrence of a low trauma (i.e. equivalent to ground level fall) fracture. When the decision to initiate treatment for osteoporosis is based only on the occurrence of a fracture, only incident hip and vertebral fractures are usually being considered.

Now well established in clinical practice is an operational definition of osteoporosis based on BMD measurement by dual-energy X-ray absorptiometry (DXA) as originally proposed by a working party of the World Health Organization (WHO) for osteoporosis in postmenopausal women and defined as a BMD value 2.5 standard deviations (SD) or more below the mean for young adult women, i.e. a *T*-score ≤ − 2.5. To improve standardization and comparability it was later proposed to use the BMD measured by DXA at the femoral neck and with the women aged 20–29 years from the Third National Health and Nutrition Examination Survey (NHANES III; USA) as the reference population [76]. Per analogy, osteoporosis in men has also commonly been defined as a DXA BMD T-score ≤ − 2.5, be it initially with less supporting data from prospective studies assessing the relation between BMD and fracture risk in men. There is, however, no consensus on whether this T-score in men should be calculated with the use of a young male or female reference population. The rationale for the use of the NHANES III reference population of women aged 20–29 years for calculation in men is based on apparent strong similarities of the relationship between DXA femoral neck BMD and fracture risk in women and men. There is a

consistent increase in women and men of relative fracture risk per SD decrease of BMD, with in both steeper risk gradient for hip fracture than for all osteoporotic fractures and in both similarly dependent on age. Furthermore, the risk of hip fracture is similar in men and women for any given absolute BMD value measured at the hip and likewise the risk of vertebral fracture is also similar in men and women for any given absolute BMD value. Thus, a man and a woman of the same age with a same absolute BMD have a similar fracture risk, even if the similarity of the BMD-fracture risk relationship must be at least in part fortuitous considering the underlying differences in bone size and structure [17, 76, 77].

The above approach, which has been recommended by the International Osteoporosis Foundation (IOF) [3] and the International Society for Clinical Densitometry (ISCD) [78], aims to identify men and women at similar fracture risk and thus likely to benefit equally from treatment. According to this approach, a smaller fraction of the male population than the female population is diagnosed as osteoporotic, reflecting the higher mean BMD in men. The alternative approach using a reference population of young adult males to calculate the T-score identifies a larger proportion of men as osteoporotic, a proportion more comparable to that of women identified as osteoporotic, but with on average a lower fracture risk. In favour of this approach, which is recommended in the clinical guidelines by the Endocrine Society (USA) [79] and by the National Osteoporosis Foundation (USA) [80], it is argued that a substantial proportion of fractures occur in men with a higher BMD [81]. It is also noteworthy that nearly all clinical trials for validation of osteoporosis treatments in men have included men on basis of a BMD T-score calculated using a male reference population. Real-life data from the 5880 men in the MrOS study cohort show that the choice of diagnostic approach has a major impact on the proportion of older men identified as warranting treatment: the prevalence of osteoporosis was 2% according to the 'WHO criterion' (female reference) and 9.4% according to the 'NOF criterion' (male reference); in the men who meet the WHO osteoporosis criterion observed 10-year hip fracture probability was 20.6% as compared to only 6.8% for men who meet the NOF but not the WHO criterion [82].

How to identify men at high fracture risk who should benefit from treatment?

Older age, a history of fracture after age 50 years not caused by a major trauma, and a low BMD are without doubt the most important risk factors for fracture. However, independent additional clinical risk factors contribute to fracture risk. The combined findings of observational studies have identified a long list of risk factors for fracture in men [29, 79, 83]. Methods have been proposed to combine clinical risk factors with or without femoral neck BMD with the aim to estimate fracture probability, such as the FRAX™ algorithm (www.shef.ac.uk/FRAX/) [84] and Garvan monogram (www.fractureriskcalculator.com) [85]. Risk factors for hip fracture in older men from the MrOS study cohort, which were independently associated with fracture risk in a multivariate model including femoral neck BMD and adjusted for competing mortality risk [83], are shown in Table 2. Clinical risk factors validated in meta-analyses involving a large number of subjects, shown to contribute to fracture risk independent of femoral neck BMD, and included in the FRAX™ risk assessment algorithm, are also listed in Table 2. The computer-based FRAX algorithm combines these clinical

Table 2 Clinical risk factors for fracture

Independent risk factors for hip fracture in the MrOS cohort (multivariate model with adjustment for competing mortality) Data from Cauley et al. [83]	Risk factors validated in meta-analyses which contribute to risk of hip and major osteoporotic fractures independent of BMD and are included in the FRAX™ algorithm According to Kanis et al. [84]
Age 75 years or older	Low body mass index
Low femoral neck BMD	Prior history of fracture
Current smoking	Parental history of hip fracture
Tall stature	Use of oral glucocorticoids
Height loss since age 25 years	Rheumatoid artritis/other secondary causes
History of fracture	Current smoking
Use of tricyclic antidepressant	Alcohol intake of 3 or more units daily
History of myocardial infarction or angina	
Hyperthyroidism	
Parkinson's disease	
Low protein intake	
Lower executive function	

risk factors with some patient characteristics (gender, age, height, weight) and with or without femoral neck BMD to calculate an estimate of the 10 year probability of hip fracture and of major osteoporotic fractures. Country-specific versions of the algorithm are calibrated according to local fracture epidemiology data. The proposed fracture probability thresholds for intervention may vary according to local guidelines and pharmaco-economic issues but lies mostly around a 10 year probability of all major fractures of 20% and of hip fracture of 3% [79, 80, 86, 87].

The importance of BMD measurement for risk assessment is illustrated by an analysis of the data from the MrOS cohort showing that in elderly men without prior fragility fracture, age with femoral neck BMD T-score (female reference population) identified men with incident fracture as accurately as more comprehensive fracture scores including the FRAX and Garvan tools. Recommendations concerning indications for case finding by BMD screening vary according to local guidelines; both the Endocrine Society (USA) and National Osteoporosis Foundation (USA) propose to screen men 70 years or older or men 50–69 years with other risk factors [79, 80]. In this context estimated fracture risk with FRAX or similar tools used without BMD can help select men who will benefit from a DXA, i.e. those men having a moderately high fracture probability although still below intervention threshold on the basis of clinical risk factors alone. Lumbar spine and hip are the usually recommended DXA measurement sites [79], although the hip is clearly the preferred measurement site in older men because of frequent spuriously elevated BMD at the spine due to osteoarthritis, prior vertebral fracture and/or vascular calcifications. Moreover, as discussed above, it is femoral neck BMD that has been used for standardized approaches to BMD-based diagnosis. Measurements at the forearm (1/3 or 33% radius) have been proposed as an alternative if valid measurements at the two other sites are not possible or as an additional measurement site in a particular situation, i.e. men with primary hyperparathyroidism or ADT for prostate cancer [79]. The more recently introduced DXA-based trabecular bone score (TBS) does not seem to contribute significantly to the prediction of incident clinical or radiographic vertebral fractures in older men when taking into account spine BMD and age [88].

Detection of undiagnosed fractures by vertebral fracture assessment (VFA) using DXA equipment or lateral spine X-ray can help to establish the diagnosis of osteoporosis and can be recommended for men at risk for osteoporosis such as men with osteopenia (*T*-score ≤ -1 and > -2.5) or with clinical risk factors; in men already diagnosed with osteoporosis it can help to define the severity of the disease and fracture risk [79].

In conclusion, there are different approaches to identify older men with osteoporosis and high fracture risk which are summarized in Table 3. Each of these have their strengths and limitations and they complement each other.

Management of osteoporosis in elderly men

Initial evaluation

Once the diagnosis of osteoporosis is established and its severity documented, to perform an appropriately comprehensive clinical evaluation with thorough history taking, physical examination and targeted biology before initiating treatment is good clinical practice and serves the following several purposes:

- To assess the clinical impact of the disease (back pain, kyphosis, mobility,…)
- To rule out major secondary causes of osteoporosis that may require specific treatment (e.g. hyperparathyroidism, multiple myeloma, hyperthyroidism, …)
- To evaluate general health status and physical function, and to identify risk factors for falls (Living arrangements? Cognitive functioning? Muscle strength? Balance? Sarcopenia? Frailty? Nycturia? …)
- To identify the presence of comorbidities that may have implications for the choice of osteoporosis treatment, its monitoring, and its outcome (gastrointestinal diseases, impaired renal function, liver disease, allergies, immobilisation, …)

Table 3 How to identify older men having a high risk for fracture and likely to benefit from treatment

Elderly men (> 70 years) to be considered as having osteoporosis with substantial risk for fracture, expected to benefit from (pharmacological) osteoporosis treatment
Men who have had a hip fracture without major trauma
Men who have had a clinical or silent radiographic vertebral fracture without major trauma
Men with femoral neck, total hip and/or lumbar spine BMD 2.5 SD or more below the mean for the women 20–29 years from NHANES III (*T*-score ≤ -2.5; female reference)
Men at substantial absolute fracture risk as calculated with FRAX™ (with or without BMD) with indicative intervention thresholds of $\geq 20\%$ ten-year probability of major osteoporotic fracture or $\geq 3\%$ ten-year probability of hip fracture

As to blood and urine investigations, measurements of serum calcium, phosphorus, creatinine, liver function, alkaline phosphatase, 25-OH-vitamin D and testosterone, complete blood count, and 24-h urinary calcium (and creatinine) excretion have been proposed as standard testing, with additional tests as appropriate according to history and physical examination [79]. Considering the specific target population of elderly osteoporotic men and the several purposes of the evaluation, it can be argued to add the following tests to the standard biology testing: serum albumin, protein electrophoresis, CRP, fasting glucose (or Haemoglobin A1c), parathyroid hormone, SHBG (and calculated free T) and thyrotropin.

Lifestyle measures and non-pharmacological management

Appropriate lifestyle- and non-pharmacological measures are an inherent and important component of the management of osteoporosis in older subjects. Older men with osteoporosis should be advised about lifestyle recommendations [79, 89, 90]. A balanced diet should ensure adequate protein consumption [79, 89, 91] and ideally contribute substantially to a recommended daily calcium intake of 1200–1500 mg [79, 89, 90]. Both for protein and calcium requirements, dairy products are an important component of such diet [89, 91, 92]. Even though efficacy data has been conflicting, in particular, if no concomitant vitamine D supplementation [93], calcium supplements, usually 500–1000 mg, depending on dietary intake, should be considered in men with (risk of) deficiency [79, 90, 94]. Calcium supplementation, usually with vitamin D, is also a required complement to other specific pharmacological treatments of osteoporosis because these supplements have been an inherent part of the therapies of osteoporosis as evaluated in clinical trials [79, 90, 94].

Vitamin D supplements are recommended for elderly men with (risk of) vitamin D deficiency/insufficiency. Although achieving a serum 25-OH-vitamin D level 20 ng/mL (50 nmol/L) is generally considered to ensure vitamin D sufficiency [93–95], some guidelines recommend a higher target level of 30 ng/mL (75 nmol/L) for osteoporotic men [79] or more specifically for the older subjects [95]. Supplementation with a starting daily dose cholecalciferol of 800–1000 IU (20–25 µg) is recommended and will achieve in many men 25-OH-levels in this range of 20 to 30 ng/mL (50–75 nmol/L) [95–98]. In elderly subjects with insufficient vitamin D status, vitamin D supplementation in the range of 800–1000 IU appears beneficial in lowering the risk of falling. Several higher dosages tested (mainly in women), in particular infrequent administration of high doses, appeared to increase the risk of falls and hip fractures [95, 97–99]. Nevertheless, some men may require higher dosages of vitamin D in specific situations such as malabsorptive diseases or the use of some antiepileptic drugs [79]. In clinical trials for validation of pharmacological therapies of osteoporosis, treatment regimens usually included besides a calcium supplement also a vitamin D supplement of 400 to 1200 IU (10–30 µg) per day.

Safe weight-bearing activities and exercises should be strongly encouraged even if there is little supportive evidence for men [79, 89]. Also logical is to discourage excessive alcohol consumption (≥ 3 units/day) and smoking as these are known risk factors for fracture [79, 89]. Finally, measures to reduce the risk of falls deserve full attention in an individualised and broad approach [89], which may include such varied aspects as an adaptation of living arrangements, critical reappraisal of prescription of psychotropic and cardiovascular drugs, exercising, use of a walking aid, or treatment of lower urinary tract symptoms with nycturia.

Pharmacological therapy

Specific therapies for secondary causes of osteoporosis, such as glucocorticoid-induced osteoporosis, are beyond the scope of this review and will not be discussed except for hypogonadism.

In sharp contrast to the extensive validation of drugs for the treatment of postmenopausal osteoporosis in large clinical trials with reduction of fracture rate as primary efficacy criterion, approval for use of these drugs for therapy in men has generally been based only on a rather small-scaled study of short duration (1 or 2 years) with BMD as a surrogate endpoint. Indeed, validation of a particular treatment in men has been considered sufficient if in a so-called 'bridging trial' a particular treatment regimen (same molecule; same dosage) previously shown to reduce fracture risk in postmenopausal women induces in men BMD changes of comparable magnitude as the BMD changes previously observed to accompany fracture risk reduction in postmenopausal women. Data showing that osteoporosis therapy reduces fracture risk in men is very limited [90] and only a single trial in men had fracture risk reduction as the primary endpoint [100].

The drugs approved in most countries for the treatment of osteoporosis in men with the main trials in support of their use in men are summarized in Table 4. The orally administered bisphosphonates alendronate and risedronate, the intravenously administered bisphosphonate zoledronic acid, and denosumab, the subcutaneously administered monoclonal antibody neutralizing the activity of human receptor activator of nuclear factor-kB (RANKL), are all 'anti-resorptive' bone-active agents acting through inhibition of osteoclastic bone resorption. Teriparatide, a synthetic peptide with 34 amino acids corresponding to the N-terminal first amino

Table 4 Drugs approved for the treatment of osteoporosis in men with the respective main trial having validated this use

Drug treatment regimen (study)	Patient number (active drug/placebo) Age	Primary end-point	Main findings
Alendronate Oral, 10 mg daily + calcium and vitamin D (Orwoll et al. [101])	241 (46/95) mean 63 years (range 31–85)	% change lumbar spine BMD at 24 months	Increase BMD spine, total hip, femoral neck, total body Reduced loss of stature Numerical decrease vertebral fractures (significance dependent on type of analysis)
Risedronate Oral, 35 mg once weekly + daily calcium and vitamin D (Boonen et al. [102])	286 (191/93) Mean 60 years (range 36–83) (> 40% aged ≥ 65 years)	% change lumbar spine BMD at 24 months	Increase BMD spine, total hip, femoral neck (few fractures; no effect)
Zoledronic acid Intravenous, 5 mg yearly (Boonen et al. [100])	1199 (558/611) Median 66 years (range 50–85 years) (18% ≥ 75 years)	New morphometric vertebral fractures over 24 months	65%reduction of vertebral fractures; reduction height loss; increase BMD No difference mortality or severe adverse events
Denosumab Subcutaneous, 60 mg every 6 months (Orwoll et al. [107])	242 (121/121) Mean 65 years (range 30–85 years) (36% ≥ 70 years)	% change Lumbar spine BMD at 12 months	Increase BMD spine, total hip, femoral neck, distal radius
Teriparatide Subcutaneous 20 or 40 µg daily (Orwoll et al. [110])	437 (151 + 139/147) Mean 59 years (range 30–85 years)	% change BMD at 24 months study interrupted after median of 11 months treatment (range 2–15 months)	Increase BMD Spine (20 and 40 µg dose), total hip (only 40 µg dose), femoral neck (20 and 40 µg), total body (only 40 µg dose) (no change distal radius)

acids of the 84 amino acids of parathyroid hormone, administered by daily subcutaneous injection, is an anabolic bone-active agent with bone-forming properties.

Bisphosphonates

Bisphosphonates are generally considered the first-line treatment for osteoporosis in men. Their action to decrease bone resorption and bone turnover is reflected in a decrease of the (urinary or blood) levels of biochemical markers of bone turnover observed in the studies in men with the different bisphosphonates.

Alendronate, as a daily oral dose of 10 mg with associated calcium and vitamin D supplements was studied in men with moderately low femoral neck and spine BMD (mean BMD, respectively, 2.2 and 2.0 SD below the mean in normal young men), with a prevalent vertebral fracture in about half of the patients. Two years treatment increased BMD at all sites with increases comparable to findings in postmenopausal women, reduced the loss of stature compared to placebo and reduced numerically (significantly according to an alternative analysis) incident vertebral fractures. [101]. Although alendronate has been validated as a daily oral dose of 10 mg, it is now more commonly used as a single weekly oral dose of 70 mg, equivalence of these two dosing regimens having been documented in postmenopausal women.

Risedronate, as a weekly oral dose of 35 mg, with associated daily calcium and vitamin D supplements, was studied in men with low spine BMD (mean 3.3 SD below mean for young men) and moderately low hip BMD (mean 2.0 SD below mean for young men), with a prevalent vertebral fracture in slightly more than a third of the men. After two years of treatment, BMD was increased at all measurement sites (spine, total hip, trochanter, femoral neck) with lumbar spine BMD changes comparable to prior findings in postmenopausal women. There was no demonstrated effect on stature; fractures were few and not allowing evaluation of efficacy on fracture reduction [102].

Zoledronic acid as a 5 mg dose administered once per year intravenously, with associated daily calcium and vitamin D supplements, has been approved for use in men based on the HORIZON Recurrent Fracture Trial (RFT) in 508 men and 1619 women (mean age 74.5 years) with surgically repaired recent low trauma hip fracture. During a median 1.9 year follow-up there was overall a 35% reduction in clinical fractures and 28% reduction in mortality. However, among the men in the study the number of incident fractures was small and not different between active treatment and placebo [103]. Nevertheless, an analysis of a subset of the participants in the HORIZON-RFT trial showed that the treatment-induced BMD increase in men was similar than that in women with recent hip fracture [104]. In a subsequent study involving 1199 men with moderately low femoral neck

BMD (mean 2.2 SD below mean for normal young men) and a third of them with a prevalent vertebral fracture, two yearly administrations of 5 mg zoledronate was shown to significantly reduce the incidence of new vertebral fractures over 24 months by 65%, to reduce the risk of new moderate-to-severe vertebral fractures and to limit the loss of stature; a numerical reduction of clinical vertebral and nonvertebral fractures was not statistically significant. This is the only clinical trial in men with fracture incidence and not BMD change as the primary endpoint [100]. In a head-to-head comparison in men, BMD changes over two years were similar for treatment with once-a-year 5 mg zoledronic acid intravenously and 70 mg oral alendronate weekly [105].

In the studies with the different bisphosphonates, men with low serum testosterone appeared to respond equally well to treatment as men with normal serum testosterone. From the mostly small-scaled studies in men there is no indication for gender-specific safety problems. Considering the only limited information for men, safety issues in postmenopausal women should be considered also relevant for men, which includes the rare occurrence of osteonecrosis of the jaw and atypical femur fracture. In older men, dental problems should be taken care of before initiation of treatment and renal function checked as in subjects with markedly impaired renal function (estimated glomerular filtration rate $\leq$ 35 ml/min) use of bisphosphonates in not advised without additional investigations [79] and intravenous zoledronic acid is contra-indicated. In frail and disabled older patients, the adherence to the strict modalities of oral bisphosphonate use may be problematic. To limit the risk of hypocalcaemia, vitamin D deficiency should be treated, and calcium/vitamin D supplements started preferably before initiation of bisphosphonate treatment, more in particular before intravenous administration of zoledronic acid. Patients should be informed of the occurrence of fever and influenza-like symptoms in the days following intravenous zoledronic acid administration.

Denosumab

Denosumab strongly inhibits osteoclastic bone resorption and bone turnover. Its use in men was initially approved to increase bone mass in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer. Subsequently, denosumab was approved for treatment to improve bone mass in men with osteoporosis at high risk for fracture.

Denosumab as a subcutaneous injection of a 60 mg dose every 6 months, with associated daily calcium and vitamin D supplements, was studied in a randomized placebo-controlled trial in men receiving ADT for nonmetastatic prostate cancer. The men (734 in each arm) with a mean age of 75.4 years (85% of men 70 years or older) had a moderately low BMD (median BMD at the spine 0.5 SD and at the femoral neck 1.5 SD below the mean for young men). Denosumab treatment decreased the levels of bone turnover markers, increased BMD at all measurement sites and all-time points over the 36 months observation and reduced the incidence of new vertebral fractures over 12, 24 and 36 months [106]. In support of its use in men with osteoporosis, denosumab as a 60 mg dose administered subcutaneously every 6 months, with associated daily calcium and vitamin D supplements, was studied in men with moderately low BMD (mean BMD at the spine 2.0 SD and at the femoral neck 1.9 SD below the mean for young men) with a history of osteoporotic fracture in 25% and prevalent vertebral fracture in 23% of the men. Denosumab treatment increased the BMD at all measurement sites, i.e. spine, total hip, femoral neck and distal radius, over the 12 months duration of the study [107]. An open-label follow-up study indicated further BMD increase during a second year of treatment [108].

As illustrated convincingly in the study in men with ATD, denosumab is equally effective in men with low serum testosterone as in men with normal serum testosterone. From the limited data in men, there is no indication of gender-specific safety issues. Possible severe hypocalcaemia, although rare, deserves particular attention in elderly men. Vitamin D deficiency should be treated and calcium and vitamin D supplements preferably initiated before administration of denosumab; adherence to calcium/vitamin D supplementation should be monitored during treatment. Possible rare adverse events also include potentially severe hypersensitivity reactions, osteonecrosis of the jaw and atypical femur fractures. Data on denosumab treatment of postmenopausal women with osteoporosis has shown that cessation of treatment is followed by rapid bone loss and a potential increase of fracture risk. Therefore, it may be advisable that interruption of denosumab treatment would be followed by a period of treatment with a bisphosphonate [109].

Teriparatide

Teriparatide, [PTH(1–34)] as a daily subcutaneous injection of a 20 µg dose, with associated calcium and vitamin D supplements, has an anabolic, bone-forming action and is indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture. Approval of this therapy for use in men is based on a trial comparing the effects of daily subcutaneous administration of 20 µg and 40 µg teriparatide with placebo in men with low BMD (mean BMD at the spine 2.2 SD and at the femoral neck 2.7 SD below the mean for young men). The study was prematurely interrupted after median of 11 months of treatment because of the development of osteosarcomas in rats during toxicological evaluation, findings later considered not predictive for increased risk in humans. Treatment induced an increase

in the levels of biochemical markers of bone formation followed by increased levels of the markers of bone resorption. At study endpoint spine and femoral neck BMD was increased with both teriparatide dosages but with the 40 µg dose these increases were greater and seen also at the total hip and total body; neither teriparatide doses increased BMD at the radius. Treatment effects were independent of age and serum testosterone levels [110].

In an 18-month follow-up study after interruption of teriparatide treatment, a fairly rapid decline of BMD was observed, which was limited in those men using a bisphosphonate [111]. From studies comparing the effect of alendronate monotherapy, teriparatide monotherapy and combination therapy of alendronate and teriparatide, teriparatide appeared more effective as judged by changes in BMD, while the concomitant use of alendronate appeared to blunt the anabolic action of teriparatide [112].

Adverse reactions with teriparatide treatment are more frequent for the 40 µg compared to the 20 µg dose. Common adverse reactions are dizziness, nausea, headache and limb pains. Although the use of teriparatide has been restricted to a duration of two years for safety reasons, post-marketing surveillance data have not shown an increased risk of osteosarcoma.

Romosozumab

Romosozumab is a humanized monoclonal antibody that binds sclerostin and inhibits its action. Sclerostin, a secretion product of the osteocytes, regulates bone formation. Inhibition of sclerostin by romosozumab has been shown to both increase bone formation and decrease bone resorption, resulting in a strong anabolic action on bone. Romosozumab treatment for 12 months was shown to increase BMD and reduce the incidence of vertebral fractures and clinical fractures in postmenopausal women. In a 'briging study' in men with osteoporosis, 245 men were randomized 2:1 to receive romosozuma 210 mg subcutaneously monthly or placebo for 12 months (163 romosozumab/82 placebo). The men included in the study with a mean age of 72 years (40% ≥ 75 years) had a low BMD (mean BMD at the spine 2.2 SD and at the femoral neck 2.3 SD below the mean for young men) and a moderate fracture risk (median 10 years probability of major osteoporotic fracture of 7.7% and of hip fracture of 3.3% according to FRAX™). Twelve months of treatment increased BMD significantly at the spine (12.1% from baseline), total hip (2.5% from baseline) and femoral neck (2.2%). Adverse events and serious adverse events were balanced between romosozumab and placebo with, however, a numerical imbalance in positively adjudicated serious cardiovascular events (romosozumab 4.9% vs placebo 2.5%) [113]. In a comparative study with alendronate in postmenopausal women, there has been a possible cardiovascular safety signal for romosozumab and an imbalance in mortality in patients 75 year and older. The drug was approved by the European Medicine Agency for use in women with severe osteoporosis who are at high risk of fracture, but not in those with history of myocardial infarction or stroke; pharmacovigilance studies have been initiated [114]. As to date, romosozumab has not yet been approved for use in men.

Role of testosterone therapy

There is an important knowledge gap regarding the effects of testosterone therapy for skeletal health in older men (see [40] for review): (1) there is no reliable data on testosterone treatment specifically in men with osteoporosis; (2) except for a couple of studies, trials did not include elderly men with unequivocally low serum testosterone; and (3) data on the effects of testosterone therapy on fracture risk is completely lacking. The data available suggests that testosterone therapy has modest suppressive effects on bone resorption, induces modest increases of lumbar spine areal BMD and inconsistent, overall nonsignificant areal BMD increases at the hip as measured by DXA. More substantial increases at the spine and significant increases at the hip were reported for volumetric BMD assessed by QCT [115]. There is evidence from several trials that BMD increase during testosterone therapy may be related to the magnitude of induced increase in serum testosterone and estradiol levels, which might explain why significant areal BMD increases according to DXA were seen only in studies with intra-muscular testosterone injections and not with transdermal testosterone treatment.

From this, it can be concluded that although modest beneficial effects on the maintenance of skeletal integrity may be an added benefit of testosterone treatment initiated for another indication in older men with low serum testosterone, there is insufficient data to support its use to treat osteoporosis. Osteoporosis is neither a specific nor sufficient indication for testosterone therapy. The implication is that specific osteoporosis treatment should be initiated in hypogonadal elderly men at high risk for fracture, regardless of whether they are also treated with testosterone to alleviate other symptoms of hypogonadism [40, 41]. In this regard, it is important to note that the different therapies approved for the treatment of osteoporosis in men appeared to be equally effective in men with either low or normal serum testosterone. Moreover, treatment with bisphosphonates and denosumab have been shown to effectively prevent bone loss in men with profound hypogonadism receiving ADT for prostate cancer [116]

Choice of therapy

Pharmacological treatment should always be an add-on to appropriate and personalized lifestyle- and non-pharmacological measures.

Bisphosphonates are considered the first-line therapy for osteoporosis. For elderly men at high risk of fracture, intravenous zoledronic acid may be the preferred treatment [79]. It is the only therapy documented by a trial in men to reduce fracture risk, whereas for other treatments assumption of efficacy to reduce fracture risk is by extrapolation from data in postmenopausal women. The administration modality of zoledronic acid may favour treatment adherence and limit the need for treatment monitoring by repeated DXA in less mobile elderly patients, whereas the strict modalities of oral bisphosphonate intake may be a challenge for disabled and frail subjects. Moreover, elderly patients are often already taking many pills. Nevertheless, oral bisphosphonates may be a valid alternative, e.g. for economic reasons, contra-indications for intravenous zoledronic acid or patient preference. Denosumab is a good alternative for high fracture risk patients in case of contra-indications for bisphosphonates or patient preference. Finally, anabolic treatment with teriparatide can be considered either as initial treatment in patients with markedly low BMD and high fracture risk, usually with (multiple) prevalent vertebral fractures, or as rescue treatment in case of therapy failure with new incident fractures under antiresorptive treatment. Teriparatide treatment for a duration of maximum 24 months should be followed by treatment with an anti-resorptive drug.

Conclusions

Awareness of osteoporosis in men has undoubtedly improved. But osteoporosis is still commonly seen as a disease of postmenopausal women and perhaps occasionally of men with secondary osteoporosis. Presently, only a small minority of elderly men with high or very high fracture risk is being treated. This should not be the case as all necessary tools to evaluate fracture risk are available and several drugs long available for the treatment of postmenopausal women with osteoporosis are now also approved for treatment in men. Unfortunately, the level of evidence for use of these therapies in men is rather limited, mostly to only small-scaled bridging studies of short duration with BMD endpoints. Moreover, these studies included only a minority of men 70 years or older. This contrasts with the many large, randomized treatment trials with fracture endpoints performed in postmenopausal and elderly women. Reassuring is that there seem to be sufficient similarities between osteoporosis in women and men to justify to some extent extrapolations. However, it could be argued that the data for men is too limited to have uncovered more subtle, yet relevant, gender-specific issues. Remarkably, even the effects of testosterone therapy on bone health in elderly men are poorly documented. Clearly, there is much work ahead: there is a need for more research, but meanwhile an urgent task is to improve the clinical care of elderly men at high risk for fracture. Perhaps, fracture liaison services could play an important role in this context, although this approach might have less added value for the oldest patients [117].

Funding No funding was received to assist with the preparation of this manuscript.

Declarations

Conflict of interest The author has no potential conflict of interest relevant to this work.

Ethical statement This manuscript contains no new data, not previously published, involving human participants or animals. All published work cited in this review appeared to comply with current research ethical standards This work has not been previously published.

References

1. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 17:1726–1733. https://doi.org/10.1007/s00198-006-0172-4
2. Burge R, Dawson-Hughes B, Solomon DH et al (2007) Incidence and economic burden of osteoporosis-related fractures in the United States. J Bone Miner Res 22:465–475
3. Hernlund E, Svedbom A, Ivergard M et al (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8:136. https://doi.org/10.1007/s11657-013-0136-1
4. Kanis JA, Johnell O, Oden A et al (2004) Epidemiology of osteoporosis and fracture in men. Calcif Tissue Int 75:90–99
5. Hopkins RB, Pullenayegum E, Goeree R et al (2012) Estimation of the lifetime risk of hip fracture for women and men in Canada. Osteoporos Int 23:921–927
6. Shah A, Prieto-Alhambra D, Hawley S et al (2017) Geographic variation in secondary fracture prevention after a hip fracture during 1999–2013: a UK study. Osteoporos Int 28:169–178
7. Bliuc D, Nguyen ND, Milch VE et al (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 301:513–521
8. Haentjens P, Magaziner J, Colon-Emeric CS et al (2010) Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med 152:380–439
9. Holt G, Smith R, Duncan K et al (2008) Gender differences in epidemiology and outcome after hip fracture: evidence from

the Scottish hip fracture audit. J Bone Jt Surg 90B:480–483. https://doi.org/10.1302/0301-620X.90B4.20264
10. Cnter JR, Nguyen TV, Schneider D et al (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353:878–882. https://doi.org/10.1016/S0140-6736(98)09075-8
11. Kanis JA, Oden A, McCloskey EV et al (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 23:2239–2256
12. Shin M, Zmuda J, Barrett-Connor E et al (2014) Race/ethnicdifferences in associations between bone mineraldensity and fracture history in older men. Osteoporos Int 25:837–845
13. Curtis JR, McClure LA, Delzell E et al (2009) (2009) Population based fracture risk assessment and osteoporosis treatment disparities by race and gender. J Gen Intern Med 24:956–962
14. Center JR, Bliuc D, Nguyen TV et al (2007) Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 297:387–394
15. Papaioannou A, Kennedy CC, Ionnadis G et al (2008) The osteoporosis care gap in men with fragility fractures: the Canadian Multicentre Osteoporosis Study. Osteoporos Int 19:581–587
16. Narla RR, Hirano LA, Lo SHY et al (2019) Suboptimal osteoporosis evaluation and treatment in older men with and without additional high-risk factors for fractures. J Investig Med 67:743–749. https://doi.org/10.1136/jim-2018-000907
17. Kanis JA, Bianchi G, Bilezikian JP et al (2011) Towards a diagnostic and therapeutic consensus in male osteoporosis. Osteoporos Int 22:2789–2798
18. Riggs BL, Melton LJ 3rd, Robb RA et al (2004) Population-based study of age and sex differences in bonevolumetric density, size, geometry, and structure at different skeletalsites. J Bone Miner Res 19:1945–1954
19. Riggs BL, Melton LJ III, Robb RA et al (2008) A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res 23:208–214
20. Szulc P, Delmas P (2007) Bone loss in elderly men: increased endosteal bone loss and stable periosteal apposition. The prospective MINOS study. Osteoporos Int 18:495–503
21. Cawthon P, Ewing S, McCulloch C et al (2009) Loss of hip BMD in older men: the osteoporotic fractures in men (MrOS) study. J Bone Miner Res 24:1728–1735
22. Bauer D, Garnero P, Harrison S et al (2009) Biochemical markers of bone turnover, hip bone loss, and fracture in older men: the MrOS study. J Bone Miner Res 24:2032–2038
23. Cauley JA, Burghardt AJ, Harrison SL et al (2018) Accelerated bone loss in older men: effects on bone microarchitecture and strength. J Bone Miner Res 33:1859–1869
24. Nguyen TV, Center JR, Eisman JA (2005) Femoral neck bone loss predictsfracture risk independent of baseline BMD. J Bone Miner Res 20(7):1195–1201
25. Cawthon PM, Ewing SK, Mackey DC et al (2005) (2012) Change in hip bone mineral density and risk of subsequent fractures in older men. J Bone Miner Res 27:2179–2188
26. Zebaze R, Ghasem-Zadeh A, Bohte A et al (2010) Intracortical remodeling and porosity: rational targets for fracture prevention. Lancet 375:1729–1736
27. Tinetti M, Speechley M, Ginter S (1988) Risk factors for falls among elderly persons living in the community. N Engl J Med 319:1701–1707
28. Orwoll ES, Fino NF, Gill TM et al (2019) The relationships between physical performance, activity levels, and falls in older men. J Gerontol A Biol Sci Med Sci 74:1475–1485
29. Cawthon PM, Shahnazari M, Orwoll ES (2016) Osteoporosis in men; findings from the osteoporotic fractures in men study (MrOS). Ther Adv Musculoskel Dis 8:15–27
30. Cawthon PM, Orwoll ES, Peters KE et al (2019) Strong relation between muscle mass determined by D3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci 74:844–852
31. Chan B, Marshall L, Winters K et al (2007) Incident fall riskand physical activity and physical performance amongolder men: the osteoporotic fractures in men study. Am J Epidemiol 165:696–703
32. Landi F, Liperoti R, Russo A et al (2012) Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. Clin Nutr 31:652–658
33. Ensrud K, Ewing S, Cawthon P et al (2009) A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc 57:492–498
34. Stone K, Blackwell T, Ancoli-Israel S et al (2014) Sleep disturbances and risk of falls in older community dwelling men: the outcomes of sleep disorders in older men (MrOS Sleep) study. J Am Geriatr Soc 62:299–305
35. Parsons J, Mougey J, Lambert L et al (2009) Lower urinary tract symptoms increase the risk of falls in older men. BJU Int 104:63–68
36. Noguchi N, Chan L, Cumming RG et al (2016) Lower urinary tract symptoms and falls in community dwelling older men: the concord health and ageing in men project. J Urol 196:1694–1699. https://doi.org/10.1016/j.juro.2016.06.085
37. Rochira V, Antonio L, Vanderschueren D (2018) EAA clinical guideline on management of bone health in the andrological outpatient clinic. Andrology 6:272–285
38. Mittan D, Lee S, Miller E et al (2002) Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 87:3656–3661
39. Shahinian VB, Kuo YF, Freeman JL et al (2005) Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 352:154–164
40. Kaufman JM, Lapauw B, Mahmoud A et al (2019) Aging and the male reproductive system. Endocr Rev 40:906–972
41. Vanderschueren D, Laurent MR, Claessens F et al (2014) Sex steroid actions in male bone. Endocr Rev 35:906–960
42. Khosla S, Melton LJ III, Atkinson EJ et al (2001) Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 86:3555–3561
43. Gennari L, Merlotti D, Martini G et al (2003) Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol Metab 88:5327–5333
44. Van Pottelbergh I, Goemaere S, Kaufman JM (2003) Bioavailable estradiol and an aromatase gene polymorphism are determinants of bone mineral density changes in men over 70 years of age. J Clin Endocrinol Metab 88:3075–3081
45. Cauley JA, Ewing SK, Taylor BC et al (2010) Sex steroid hormones in older men: longitudinal associations with 4.5-year change in hip bone mineral density—the osteoporotic fractures in men study. J Clin Endocrinol Metab 95:4314–4323
46. Woo J, Kwok T, Leung JC et al (2012) Sex steroids and bone health in older Chinese men. Osteoporos Int 23:1553–1562
47. Bjørnerem A, Emaus N, Berntsen GK et al (2007) Circulating sex steroids, sex hormone-binding globulin, and longitudinal changes in forearm bone mineral density in postmenopausal women and men: the Tromsø study. Calcif Tissue Int 81:65–72
48. Amin S, Zhang Y, Felson DT et al (2006) Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. Am J Med 119:426–433
49. Roddam AW, Appleby P, Neale R et al (2009) Association between endogenous plasma hormone concentrations and

fracture risk in men and women: the EPIC-Oxford prospective cohort study. J Bone Miner Metab 27:485–493
50. Mellström D, Vandenput L, Mallmin H et al (2008) Older men with low serum estradiol and high serumSHBG have an increased risk of fractures. J Bone Miner Res 23:1552–1560
51. LeBlanc ES, Nielson CM, Marshall LM et al (2009) The effects of serum testosterone,estradiol, and sex hormone binding globulinlevels on fracture risk in older men. J Clin Endocrinol Metab 94:3337–3346
52. Vandenput L, Mellström D, Kindmark A et al (2016) High serum SHBG predicts incident vertebral fractures in elderly men. J Bone Miner Res 31:683–689
53. Cawthon PM, Schousboe JT, Harrison SL et al (2016) Sex hormones, sex hormone bindingglobulin, and vertebral fractures inolder men. Bone 84:271–278
54. Bjørnerem A, Ahmed LA, Joakimsen RM et al (2007) A prospective study of sex steroids, sex hormone-binding globulin, and non-vertebral fractures in women and men: the Tromso Study. Eur J Endocrinol 157:119–125
55. Meier C, Nguyen TV, Handelsman DJ et al (2008) Endogenous sex hormones and incident fracture risk in older men: the Dubbo osteoporosis epidemiology study. Arch Intern Med 168:47–54
56. Yeap BB, Alfonso H, Chubb SAP et al (2020) U-shaped association of plasma testosterone, and no association of plasma estradiol, with incidence of fractures in men. J Clin Endocrinol Metab 105:1489–1500
57. Orwoll E, Lambert LC, Marshall LM et al (2006) Endogenous testosterone levels, physical performance,and fall risk in older men. Arch Intern Med 166:2124–2131
58. Vandenput L, Mellstrom D, Laughlin GA et al (2017) Low testosterone, but not estradiol, is associatedwith incident falls in older men: the InternationalMrOS Study. J Bone Miner Res 32:1174–1181
59. Orwoll ES, Lapidus J, Wang PY et al (2017) The limited clinical utility oftestosterone, estradiol and sex hormone bindingglobulin measurements in the prediction of fracturerisk and bone loss in older men. J Bone Miner Res 32:633–664
60. Ensrud K, Taylor B, Paudel M et al (2009) Serum25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab 94:2773–2780
61. Cauley J, Parimi N, Ensrud K et al (2010) Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. J Bone Miner Res 25:545–553
62. Looker AC (2013) Serum 25-hydroxyvitamin D and risk of major osteoporotic fractures in older US adults. J Bone Miner Res 28:997–1006
63. Swanson C, Srikanth P, Lee C et al (2015) Associations of25-hydroxyvitamin D and 1,25-dihydroxyvitaminD with bone mineral density, bone mineral densitychange, and incident nonvertebral fracture. J Bone Miner Res 30:1403–1413
64. Snijder MB, van Schoor NM, Pluijm SM et al (2006) Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab 91:2980–2985
65. Barrett-Connor E, Laughlin G, Li H et al (2012) The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: the osteoporotic fractures in men (MrOS) study. J BoneMiner Res 27:2306–3231
66. Lips P (2001) VitaminD deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 22:477–501
67. Szulc P, Munoz F, Marchand F et al (2003) Role of vitamin D and parathyroid hormone in the regulation of bone turnover and bone mass in men: the MINOS study. Calcif Tissue Int 73:520–530
68. Carrivick SJ, Walsh JP, Brown SJ et al (2015) Brief report: does PTH increase with age, independent of 25-hydroxyvitamin D, phosphate, renal function, and ionized calcium? J Clin Endocrinol Metab 100:2131–2134
69. Curtis J, Ewing S, Bauer D et al (2012) Association of Intact parathyroid hormone levels with subsequent hip BMD loss: the osteoporotic fractures in men (MrOS) study. J Clin Endocrinol Metab 97:1937–1944
70. Giustina A, Mazziotti G, Canalis E (2008) Growth hormone, insulin-like growth factors and the skeleton. Endocr Rev 29:535–559
71. Perrini S, Laviola L, Carreira MC et al (2010) The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J Endocrinol 205:201–210
72. Van den Beld AW, Kaufman JM, Zillikens MC et al (2018) The physiology of endocrine systems with ageing. Lancet Diabetes Endocrinol 6:647–658
73. Ebeling PR (2008) Clinical practice. osteoporosis in men. N Engl J Med 358:1474–1482
74. Adler R (2018) Update on osteoporosis in men. Best Pract Res Clin Endocrinol Metab 32:759–772. https://doi.org/10.1016/j.beem.2018.05.007
75. Fink HA, Litwack-Harrison S, Taylor BC et al (2016) Clinical utility of routine laboratory testing to identify possible secondarycauses in older men with osteoporosis: the osteoporotic fractures in men (MrOS) study. Osteoporos Int 27:331–338
76. Kanis JA, McCloskey EV, Johansson H et al (2008) A reference standard for the description of osteoporosis. Bone 42:467–475. https://doi.org/10.1016/j.bone.2007.11.001
77. Kanis JA, Johnell O, Oden A et al (2001) Diagnosis ofosteoporosis and fracture threshold in men. Calcif Tissue Int 69:218–221
78. Watts NB, Leslie WD, Foldes AJ et al (2013) International society for clinical densitometry position development conference: task force on normative databases. J Clin Densitom 16:472–481. https://doi.org/10.1016/j.jocd.2013.08.001
79. Watts NB, Adler RA, Bilezikian JP et al (2012) Osteoporosis in men: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 97:1802–1822
80. Cosman F, de Beur SJ, LeBoff MS et al (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25:2359–2381
81. Pasco JA, Lane SE, Brennan SL et al (2014) Fracture risk among older men: osteopenia and osteoporosis defined using cut-points derived from female versus male reference data. Osteoporos Int 25:857–862
82. Ensrud K, Taylor B, Peters K et al (2014) Implicationsof expanding indications for drug treatment to preventfracture in older men in United States: cross sectionaland longitudinal analysis of prospective cohort study. BMJ 349:g4120
83. Cauley JA, Cawthon PM, Peters KE et al (2016) Risk factors for hip fracture in older men: the osteoporotic fractures in men study(MrOS). J Bone Miner Res 31:1810–1819
84. Kanis JA, Johnell O, Oden A et al (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385–397
85. Nguyen ND, Frost SA, Center JR et al (2008) Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int 18:1109–1117
86. Kanis JA, Harvey NC, Cooper C et al (2016) A systematic review of intervention thresholds based on FRAX: a report prepared by the national osteoporosis guideline group and the international osteoporosis foundation. Arch Osteoporos 11:25. https://doi.org/10.1007/s11657-016-0278-z
87. Kanis JA, Harvey NC, Johansson H et al (2020) A decade of FRAX:how has it changed the management of osteoporosis? Aging Clin Exp Res 32:187–196. https://doi.org/10.1007/s40520-019-01432-y

88. Schousboe JT, Vo TN, Langsetmo L et al (2017) Association of trabecular bone score (TBS) with incident clinical and radiographic vertebral fractures adjusted for lumbar spine BMD in older men: a prospective cohort study. J Bone Min Res 32:1554–1558
89. Body J-J, Bergmann P, Boonen S et al (2011) Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. Osteoporos Int 22:2769–2788. https://doi.org/10.1007/s00198-011-1545-x
90. Kaufman J-M, Lapauw B, Goemaere S (2014) Current and future treatments of osteoporosis in men. Best Pract Res Clin Endocrinol Metab 28:871–884. https://doi.org/10.1016/j.beem.2014.09.002
91. Langsetmo L, Shikany JM, Burghardt AJ et al (2018) High dairy protein intake is associated with greater bone strength parameters at the distal radius and tibia in older men: a cross-sectional study. Osteoporos Int 29:69–77. https://doi.org/10.1007/s00198-017-4261-3
92. Rozenberg S, Body JJ, Bruyere O et al (2016) Effects of dairy products consumption on health: benefits and beliefs-a commentary from the belgian bone club and the european society for clinical and economic aspects of osteoporosis, steoarthritis and musculoskeletal diseases. Calcif Tissue Int 98:1–17. https://doi.org/10.1007/s00223-015-0062-x
93. Chandran M, Tay D, Mithal A (2019) Supplemental calcium intake in the aging individual: implications on skeletal and cardiovascular health. Aging Clin Exp Res 31:765–781. https://doi.org/10.1007/s40520-019-01150-5
94. Harvey NC, Biver E, Kaufman JM et al (2017) The role of calcium supplementation in healthy musculoskeletal ageing: an expert consensus meeting of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO) and the international foundation for osteoporosis (IOF). Osteoporos Int 28:447–462
95. Rizzoli R, Boonen S, Brandi ML et al (2013) Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 9:305–313
96. Hurley DL, Binkley N, Camacho PM et al (2018) The use of vitamins and minerals in skeletal health: American association of clinical endocrinologists and the American college of endocrinology position statement. Endocr Pract 24:915–924. https://doi.org/10.4158/PS-2018-0050
97. Giustina A, Adler RA, Binkley N et al (2020) Consensus statement from 2nd international conference on controversies in vitamin D. Rev Endocr Metab Disord 21:89–116
98. Dawson-Hughes B (2017) Vitamin D and muscle function. J Steroid Biochem Mol Biol 173:313–316. https://doi.org/10.1016/j.jsbmb.2017.03.018
99. Rizzoli R (2021) Vitamin D supplementation: upper limit for safety revisited? Aging Clin Exp Res 33:19–24
100. Boonen S, Reginster JY, Kaufman JM et al (2012) Fracture risk and zoledronic acid therapy in men with osteoporosis. New Engl J Med 367:1714–1723. https://doi.org/10.1056/NEJMoa1204061
101. Orwoll E, Ettinger M, Weiss S et al (2000) Alendronate for the treatment of osteoporosis in men. N Engl J Med 343:604–610. https://doi.org/10.1056/NEJM200008313430902
102. Boonen S, Orwoll ES, Wenderoth D et al (2009) Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res 24:719–725. https://doi.org/10.1359/jbmr.081214
103. Lyles KW, Colon-Emeric CS, Magaziner JS et al (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809. https://doi.org/10.1056/NEJMoa074941
104. Boonen S, Orwoll E, Magaziner J et al (2011) Once-yearly zoledronic acid in older men compared with women with recent hip fracture. J Am Geriatr Soc 59:2084–2090. https://doi.org/10.1111/j.1532-5415.2011.03666
105. Orwoll ES, Miller PD, Adachi JD et al (2010) Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5mg versus a once-weekly 70 mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter; double-blind, active control study. J Bone Miner Res 25:2239–2250
106. Smith MR, Egerdie B, Hernandez Toriz N et al (2009) Denosumab in men receiving androgen-deprivationtherapy for prostate cancer. N Engl J Med 361:745–755
107. Orwoll E, Teglbjærg CS, Langdahl BL et al (2012) A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 97:3161–3169. https://doi.org/10.1210/jc.2012-1569
108. Langdahl BL, Teglbjærg CS, Ho PR et al (2015) A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab 100:1335–1342. https://doi.org/10.1210/jc.2014-4079
109. Tsourdi E, Langdahl B, Cohen-Solal M et al (2017) Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. Bone 105:11–17. https://doi.org/10.1016/j.bone.2017.08.003
110. Orwoll ES, Scheele WH, Paul S et al (2003) The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17. https://doi.org/10.1359/jbmr.2003.18.1.9
111. Kaufman JM, Orwoll E, Goemaere S et al (2005) Teriparatide effects on vertebralfractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 16:510–516. https://doi.org/10.1007/s00198-004-1713-3
112. Finkelstein JS, Hayes A, Hunzelman JL et al (2003) The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 349:1216–1226
113. Lewiecki EM, Blicharski T, Goemaere S et al (2018) A Phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab 103:3183–3193. https://doi.org/10.1210/jc.2017-02163
114. Fuggle NR, Cooper C, Harvey NC et al (2020) Assessment of cardiovascular safety of anti-osteoporosis drugs. Drugs 80:1537–1552. https://doi.org/10.1007/s40265-020-01364-2
115. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ et al (2017) Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 177:471–479
116. Brown JE, Handforth C, Compston JE et al (2020) Guidance for the assessment and management of prostate cancer treatment-induced bone loss A consensus position statement from an expert group. J Bone Oncol 25:100311. https://doi.org/10.1016/j.jbo.2020.100311
117. Sanli I, van Helden SA, ten Broeke RHM et al (2019) The role of the fracture liaison service (FLS) in subsequent fracture prevention in extreme elderly. Aging Clin Exp Res 31:1105–1111. https://doi.org/10.1007/s40520-018-1054-2