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Title page

Title Osteoporosis in men

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Abstract

Osteoporosis in men is common and often overlooked. The criterion for osteoporosis diagnosis in men is similar to that for women, BMD 2·5 standard deviations (SD) or more below the mean for young adult population (T-score ≤ − 2·5), measured at the hip or lumbar spine. Sex steroids are important for bone health in men, and it is oestrogens that play a key role, as in women. Men have bigger and stronger bones than women and suffer less bone loss during lifetime. Men fracture less often than women, although they have a higher mortality after a fracture. Secondary osteoporosis is more common in men than women. Lifestyle changes, adequate calcium and vitamin D intake and exercise programs are recommended for the management of osteoporosis in men. Bisphosphonates, denosumab, and teriparatide have been shown to increase bone mineral density (BMD) and are used for pharmacological treatment.

Introduction

Osteoporosis increases the risk of fractures and is defined operationally as a BMD value of 2·5 standard deviations or more below the mean for young adults (T-score ≤ − 2·5).[1] This overlooked disorder is more common in women, but men suffer from it too. This is a narrative review on the diagnosis and management of osteoporosis in men. We report an updated overview of osteoporosis in men, describe new treatments and concepts and discuss persistent controversies in the area.

Epidemiology

In 2015, there were approximately 20 million people in the European Union with osteoporosis; 4·2 million of them were men.[2] The prevalence of osteoporosis over the age of 50 years is 7% in men, lower than the 23% reported for women. As in women, fractures do not always occur at BMD in the osteoporosis range; between 27 to 45% of fractures occur in men with osteopenia (T-score <1·0, >-2·5).[3]

The economic burden of fractures in men and women was estimated at €37·5 billion a year in 2017 (data from Europe), with an expected 27% increase in the next 13 years (€47·4 billion). Hip fractures accounted for the greatest percentage of the cost in men and women (57%).[2] In the United States, men accounted for 25% of the costs of fracture care .[4]

Men and women have different patterns of fractures. In elderly men and women, fractures occur in the distal forearm, proximal humerus, thoracic and lumbar vertebra, and proximal femur (called 'major osteoporotic fractures').[5] Distal forearm fractures are not as common in men as women at 50 years have about a 5-times higher risk of a forearm fracture (13% vs 4%) than men. [6]

Although the rate of hip fractures is higher in women, male rates approach the female ones with increasing age. The remaining lifetime risk of having a hip fracture after the age of 50 for men ranged from 6% to 14%, while in women from 10% to 23%.[2] The female/male ratio was 4·5 in the 60–69 group, 1·5 in the 70–79 group and 1·9 in the 80+ year age group. In men, the incidence rate of hip fracture peaked at 80-84 years and then decreased unlike in women in whom the incidence rate continued to increase with age. One half of the hip fractures (48%) occur before the age of 80 in men, underlying the need for earlier diagnosis and intervention.[7]

Men are at risk of vertebral fractures but the risk estimates are inconsistent between studies. We cite here the results from longitudinal studies as these allow study of incident fractures, a more robust measure than prevalent fractures. After 50 years, the age standardized incidence of morphometric fracture was 5·7/1000 person-years (pyr) in men, 10·7/1000 pyr in women.[8] A study using MRI of the whole spine found that elderly men have lower vertebral fracture rates than women.[9]

Mortality

One in 15 patients with hip fracture aged 60 years and above will die during hospitalisation, with men having higher in-hospital mortality than women (10% vs 5%). One third of those who survive will die within a year, with men having higher rates than women (38% and 28%, respectively). Male gender was an independent factor associated with mortality.[10] Men experiencing a hip fracture at an older age have an 8-fold increased mortality risk during the first 3 months,[11] and mortality seems to remain high for more than 10 years.[12] Mortality is also higher after vertebral and other osteoporotic fractures. [13] The mortality excess in men is probably associated with the higher prevalence of comorbidities.[6] In men after a hip fracture, the relative risk of

dying from cardiovascular disease was 2.7 [1.6– 4.4]. [14] Osteoporosis treatment have little effect on the risk of mortality. For example, treatment with zoledronate did decrease mortality on the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial (RFT), but only 8% of the reduction in mortality was as a result of the reduction in fractures.[15] This could suggest that medications used to treat osteoporosis have direct effects on other drivers of mortality such as cardiovascular disease and cancer. However, data from meta-analyses are conflicting; one study reported that osteoporosis treatment has resulted in 11% decrease in mortality [16] while a more recent meta-analysis suggested that treatment with bisphosphonates was not related to reduction in overall mortality. [17]

Bone mass in men

In the first decades of life, the skeleton changes its shape (modelling), grows and bone mass is accrued up to a peak. The magnitude of this peak is influenced by genetic and environmental factors. The difference in peak bone mass between genders starts during puberty, and peak bone mass is greater in males due to a more prolonged bone maturation period in males than in females.[18] In addition, animal studies have shown that androgens stimulate periosteal bone formation in rats, and this may play a role in sexual dimorphism.[19] The results are larger increases in bone size and cortical thickness and consequently bigger and stronger bones in men.[18,20]

The peak in bone mass is an important determinant for future osteoporotic fracture risk.[18] Data from a Caucasian American cohort have shown that young men have bone cross-sectional area 30% and bone mass 20% higher than young women, both at central and peripheral sites.[21] The peak in BMD occurs at age 20 at the hip and age 30 at the spine [22,23] and is followed by subsequent bone loss. In older adults, the BMD

is the result of the peak bone mass and the subsequent bone loss. Bone is remodelled throughout life through an orderly process during which bone resorption is followed by bone formation, mediated by osteoclasts and osteoblasts, respectively. When bone resorption exceeds bone formation, there is negative remodelling imbalance and bone loss.[24,25] Bone loss can also be a consequence of an increase in bone turnover, but the increase in bone turnover in men with age is quite small as compared to women.[26,27] All these features contribute to the occurrence of fewer fractures in men compared to women (Figure 1).

Pathophysiology of ageing in bone

Age-related bone loss is associated with three main processes: trabecular bone loss, continued net resorption at the endocortical surface and decrease in cortical volumetric bone mineral density (vBMD).[21]

Trabecular bone

Riggs et al have shown that trabecular bone loss begins in early adulthood in both men and women in cross-sectional and longitudinal studies using central and peripheral QCT.[21,25] Men experience 42% of their total lifetime trabecular bone loss before the age 50.[25] The mechanisms for this bone loss are unknown. The onset of trabecular loss shortly after the peak of bone mass achievement cannot be explained by deficiencies in sex steroids, as these are 'normal' in young adulthood. This is confirmed by the absence of correlations between bone loss and sex steroids levels in this age group.[25] In another cohort that included 1149 men from 19 to 85 years old, bone turnover markers (BTM) did not correlate with features of trabecular

microarchitecture in any age range. These findings suggest that in men younger than 50 years old, trabecular features are not associated with the rate of bone turnover.[27] The pattern of trabecular bone loss differs between men and women; while women lose preferentially trabecular number, men lose trabecular thickness. These data came from central [21,25] and peripheral QCT [21,25],HR-pQCT [28-30] and histomorphometric studies [31] suggesting that changes are similar at several skeletal sites. Reductions in trabecular number have a more pronounced effect on bone strength than trabecular thickness [32] and contribute to the favourable fracture profile observed in men compared to women (figure 1).

Cortical bone

Several studies have shown an increase in resorption in the endocortical surface with ageing.[21,25,27,29,30,33] This increase in resorption is associated with the decrease in sex steroids. The process begins at midlife and accelerates in the seventies in men, in contrast with the perimenopausal acceleration in women.[21,25] Riggs et al have estimated that after 70-years this process would result in a 0·5%/year cortical bone loss in men.[25]. This is in agreement with data from another cohort where higher BTMs were associated with lower cortical thickness and cortical vBMD after 70 years of age.[27] The apparent increase in trabecular area suggests trabecularisation of the cortex.[27,30,33] Periosteal apposition observed with ageing partially offsets endosteal resorption and the cortex is displaced outwardly.[25] [27] This is favourable to biomechanics but not enough to compensate for endosteal resorption. A decrease in cortical area and width is observed, resulting in thinning of the cortex. [21,25,29,30] In addition, Shanbogue et al showed an increase in peripheral cortical porosity in men older than 50 years.[29] Cortical porosity favors crack propagation during mechanical

loading and aggravate the loss of failure load.[34] The thinning of the cortex and increase in cortical porosity result in a decrease in cortical vBMD and reduced bone resistance to fractures.

The role of sex steroids

Ageing is also associated with a decrease in sex steroids in men even though there is no evidence of acute gonadal failure.[35] An increase in SHBG is observed and results in a decrease in bioavailable sex steroids.[35,36] Testosterone (T) produced by the testis undergoes aromatization into oestradiol (E_2). Therefore, the levels of both steroids change in parallel and both will be decreased in hypogonadal men.[37] Observational data suggested that E_2 plays a key role in bone homeostasis in men.[38-41] Elegant intervention studies have blocked endogenous T production using gonadotropin-releasing hormone (GnRH) agonist and T aromatization to E_2 using aromatase inhibitors and have selectively investigated the effects of T and E_2 on bone turnover.[42,43] In a 3-week study, E_2 replacement prevented most of the increase in bone resorption.[42] In a longer study (16 weeks), T replacement did have a dose-dependent effect on bone resorption, although the effect was smaller in the presence of E_2 deficiency. The increase in bone resorption led to a decrease in vBMD and findings suggestive of an increase in endosteal resorption. The results suggest that serum E_2 levels below 10 pg/mL (36.7pmol/L) (measured by liquid chromatography-tandem mass spectroscopy) and serum total T below 200 ng/dL (6.9 nmol/L) (chemiluminescent immunoassay) might be harmful to bone health.[43] This is further discussed in Panel 1.

Other determinants

Insulin-like growth factor 1 (IGF-1) may also play a role in bone loss associated with ageing. Decreased levels of IGF-1 were detected in men with male idiopathic

osteoporosis and were associated with the presence of an osteoporotic fracture, even after adjustment for testosterone and BMI.[44] In a large cohort of Swedish men (n=2902), low IGF-1 was associated with an increase in the risk of both vertebral and hip fractures and low total body lean mass and grip strength. The negative association with the risk of fractures was lost when adjusted for BMD but not affected when adjusted for total body lean mass and grip strength suggesting that IGF-1 mediated structural effects.[45] Conversely, longitudinal studies failed to establish correlations between IGF-1 levels and changes in bone geometry or microarchitecture assessed by QCT in men > 50 years.[25]

Both dynapenia (the age-associated loss of muscle strength), and sarcopenia (the loss of muscle mass associated with the presence of low muscle function) contribute to the deterioration of bone microarchitecture and the increase in the risk of falls and fractures in older men.[30,33] In a cohort where 821 men over 60 years old were followed for 8 years, low appendicular muscle mass and muscle strength were associated with a more rapid decrease in total vBMD and cortical variables evaluated by HR-pQCT.[30,33] Bone microarchitecture decline was associated with poor physical performance more strongly than with muscle mass.[33] Poor physical performance was also associated with a higher risk of falls and nonvertebral fractures.[33]

Imaging for osteoporosis in men

There are several recommendations [46-53] regarding the screening for osteoporosis in men, using BMD of the spine and hip. There is a long-standing debate on which database should be used as a reference for the T-score calculation in men (appendix 1). In summary, testing for osteoporosis has been recommended in older men, or earlier if there are risk factors. Vertebral fracture assessment is also usually

recommended by some authorities in older men (>80) and in men with height loss (>4 cm), prior vertebral fracture and prolonged steroid requirements (more than 3 months). [53] Forearm BMD is an alternative way of imaging which is usually recommended in subjects with primary hyperparathyroidism and when other sites cannot be measured, as in the case of obese people. Imaging techniques like trabecular bone score (TBS) and ultrasound are not part of the recommendations, while high resolution peripheral quantitative computed tomography (HR-pQCT) is currently used only in research. Quantitative Computed Tomography (QCT) of the spine and hip can occasionally be used for the diagnosis of osteoporosis, although DXA is preferred since the DXA threshold for osteoporosis has been defined and used in clinical trials. Finally, CT and MRI scans can be used in the detection of vertebral fractures, sometimes leading to an opportunistic diagnosis. [54]

Fracture risk assessment in men

Fracture prediction tools can also be used to predict the risk of fractures and to identify the need for BMD measurement. There are several tools available in clinical practice, the best known ones being Fracture Risk Assessment Tool (FRAX)[55], Garvan [56] and QFracture. [57] These can predict the risk of fracture over 1 to 10 years. The first two can incorporate BMD measurements. Just using the femoral neck T-score was equally good as the above-mentioned tools that were found to be poorly calibrated for hip fracture for men aged 65 years or more. [58] Another study has shown that for hip fracture, there was good agreement between FRAX and Garvan in older men. However, for any fracture, there was poor concordance between the two tools, with FRAX leading to risk underestimation of any fracture.[59] Other studies have also shown that while FRAX is a good prediction tool in women, it is probably not so accurate in

men.[60] In summary, prediction tools can give results for fracture risks that can be easier to communicate to patients, but they are less accurate in men than in women.

Causes of osteoporosis in men

Idiopathic osteoporosis is defined by the development of osteoporosis and/or fractures in early age, i.e. before the abnormalities associated with ageing are expected.[61] It is a heterogeneous condition, often associated with family history, where both genetic and environmental factors might play a role. A recent cohort of men with idiopathic osteoporosis has identified variants of the Low-Density Lipoprotein-Related Receptors 5 (*LRP5*) gene using next-generation sequencing of genes potentially linked to low BMD.[62] The product of this gene is involved in the canonical Wnt/β-catenin signaling cascade, a pathway that promotes bone formation.[62] Another genetic cause of osteoporosis is a loss-of-function *PLS3* variant. *PLS3* encodes plastin-3, a protein involved in the formation of filamentous actin (F-actin) bundles whose absence leads to bone abnormalities.[63] These variants are associated with X-linked male osteoporosis and should be investigated when severe osteoporosis in a family affects preferentially males. Osteoporosis and fractures in young men have also been associated polymorphisms and variants of unknown significance in several genes such as the aromatase (*CYP119A1*), oestrogen receptor alpha (*ESR1*), vitamin D receptor, collagen type I alpha 1 and IGF-I.[64] However, the contribution of these genetic factors to the variations on BMD and fracture risk remain unknown.[62-64]

Other causes of osteoporosis should always be investigated. Secondary osteoporosis is more common in men than in women.[13,65] Panel 2 lists the common causes of osteoporosis in men. The Endocrine Society recommends measuring morning fasting testosterone and in cases where this is borderline or sex hormone binding globulin

(SHBG) is altered, then free testosterone should be measured.[66] Other tests should include calcium and parathyroid hormone, liver function tests, assessment of kidney function, thyroid function (TSH), a complete blood count, serum protein electrophoresis and urinary sample for Bence Jones protein and anti–tissue transglutaminase antibodies. Extensive discussion of secondary osteoporosis is beyond the scope of this review but since androgen deprivation therapy is a common male-specific cause of osteoporosis it will be discussed in more detail.

Bone fragility associated with androgen deprivation therapy

Bone health is an emerging concern in men receiving treatment for prostate cancer. One in eight men will receive a diagnosis of prostate cancer in their lifetime. However, early diagnosis and advances in therapy currently result in an 85% survival rate. This raised the importance of the long-term consequences of treatment such as cancer treatment induced bone loss (CTIBL) and the resulting increased risk of fractures.[67]

Continuous or intermittent androgen deprivation therapy (ADT) is offered to men in several different clinical settings of prostate cancer.[67] Gonadotrophin releasing hormone agonists (such as goserelin and leuprorelin) and antagonists (such as degarelix) are commonly used and lead to a rapid and substantial reduction in circulating androgens and oestrogens and disruption of bone remodelling balance. Prospective studies have shown that the bone loss in the first year of ADT (5-10% BMD loss) [68,69] is greater than the expected age-related male bone loss (0·5-1·0% per annum) and perimenopausal bone loss in women (1-1·5%). In addition, glucocorticoids are often associated with cancer therapies adding extra harmful effects.[67] Finally, both anti-androgens and glucocorticoids increase adiposity,

decrease lean body mass and lead to sarcopenia. The compromised muscle mass and function might contribute to an increase in the risk of falls and fractures.[69]

Fracture risk assessment in men in androgen deprivation therapy

Neither FRAX nor QFracture have been specifically developed or calibrated for use in prostate cancer patients in ADT.[67] Current evidence suggests that fracture risk in ADT users is BMD-dependent [70]. In the absence of BMD measurement, the secondary osteoporosis variable should be ticked in men in use of ADT. If FRAX probabilities calculated without the BMD lies close to the intervention threshold, BMD should be measured and included.[67]

Men with previous osteoporosis or history of fracture should be investigated to exclude other causes of osteoporosis. A change in the systemic cancer therapy or a change in the risk factor profile, such as a new fracture, should lead to new fracture risk reassessment. In those taking ADT but below the treatment threshold, BMD and FRAX fracture risk should be reassessed in 12-18 months. In all patients taking ADT, fracture risk should be reassessed after 5 years.[67]

<u>General approach to the management of a man with osteoporosis</u>

The management approach begins by considering the impact of osteoporosis on the man's health. For example, is he suffering back pain, height loss or kyphosis? This is important as these are often the most pressing issues of concern and call for adequate analgesia. Vertebral augmentation may reduce pain early, but the ASBMR Task Force concluded that routine use was not supported by evidence. [71]

The risk factors for fracture need to be identified. It is particularly important to start treatment in men with a recent fracture, since these men are at increased risk of

another osteoporotic fracture in the next 12 to 24 months, the so-called 'imminent fracture risk'. [72] Two studies have shown that a second fracture is 40% more likely in women than in men, but even so, it is an important risk factor .[73] [74]

There are lifestyle factors that are reversible, such as smoking, alcohol abuse, low body weight, inadequate sunshine exposure, and a sedentary lifestyle. There are diseases that may cause osteoporosis and need optimal treatment. He may be at increased risk of falls and so medical and domiciliary issues need to be addressed. Falls may be prevented by group and home-based exercise programmes, home safety interventions and the practice of Tai Chi.[75] The benefits of exercise are mostly through improvement in falls rather than through an increase in BMD - for example one year of high impact exercise in one leg resulted in less than a 1% increase in femoral neck BMD in men.[76]

There is little evidence from studies in men, but it is usually recommended that an intake of 1000 mg calcium and 800 IU of vitamin D should be taken to prevent osteoporosis; these were the amounts often included in clinical trials of anti-osteoporotic drugs.[47] The NOS Vitamin D Guideline recommends a 25-hydroxyvitamin D level of at least 50 nmol/L for vitamin D sufficiency and a maintenance dose of at least 800 IU/day [77]. Vitamin D deficiency is particularly common in the housebound who would need around 800IU/day, those with malabsorption and those taking drugs altering vitamin D metabolism, such as phenytoin both of whom would need up to 4000 IU/day. [77] Some patients with malabsorption benefit from intramuscular administration of vitamin D. Calcium supplements should only be taken if the dietary calcium is inadequate, as supplements have been associated with increased cardiovascular risk in some [78,79] but not all studies. For example, a meta-analysis supported by the

National Osteoporosis Foundation found no significant harm; it did identify an increase in stroke risk at intakes above 1000 mg daily but only in women. [80]

Pharmacological therapy

We assess fracture risk and recommend specific treatment in those men who are at high risk. It is usual to recommend pharmacological therapy in men with a T-score at the spine or hip of -2·5 or less, a history of vertebral or hip fracture. In some countries (e.g., USA) it is also usual to use a 10-year fracture risk at the hip of 3% or more or of major fractures of 20% or more [47] while in other countries (e.g. UK) it is usual to use an age-dependent threshold of absolute fracture risk. [52] It is also often recommended that men taking drugs that accelerate bone loss, such as glucocorticoids and anti-androgen therapy be considered for treatment. The decision to give pharmacological therapy in such patients is based on the risk of fracture.

The clinical trials of anti-osteoporosis drugs have been much smaller in men than those in women and usually use BMD rather than fracture as an outcome (Panel 3, Table 1). We should consider co-morbidities when choosing the type of treatment and use oral bisphosphonates with caution in patients with heartburn.

Bisphosphonates

In a meta-analysis of 22 studies, there was evidence that bisphosphonates reduced vertebral (relative risk RR 0·37, 95% CI 0.25 to 0.54) and non-vertebral fracture (RR 0·60, 95% CI 0.40 to 0.90) in men, but the analysis for non-vertebral fractures was not robust.[81] There has only been one clinical trial that was sufficiently powered for vertebral fracture as an endpoint and that showed a reduced in vertebral fractures by zoledronate (Panel 3, Table 1).[82]

The oral bisphosphonates alendronate and risedronate can cause oesophageal irritation and are poorly absorbed and so they are usually taken once a week before breakfast with a full glass of water and the patient is advised not to lie down; they may have breakfast after 30 minutes. In some countries, weekly alendronate is available as an effervescent tablet, and weekly risedronate is available as an enteric-coated tablet (gastric-resistant) that can be taken after breakfast. Zoledronate may result in fever and arthralgia (the acute phase response) in about one third of patients and this can be attenuated using non-steroidal anti-inflammatory drugs. There is an increase in the risk of atypical femur fractures with increasing length of treatment with bisphosphonates. Therefore, after a five-year course of oral bisphosphonates and a three-year course of zoledronate a 'drug holiday' of around two years should be considered. After this planned pause, bisphosphonates may be re-started.[83]

Denosumab

Denosumab is licensed for use in men with osteoporosis.[84] Care needs to be taken to ensure adequate intake of calcium and vitamin D as hypocalcaemia is an adverse effect, particularly in patients with chronic kidney disease, so measurement of calcium and creatinine before the 6-monthly injection is advised. After long-term therapy in men and women, stopping denosumab is associated with an overshoot in bone turnover and an increase in the risk of vertebral fractures; the overshoot in bone turnover in men as well as women can be partially prevented by zoledronate, but we don't know if this reduces the risk of vertebral fracture [85].

Teriparatide

Teriparatide is licensed as an anabolic treatment for osteoporosis in men; it is given as a daily subcutaneous injection for two years and then followed by an anti-resorptive treatment such as bisphosphonates. Teriparatide increases BMD [86] and decreases

the risk of vertebral fractures.[87] It can cause hypercalcaemia and dizziness, nausea and headache. There is no benefit in adding alendronate to the teriparatide treatment.[88]

Treatments not yet licenced in men

Romosozumab has been developed as an anabolic treatment. It is an antibody to sclerostin, an inhibitor of bone formation. It is given monthly by subcutaneous injection. It is effective at reducing fractures in women and in both men and women it increases BMD (Table 1). In women it is licenced for use in severe osteoporosis with a warning not to use it in patients with prior stroke or myocardial infarction; it has not been licensed in men.

Testosterone

Low testosterone is commonly found in the older man and may be due to obesity and the use of drugs such as anti-androgens for prostate cancer.[51] The replacement of testosterone does result in small increases in BMD but not as large as anti-osteoporosis treatments; for example, in older men with low testosterone, the lumbar spine increased by 1·2% and the total hip by 0·7% over one year.[89] There has been no trial to show a reduction in fracture risk. Thus, testosterone is not considered an adequate treatment for osteoporosis in men. Anti-osteoporosis treatment is effective in increasing BMD in men with hypogonadism.[67] The Endocrine Society recommends using testosterone replacement in men with symptoms of hypogonadism in whom there is no contraindication to its use.[66]

Treatment in men in androgen deprivation therapy

ADT result in accelerated bone loss from the peripheral and central skeleton. Like in other groups of men, lifestyle changes and adequate calcium and vitamin D intake are

recommended. The bone loss can be prevented by bisphosphonates. Several clinical trials have shown increase in BMD with the use of bisphosphonates associated with ADT when compared to placebo, but we don't know whether fractures are reduced.[67] Vertebral fractures were reduced and bone loss prevented by denosumab given at the osteoporosis dose.[67,84] For patients taking ADT and protective bone therapy, treatment reassessment follows the same time frames as men in osteoporosis treatment, i.e., after 3 years of intravenous zoledronate and 5 years for oral bisphosphonates and denosumab.[67] Patients with metastatic prostate cancer often receive anti-resorptive therapy for the management of their metastatic disease, usually at higher doses than required for osteoporosis. In these patients, there is no benefit on bone health monitoring as they will be receiving the appropriate therapy to prevent/treat bone loss.[67]

Treatment guidance for osteoporosis in men

Bisphosphonates have shown the strongest evidence for treatment efficacy and cost-effectiveness in men and so they are often used as first line treatment. [90] If the man is intolerant of oral bisphosphonates, prefers an intravenous treatment or treatment fails, then zoledronate is recommended. It has the advantage of being the only treatment proven to reduce fracture risk in men in a clinical trial. If the patient develops a vertebral fracture while on treatment, then teriparatide should be considered. There is evidence for efficacy of teriparatide in men [88], but there is no additional benefit of giving the teriparatide along with alendronate as the spine and femoral neck BMD increase is less than giving teriparatide to men alone.[88] Teriparatide is always followed by anti-resorptive therapy to prevent loss of bone, but the evidence for this approach is based mostly on observational studies in women. [91]

Issues with treatment

Undertreatment of osteoporosis may be due in part to concerns about side effects such as atypical femur fractures and inadequate access to the appropriate diagnostic and treatment facilities. [92] The undertreatment is often referred to as the 'treatment gap'. For example, in the USA the proportion of men tested or treated after a fracture was even less than for women (6 vs. 12%).[93]

Men have poor compliance with anti-osteoporotic drugs; oral bisphosphonates are the most prescribed but adherence at one year is only 54 to 71% and failure to take 80% of medication is associated with a greater risk of fracture.[94] Men were reported to have lower medication possession ratio than women (40 vs. 48% at 2 years) in a Japanese study of health insurance claims.[95] Thus, it is important to assess treatment compliance as well as ensuring the improvement in BMD and absence of fractures during treatment in men.[96]

Compliance or adherence can be tested by monitoring the response of BMD after two years or bone turnover markers after 3 months. The International Osteoporosis Foundation (IOF) and European Calcified Tissue Society (ECTS) have recommend that the bone resorption marker carboxy-terminal collagen crosslinks (CTX) and/or the bone formation marker procollagen type 1 N propeptide (PINP) be measured before starting oral bisphosphonate therapy and three months later.[97] If the CTX and/or PINP decrease beyond the least significant change of 30% [98] the patient is likely to be adherent. Similarly, if a patient has an increase in lumbar spine or total hip BMD beyond the least significant change (4%) after 2 years, the patient is likely to be adherent. [98] However, fractures can occur even in men who are fully compliant with treatment.

In conclusion, men are at risk of fragility fractures and they have higher mortality than women after a fracture. We have stressed the importance of identifying secondary osteoporosis and treating contributing conditions. Many of the risk factors for fracture in men are like those in women and advice should be given concerning an adequate diet (in calcium, protein and vitamin D) and regular exercise and avoidance of smoking or excessive consumption of alcohol. Antiresorptive (bisphosphonates and denosumab) and anabolic (teriparatide) treatments are licenced for men with osteoporosis but undertreatment and poor adherence are important issues. Most of our knowledge about these drugs is based on the evaluation of BMD; there is a need for fracture trials to be conducted in men in the future.

Search strategy

We ran a literature search since a Clinical Guideline was published on osteoporosis in men by the Endocrine Society.[47] We searched Ovid MEDLINE for articles published from 1st January 2012, to 25th November 2021, with the terms "osteoporosis", and "fractures" in combination with the terms such as "male" and "men". Only articles published in English and research in humans were included in this search strategy. Peer-reviewed full articles resulting from this search strategy and key references cited in those articles and previous reviews were reviewed.

Panel 1. Should oestradiol be part of the work up in osteoporosis in men?

There is evidence suggesting that measuring E_2 in osteoporosis in men could be useful in clinical practice. Several studies have shown that E_2 is the main driver of cortical bone loss associated with the decrease in sex steroids.[42,43] Therefore, low levels of E_2 could identify patients at high risk of bone loss who could potentially benefit from antiresorptive treatment. In addition, both observational and interventional studies have suggested thresholds for E_2 measured both by radioimmunoassay and mass spectroscopy.[41,43] However, there are also several drawbacks. Currently, little is known on the threshold of E_2 needed to maintain bone health in men.[43] E_2 administration, even in low doses, has treatment-limiting side effects, such as gynaecomastia. The method of choice for measuring E_2 is tandem mass spectroscopy as it can measure low values and is specific to E_2, in contrast to radio-immunoassays, but it is not widely available. Finally, there is no clinical data on the efficacy of using E_2 levels to guide intervention. Therefore, we do not recommend measuring E_2 as part of the investigation of osteoporosis in men.

Panel 2 Secondary osteoporosis in men

	Disease/ Condition
Endocrine	
	Glucocorticoid excess (usually exogenous)*
	Hyperthyroidism
	Hyperparathyroidism
	Hypogonadism (Idiopathic or androgen deprivation therapy for prostate cancer)*
	Type 1 Diabetes
	Type 2 Diabetes**

Gastrointestinal disorders	
	Malabsorption syndromes
	Inflammatory bowel disease, coeliac disease
	Chronic liver disease
	Post-gastrectomy & bariatric surgery
Others	
	Alcoholism*
	Smoking
	Neuromuscular disorders
	Post-transplant osteoporosis
	Chronic kidney disease***
	Chronic obstructive pulmonary disease
	Rheumatoid arthritis & other inflammatory arthritis
	Monoclonal gammopathy of unknown significance & multiple myeloma
	Mastocytosis
	Idiopathic hypercalciuria
	Cystic fibrosis
	Osteogenesis imperfecta
	Human immunodeficiency virus infection (HIV)
Medications	
	Anticonvulsants
	Proton pump inhibitors

	Chemotherapeutics
	Protease inhibitors
	Antidiabetics (thiazolidenediones and SGLT2)

* Most common causes

** The increase in the risk of fractures is not associated with a decrease in BMD

***Also associated with renal osteodystrophy

Panel 3 Comparison of anti-osteoporosis treatments in men and women

The key trials of anti-osteoporosis treatments in men and women are shown in Table 1. The striking features are the small study size of trials in men and that BMD rather than vertebral fracture was the primary endpoint in all but one of these trials. In the clinical trial of zoledronate in men, there was a 67% reduction in vertebral fractures,[82] similar to the 70% reduction reported in women. All the other drugs reduced vertebral fracture risk in women, but we don't know for certain their effect on fracture risk in men. There is evidence that the two-year change in BMD at the total hip in the active as compared to the placebo group is strongly related to fracture risk reduction.[99] The evidence is more robust for women, but data from trials in men were also included. Thus, we can consider the clinical trials that lasted for two years and had a placebo group and compare men and women - almost all drugs were studied separately in men and women. The only exception was a trial of zoledronate in which men had a 2% and women a 3.8% increase in total hip BMD at two years. [100] In all trials in Table 1, the increase in BMD in men over two years at the total hip was less than in women. This observation was confined to the proximal femur; it wasn't present at the lumbar spine.

Why do men have a lesser total hip BMD response?

It could be because we have expressed the change in BMD in percentage and men have a greater BMD at baseline by 11% at total hip.[101] It could be that the drugs are less effective in men who are bigger and have lower bone turnover - for example, in response to zoledronate the serum CTX and PINP decreased by about 50% [102] in men and about 70% in women.[103] Bone turnover is higher in older women than in older men.[26] The higher bone turnover may relate to all women in these trials being postmenopausal but only 30% of men were hypogonadal.[104] Thus, consideration should be given to differences in pharmacokinetics in men as compared to women in future trials.

Table 1 Comparison of drug effects on vertebral fracture risk and BMD change in trials of anti-osteoporosis drugs

Drug	Number of subjects		Total Hip BMD difference at 2 years, %		Vertebral fracture reduction, % (95% CI)	
	Men	Women	Men	Women	Men	Women
Alendronate 10 mg daily po [104,105]	241	2027	2.5	3.7	N/A	47 (28 to 73)
Risedronate, 35 mg weekly or 5 mg daily po[106,107]	284	2458	1.7	2.2	N/A	41 (18 to 58)
Zoledronate 5 mg annually iv [82,103]	1199	7765	2.1	4.7	67 (30 to 84)	70 (62 to 76)
Teriparatide 20 mcg daily sc[86,108]	241	1637	0.6 (11 months)	5.3	N/A	65 (45 to 78)
Denosumab 60 mg 6-monthly sc[109,110]	241	2017	2.5	3.7	N/A	68 (59 to 74)
Romosozumab 210 mg	245	2027	3.0 (12 months)	3.7 (12 months)	N/A	73 (53 to 84)

monthly sc [111] [112]						

N/A Not available as vertebral fracture was not a primary endpoint.

Figure and table legends

Figure 1 Characteristics of bone development and ageing in men and women.

E Oestrogen

Table 1 Comparison of drug effects on vertebral fracture risk and BMD change in trials of anti-osteoporosis drugs

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