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5

Osteoporosis in older men: Recent advances in pathophysiology and treatment

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Osteoporosis remains underrecognized and undertreated but more so in men, adding considerably to fracture burden and costs. Fracture-related morbidity and mortality is higher in men, partly due to greater frailty. Improved peak bone mass, geometry and turn-over contribute to lower fracture incidence in men. Bioavailable androgens and oestrogens regulate these aspects of musculoskeletal sexual dimorphism, yet the direct cellular and molecular targets of sex steroids in bone remain incompletely understood. Screening with clinical risk factors and dual energy X-ray absorptiometry are advised in men from age 70 (or 50 with additional risk factors). We now have compelling evidence that osteoporosis drugs are equally effective in men and women, not only to increase bone density but also to prevent osteoporotic fractures. The use of testosterone or selective androgen

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teriparatide
strontium ranelate

receptor modulators for osteoporosis, sarcopenia, frailty and falls in men with late-onset hypogonadism requires further investigation.

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and fracture risk.[1] Osteoporosis and osteopenia can be diagnosed by dual energy X-ray absorptiometry (DXA) when bone mineral density (BMD) T-score (standard deviations below normal values for white 20 to 30-year-old U.S. women) is respectively ≤ -2.5 or between -1 and -2.5, although there is some controversy regarding the use of female references in men (see below). DXA measures areal BMD (aBMD), whereas quantitative computed tomography (qCT) allows volumetric BMD (vBMD) measurement of cortical and trabecular bone (Fig. 1).

Epidemiology

Fracture incidence

Fracture incidence follows a bimodal distribution, and the childhood peak is more pronounced in boys (Fig. 2). This is not only because boys have more accidents, but also because mineralization lags behind rapid bone expansion during the growth spurt, transiently decreasing aBMD, trabecular vBMD and increasing cortical porosity, especially in boys.[2] From age 55, fracture incidence in women

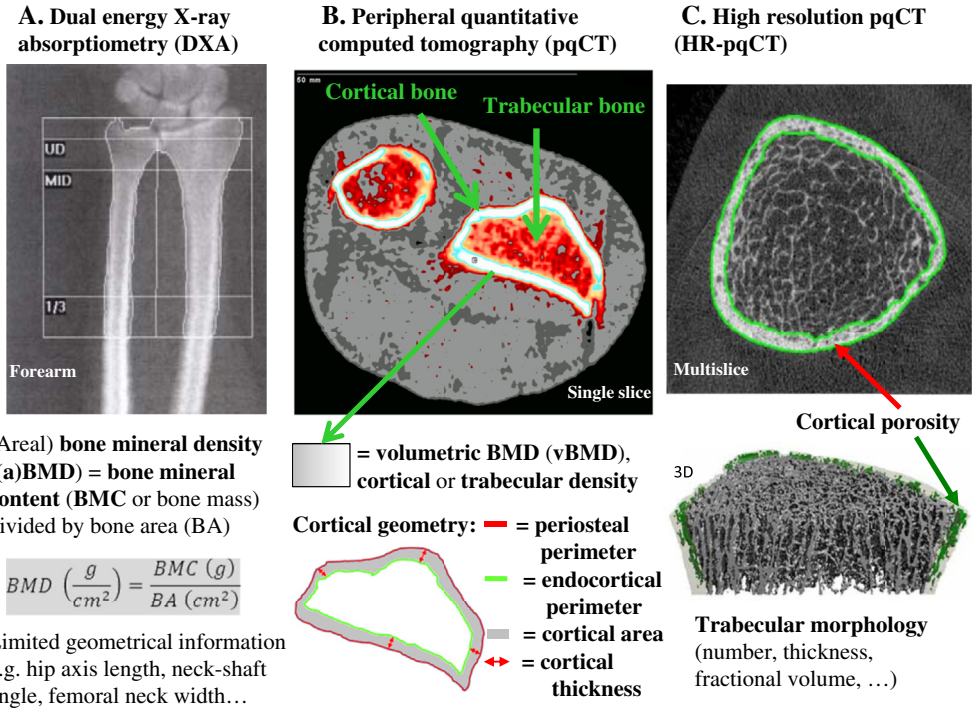

Fig. 1. Imaging modalities used in osteoporosis research and their relevant parameters. A and B: courtesy of Herman Borghs, Centre for Metabolic Bone Diseases, University Hospitals Leuven, Belgium, with permission. C: Adapted, with permission, from Burghardt AJ, Kazakia GJ, Ramachandran S et al. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. *Journal of Bone and Mineral Research* 2010; **25**: 983–993.

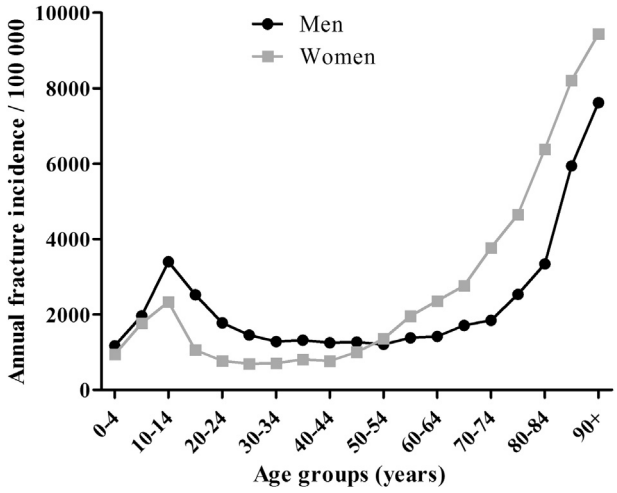

Fig. 2. Annual fracture incidence in a population-based registry from Umeå, Sweden over a 12-year period (1993–2004). Adapted, with permission, from Bergström U, Björnstig U, Stenlund H et al. Fracture mechanisms and fracture pattern in men and women aged 50 years and older: a study of a 12-year population-based injury register, Umeå, Sweden. *Osteoporosis International* 2008; **19**: 1267–1273.

increases and surpasses that in men, in whom fracture incidence rises with about 10 years delay (Fig. 2). The remaining lifetime risk of osteoporotic fracture at age 50 is 20–25% in men (versus 45–55% in women) in Caucasian populations.[3,4] Recurrence rates after an initial low-trauma fracture however are similar in both genders (40–60% of survivors after 10 years).[5] Men account for 39% of 9 million osteoporotic fractures worldwide, with similar figures at the hip (30%), spine (39%), humerus (25%), forearm (20%) and other sites (54%).[6] In the U.S., male osteoporosis is responsible for 29% of the 2 million fractures and 25% of the $17 billion costs annually.[7]

Hip fractures account for the greatest costs and mortality. Despite marked global variation in hip fracture incidence, the male–female ratio is constant at about 1:2.[8] One in three men die in the first year after a hip fracture, and one-third will fracture again.[9] Osteoporosis is more strongly related to frailty and co-morbidities in men, which probably explains the higher, long-lasting mortality of hip fractures in men[10] and high rate of long-term care and institutionalisation, which greatly adds to the economic burden of osteoporosis.[11] Vertebral fractures are less disabling and often escape clinical attention, yet are associated with subsequent morbidity, fractures and mortality. Rib fractures are the commonest fractures in men and have been associated with low-energy trauma, age, low BMD and other osteoporotic fractures.[12] Distal radius fractures are the least common type in men, yet constitute an early and sensitive marker for subsequent hip fracture and mortality.[13]

Male bone mineral density

BMD-defined osteoporosis and osteopenia (using female references) occur in respectively 4% and 38% of U.S. men versus 16% and 61% of women $\geq$50 years.[14] Several reports suggest that time trends towards improved BMD and lower hip fracture rates have been more pronounced in women.[15] Compared to Caucasian men, Afro-Americans have higher and Asians lower aBMD, but the latter is partly confounded by smaller body size.[14]

Pathophysiology

Hierarchical determinants of fracture risk

Fracture risk is determined by risk of falls, bone size and geometry, BMD, microarchitecture, higher peak bone mass (PBM) and the balance between bone resorption and formation, all of which contribute

to fracture resistance in older men, although for other determinants e.g. material properties this requires further study.

Peak bone mass

Theoretically, small increases in PBM confer large delays in osteoporosis onset. Family studies have shown that lower PBM, lower trabecular vBMD and a thinner cortex are evident in sons of men with idiopathic osteoporosis, without increased bone turnover markers (BTMs).[16] Therefore, screening men <50 years without relevant co-morbidities or fractures because of family history will primarily detect cases of low PBM. Whether childhood interventions which improve PBM can prevent osteoporotic fractures remains to be shown.

Bone geometry and microarchitecture

Men develop wider bones (after adjustment for height) due to greater periosteal apposition (which is stimulated by androgens but inhibited by oestrogens from late puberty onwards), whereas girls predominantly decrease their endosteal perimeter.[17] As a result, cortical bone in men is not thicker but placed further outward, improving strength exponentially. For the same femoral neck aBMD, men have similar strength, greater bone area and lower vBMD.[18] The cortex thins with age in both sexes, but men better retain periosteal apposition. Bone width predicts fractures in older men independently of aBMD, and men with low bone width and BMD <-1 have similar fracture risk as those with T-scores <-2.[19] Trabecular microarchitecture and finite element modelling (FEM) have recently been shown to improve fracture prediction based on aBMD in men,[20–22] but whether bone geometry and microarchitecture are clinically superior to BMD (Fig. 1) requires further study.

Falls, sarcopenia and frailty

Falls, sarcopenia and frailty are independent and potentially modifiable fracture risk factors. Older men appear less prone to injurious falls than women, contributing to their lower fracture risk.[23] Sarcopenia correlates negatively with bone density, geometry, balance and positively with falls and fractures.[24,25] Frailty is a geriatric syndrome consisting of a decline among multiple physiological reserves resulting in greater vulnerability and a higher risk for functional deficits, co-morbid disorders, institutionalization, hospitalization and death.[24] Poor physical performance and clinical tests of balance and frailty also correlate with BMD and microarchitecture.[26] Frailty, falls, sarcopenia and osteoporosis share several risk factors including sex steroids, vitamin D, insulin-like growth factor 1 (IGF-1) and inflammatory markers, which may be biomarkers as well as therapeutic targets.[24]

Sex steroids and bone

Sexual dimorphism in bone signalling pathways

Bone density, geometry, turn-over and muscle mass have been associated with multiple hormones (e.g. IGF-1 and binding proteins, vitamin D, thyroid hormone), immunological pathways (e.g. C-reactive protein, nuclear factor kappa B (NF-κB), receptor activator of NF-κB ligand (RANKL)) etc. in both genders. Fundamental gender differences in these pathways seem unlikely, and a recent meta-analysis of genome-wide BMD association studies identified no significant gene-by-sex interactions.[27] Sex steroids and especially oestrogens were once considered central regulators of bone metabolism, but generic ageing mechanisms are increasingly being recognised in bone.[28] However, sex steroids remain key determinants of musculoskeletal sexual dimorphism, given that in transsexuals, patients with androgen receptor (AR) mutations and gonadal dysgenesis, the phenotype appears largely determined by sex steroid signalling regardless of chromosomal status.[29,30]

Cellular and molecular actions in bone

Androgens and oestrogens control osteoblast proliferation and osteoblastic stimulation of osteoclasts. Oestrogens directly inhibit osteoclasts, but for androgens this remains uncertain.

Osteoblast- and osteocyte-specific AR knockout as well as AR pre-osteoblast overexpressing mice have confirmed that androgens contribute directly to male periosteal bone expansion, mineralization and trabecular bone maintenance.[31–34] The transcriptional targets of the androgen and oestrogen receptor (ER) in these bone cells remain incompletely understood. In addition, sex steroids influence bone indirectly, e.g. via IGF-1 or systemic inflammatory or oxidative stress.[35] Some evidence also links hypogonadism with vitamin D deficiency.[36,37] Finally, sex hormone-binding globulin (SHBG) may independently influence PBM acquisition[38,39] and turnover (see below) via currently unknown mechanisms.

Role in male bone maintenance

The historic idea that oestradiol (E2) and testosterone (T) were only important for premenopausal and male bone maintenance, respectively, changed when low BMD was shown in men with ERα or aromatase mutations.[17] Subsequently, most studies found associations between (bioavailable) oestradiol (E2) and BTMs, BMD and bone losses in men, whereas the association with T was absent, weaker or disappeared after correcting for E2 or other variables.[35,40–42] Experimental studies using gonadotropin inhibition and T ± aromatase inhibition found that E2 is the primary mediator of bone loss in hypogonadal men.[43] Non-aromatizable androgens such as dihydrotestosterone (DHT) did not increase bone formation or even decreased BMD in some studies.[44–46] Aromatase inhibition increases T but decreases E2 and BMD, and longer AR CAG-repeats have the opposite effect.[47,48] Polymorphisms in oestrogen but not androgen signalling appear important for male bone.[49] Finally, AR antagonist or 5α-reductase inhibitors do not decrease BMD or increase fractures as opposed to androgen deprivation therapy (ADT), which is also oestrogen depriving.[50] Although the overall conclusion is that oestrogens have the dominant effect on male bone maintenance, T nevertheless has been associated with BMD (at predominantly cortical sites), bone area, muscle area and strength, reduced fat mass and fractures in several studies.[51–53] Furthermore, BMD losses and fractures are highest when low bioavailable E2 is combined with low T and high SHBG.[54,55] Although the effects of E2 and SHBG on bone loss may appear below certain thresholds,[55,56] their routine measurement may have limited clinical value (see below).

Secondary causes

In the absence of secondary causes, osteoporosis is termed age-related above age 70 and idiopathic in men below that age. Older studies found secondary causes of osteoporosis in 50–55% of men (mostly glucocorticoid treatment, alcohol abuse and hypogonadism) compared to around 30% in women.[41] However, referral bias has probably contributed to this finding. Some recent reports found no increased risk of secondary osteoporosis in men.[57] Population-based studies should probably re-examine this.

Medication

The main culprits in male drug-induced osteoporosis are glucocorticoids and ADT. Men are often treated with glucocorticoids for chronic obstructive pulmonary disease (COPD), inflammatory bowel disease or transplantation. Men and younger patients are less likely than older women to receive preventive treatment for glucocorticoid-induced osteoporosis (GIOP), and effective strategies are urgently needed to promote preventive therapy.[58]

The fracture rate after 5 years of ADT may be up to 20%.[41] Although DXA is recommended in all men before ADT, less than 20% are screened.[59] Importantly, 90% of castrated men with vertebral fractures have impaired microarchitecture without BMD-defined osteoporosis.[60]

Many other drugs are associated with bone loss or protection in population-based studies. Thiazide diuretics may be useful as an adjunctive therapy in patients with hypercalciuria and/or calcium kidney stones, although the evidence for men remains inconclusive.

Lifestyle factors

Smoking and alcohol abuse are more common in men and contribute significantly to the burden of male osteoporosis.[61] Smoking adversely influences trabecular microarchitecture in older men, which is reflected in fracture risk calculators like FRAX but not in aBMD.[62] Young adult male smokers have lower

aBMD and lower cortical thickness despite higher T and independent of lower body mass, physical activity, calcium intake and vitamin D.[63] Oxidative stress and inflammation are possibly involved, but this requires further study.

Physical activity is higher in men and can increase PBM.[64] Exercise programs and whole-body vibration therapy have been shown to maintain or improve bone mass during ageing, but more studies in men are needed.[65]

Body composition

Body composition (mainly body mass index) correlates substantially with BMD. Low body weight together with medication may largely account for low BMD in diseases like COPD. Skeletal muscle mass is related not only to BMD but also to bone geometry and microarchitecture in both sexes.[66] Several studies suggest that fat mass is only weakly related to bone mass and mainly in women.[25]

Obesity and insulin resistance may impair PBM acquisition while protecting against BMD loss in older age. Metabolic syndrome has been associated with lower BMD and lower fracture rates.[67] Type 1 diabetes mellitus decreases PBM while type 2 decreases BMD losses, yet both types increase fracture risk, possibly via falls, micro-/ultrastructural changes and endocrine or other signalling pathways.

Diagnosis

Clinical evaluation

History taking and physical examination is based on expert opinion in most guidelines and does not differ greatly between genders.[68] The aims of the clinical evaluation are to identify secondary causes, risk of falls, differential diagnoses and to inform treatment options. A broad biochemical screening in osteoporotic men will frequently detect treatable, subclinical conditions with consequences beyond bone (e.g. hyperthyroidism, hyperparathyroidism, coeliac disease, chronic kidney disease, multiple myeloma or bone metastasis).[57,69] Contrary to their importance in pathophysiology, guidelines on male osteoporosis suggest measuring total T, SHBG in selective cases but not E2 because accurate assays for men (mass spectrometry) are not widely available and because algorithms that incorporate results into clinical decision making are lacking.[68] However, recent data in older, ambulatory men failed to confirm that T, E2 or SHBG would add to the diagnostic capacity of BMD or clinical factors for fracture prediction.[70] Measuring T is probably only useful in younger men with severe unexplained osteoporosis or in symptomatic hypogonadism, which also constitute indications for T replacement (see below).

Dual energy X-ray absorptiometry

Although randomized controlled trials (RCTs) are lacking, several societies like the U.S. Endocrine Society suggest DXA screening in men aged $\geq$70 years, or younger men (but not below age 50) with clinical risk factors.[68] In a population-based study, the number needed to screen to detect BMD-defined osteoporosis was six in women aged $\geq$65, 13 in men aged $\geq$65, and 10 in men aged $\geq$70.[71] Forearm DXA, although generally not reimbursed, can be considered when other sites are unreliable due to degenerative changes or prosthetic material or in hyperparathyroidism or ADT. Because vertebral fractures are common and often undiagnosed, screening with either dedicated DXA equipment or lateral spine radiographs is recommended.

The International Osteoporosis Foundation and World Health Organisation recommend using reference values from 20 to 30-year-old white U.S. women to define DXA T-score (which actually corresponds to a male-specific T-score of approximately -2.75) whereas the International Society of Clinical Densitometry and the U.S. National Osteoporosis Foundation (NOF) recommend a sex-specific T-score. Proponents of male-specific T-scores argue that lowering the threshold increases sensitivity. In one study for example, T-score <-2.5 identified 44% of women and only 21% of men who fractured.[72] However, male-specific T-scores would decrease specificity and modestly increase

disease prevalence. Furthermore, for the same femoral neck aBMD, men have similar strength,[18] similar relative risk of fractures[73] and similar positive predictive value. Regardless of this issue, there is great need to improve fracture prediction in both genders, and aBMD should not be considered in isolation.

Fracture risk assessment tools

Tools based on clinical risk factors (CRFs), most notably FRAX (http://www.shef.ac.uk/FRAX/) have been advised to target DXA screening or osteoporosis therapy (see below). The benefit of BMD testing may be greatest in those with intermediate fracture probability, and this would reduce DXA testing to about one-third.[74] Simpler instruments such as the Osteoporosis Self-Assessment Tool or the Male Osteoporosis Screening Tool may have comparable, modest predictive value, whereas their good negative predictive value may effectively rule out osteoporosis.[74] Although FRAX is based on larger databases, small external validations have suggested poor discriminative value in men, and this requires further investigation.[75,76]

Bone turnover markers

BTMs are classified as formation or resorption markers, but since remodelling is a coupled process, formation markers can also rise during resorption and vice versa. Resorption markers increase later and less pronounced in ageing men.[77] BTMs are significantly but weakly associated with aBMD losses and fractures and haven't been shown consistently to improve fracture prediction in models adjusted for aBMD.[77–80]

Treatment

The key objective of osteoporosis treatment is preventing fractures and not merely increasing BMD. Most RCTs in male osteoporosis have been underpowered for fracture endpoints, but fracture prevention was assumed because effects on bone density and remodelling in men were of identical magnitude as in postmenopausal women. Final proof of this concept has recently come from an RCT in which yearly intravenous zoledronate in men with prevalent vertebral fractures or BMD T-score ≤ -2.5 decreased morphometric vertebral fractures by two-thirds, just as in women.[81]

Whether bisphosphonates prolong survival in men is conflicting in observational studies, and for calcium and vitamin D this remains unknown.[82–84] In one RCT in male hip fracture patients, the mortality reduction just bordered significance.[85]

Indications for pharmacological treatment

Since 2008, NOF guidelines recommend osteoporosis treatment not only after hip or vertebral fractures or with T-scores ≤ -2.5, but also in postmenopausal women and men aged ≥ 50 with osteopenia if FRAX-based 10-year hip or major osteoporotic fracture probability is $\geq 3\%$ or $\geq 20\%$. This implies that treatment is now recommended in one in five, three and two white U.S. men over age 50, 65, and 75.[86] Although this would be cost-effective, it contrasts sharply with undertreatment and reimbursement criteria worldwide. In a recent RCT, only 5.7% and 0.4% of female and male fracture patients underwent DXA, and only 12.2% and 7.3% received medication.[87]

Calcium and vitamin D

Vitamin D insufficiency and consequent secondary hyperparathyroidism is common in older men. It leads to bone loss, muscle weakness, decreased balance and falls. All major osteoporosis trials have included calcium and vitamin D, which reduce fractures by 10–15%. The benefits depend on baseline deficiency, and are significantly greater with daily doses of ≥ 1200 mg calcium and

800 IU vitamin D. If and to what extent the risk of cardiovascular disease is increased with calcium supplements remains to be confirmed, but there has been no evidence of increased risk when vitamin D is added to calcium supplements, and this combination is essential for fracture benefits.[88,89]

Antiresorptive drugs

RCTs in male osteoporosis have now been completed for all commonly used osteoporosis drugs, including alendronate and risedronate (daily and weekly), intravenous zoledronate and ibandronate, and most recently, denosumab and strontium ranelate.[41,81,85,90–92] Most modern RCTs in GIOP have included men, and RCTs specifically in men receiving ADT have shown effectiveness of pamidronate, alendronate, risedronate, zoledronic acid, denosumab and the selective oestrogen receptor modulators raloxifene and toremifene.[93] In practice, drug choice will depend on availability, cost, reimbursement criteria, disease severity, side effects, co-morbidities and (relative) contraindications. Potential side effects of bisphosphonates (e.g. osteonecrosis of the jaw or atypical femoral fractures) and preventive measures are reviewed elsewhere.[94] These complications are so rare that the proven benefits of bisphosphonates are far more likely to outweigh these potential risks. Evidence on drug holidays in men is lacking.

Bone anabolic drugs

Intermittent parathyroid hormone (PTH) therapy

The only evidence-based and approved anabolic agent for men remains intermittent PTH with the 1–34 fragment teriparatide. Treatment is usually given for two years maximum (at which time bone resorption catches up and exceeds formation) followed by antiresorptive treatment to maintain benefits. Simultaneous therapy with antiresorptives is not advised in recent guidelines because it increases costs and risk of side effects, has no proven benefit and may even blunt the anabolic response, although this requires confirmation.[68]

Androgens and selective androgen receptor modulators (SARMs)

In theory, androgen therapy could be anabolic for bone and muscle simultaneously in older men with osteoporosis, sarcopenia and falls. Apart from their benefits for lean body mass, fat mass and emotional well-being, RCTs have shown that T (and dehydroepiandrosterone[95]) prevent bone loss or increase BMD. A meta-analysis concluded that this was inconclusive for the femoral neck.[96] Lack of benefit from T in some studies may have been due to short treatment duration and high pre-treatment T levels; a cut-off of $<$200 ng/dL (6.9 nmol/L) has been suggested by some studies and recent guidelines.[43,68] Another recent study did show lumbar and femoral BMD increases in men with late-onset hypogonadism (LOH) and metabolic syndrome.[97] Bone formation markers increase and resorption markers decrease during the first months of androgen replacement therapy (ART), followed by a decrease in formation markers as bone turnover slows down.[77] Guidelines on male osteoporosis suggest that in hypogonadal men with high fracture risk, a drug with proven bone efficacy should be prescribed even with ART. Low bone mass may be an element to consider ART in men with T repeatedly $<$200 ng/dL and (i) contraindication to approved osteoporosis drugs, (ii) hypothalamic, pituitary or testicular disorders, or (iii) idiopathic LOH if accompanied by signs of androgen deficiency which are alleviated by ART.[68]

There is concern about the cardiovascular safety of androgens, especially in frail older men.[98] Although androgens can stimulate pre-existing prostate cancer, ART in older men appears to have little detrimental effects on prostate tissue. Most guidelines recommend monitoring haematocrit and PSA during ART. Other concerns include a small decrease in high-density lipoprotein and possible androgen abuse.[99] The market for prescription T is considerable, yet LOH as defined by criteria from the European Male Ageing Study (combining low T with three sexual symptoms) was rather uncommon (2% from age 40, increasing to 5% in men aged 70–79 years), and more strongly correlated than low T alone with ultrasound-estimated BMD, muscle circumference and gait speed.[100]

SARMs could potentially avoid some concerns related to ART and have shown promise in animal studies. In a recent short-term phase II trial in older men and women, enobosarm improved lean body mass, physical functioning and insulin resistance without improving BMD.[46]

Follow-up

Many questions remain about the optimal follow-up of patients with osteoporosis (both men and women). Hip BMD change has been shown to predict fracture risk independent of initial BMD, suggesting that repeat testing may be useful,[101] although the best interval remains uncertain. For patients already treated for osteoporosis, the benefit of DXA remains unknown.

Non-adherence is an independent fracture risk predictor occurring commonly with all treatments and more so in men. Follow-up should probably focus on adherence and potentially modifiable risk factors (e.g. patient education, side effects, overall pill burden, drug cost) and less on frequent DXA testing.

Summary

Men contribute greatly to the costs and burden of osteoporosis, yet it is still generally perceived as a condition affecting mainly women, resulting in even greater underdiagnosis and undertreatment in men. Oestrogens have the dominant effect on male bone loss but cannot be measured reliably in most clinical settings, while T measurement and treatment should only be considered in selected cases, mostly in younger men. Strategies are needed to improve all aspects of the clinical management of male osteoporosis, especially disease awareness, prevention and management, fracture risk prediction and treatment monitoring with advanced imaging techniques, strength measures and/or bone turnover markers, adherence improvement and population screening. Recent data provides conclusive evidence that osteoporosis treatment reduces fractures in men. In addition to antiresorptive drugs, additional strategies should be pursued targeting bone anabolism or other components of osteoporosis including falls and neuromuscular function.

Practice points

- Osteoporosis screening should be considered in men aged $\geq$70 or those aged 50–69 with clinical risk factors. DXA and clinical risk factors should be combined, as each identifies a different group at high risk of fractures.
- History taking, clinical examination, laboratory tests and vertebral fracture assessment should focus on excluding differential diagnoses and secondary causes and informing treatment options. Although recommended by guidelines, testosterone measurement is probably only useful in younger men or those with possible symptoms of hypogonadism.
- Pharmacotherapy is recommended in men $\geq$50 years with a previous low-energy hip or vertebral fracture, BMD T-score ≤ -2.5, or (in the U.S.) osteopenia with increased fracture risk (10-year absolute risk of hip or any fracture of $\geq$3% or $\geq$20%) or in men at risk of fracture receiving long-term glucocorticoids or androgen deprivation therapy.
- Treatment options for male osteoporosis include alendronate, risedronate, zoledronate, denosumab and teriparatide, in combination with calcium and vitamin D supplementation.
- For men with idiopathic hypogonadism (morning testosterone repeatedly $<$200 ng/dL) at high risk of fracture, consider adding an anti-osteoporosis drug to androgen replacement therapy. Testosterone alone can be given in younger men, those with contraindications to first line drugs, or when fracture risk is moderate and symptoms of hypogonadism are present and respond to treatment.

Research agenda

- The cellular and molecular targets of sex steroids in the musculoskeletal system require further investigation.
- Population screening of men and appropriate DXA screening intervals should be evaluated.
- Fracture risk prediction using clinical risk factors, (HR-)qCT or FEM requires further study.
- The benefits of pharmacotherapy for men without BMD-defined osteoporosis need to be established.
- The value of monitoring treatment with imaging or BTMs should be investigated.
- Trials should evaluate the long-term safety and efficacy as well as selection criteria for androgen replacement therapy, SARMs or other drugs which target not only osteoporosis but also sarcopenia, frailty and falls.

Conflict of interest

The authors have no conflict of interest.

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