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Review article

Osteoporosis in men—East and West: Can the twain meet? A perspective from Asia

Gerald Gui Ren Sng [a], Jean-Yves Reginster [b], Majed S. Alokail [b], Manju Chandran [c,d,*]

[a] Department of Endocrinology, Singapore General Hospital, Singapore
[b] Department of Biochemistry, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia
[c] Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, Singapore
[d] Duke-NUS Medical School, Singapore

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ABSTRACT

Osteoporosis in men remains a significantly underrecognized condition, with notable differences in bone mineral density (BMD) and fracture risk between Asian and Western populations. Despite 30% of hip fractures globally occurring in men, they are less likely to be diagnosed or treated for osteoporosis, especially in resource-limited settings. Given these disparities, a deeper understanding of osteoporosis epidemiology and treatment efficacy in men is essential, particularly in Asian populations.

This review synthesizes the latest evidence on the epidemiology, screening, and treatment of osteoporosis in men, with a focus on genetic, environmental, and epidemiological disparities between Eastern and Western populations. Additionally, the review examines existing controversies surrounding fracture risk screening in men and evaluates the efficacy and cost-effectiveness of pharmacological treatments such as bisphosphonates, denosumab, and anabolic agents.

Asian men exhibit lower peak BMD compared to their Caucasian counterparts, leading to potential misdiagnoses when using Caucasian-based BMD reference ranges. Screening tools like the Fracture Risk Assessment Tool (FRAX)® show variability in performance across populations. Data on pharmacological treatment in men remain limited, although studies suggest comparable benefits to those observed in women. Larger studies, particularly in male and Asian populations, are urgently needed to refine diagnostic and therapeutic guidelines.

Osteoporosis in men is underdiagnosed and undertreated globally, with pronounced disparities between populations. Current diagnostic tools and treatment protocols are not fully tailored to male and Asian populations. There is an urgent need for longitudinal studies focusing on male-specific osteoporosis management to reduce fracture risk and improve outcomes.

1. Introduction

Osteoporosis is classically described as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. The World Health Organization (WHO) offers densitometric diagnostic criteria, which defines osteoporosis as a bone mineral density (BMD) greater than 2.5 standard deviations below the young adult mean peak bone density at any of the three axial sites [2].

Using the WHO criteria, osteoporosis has been reported to be four times more prevalent in women above the age of 50 as compared to their male counterparts [3]. Osteoporosis is often seen as a woman's problem, with most published reports focusing on post-menopausal osteoporosis. As a result, osteoporosis in men is underdiagnosed and undertreated. In a global epidemiology study of hip fractures that analyzed patient-level health care data from 19 countries and regions, approximately 30% of hip fractures among individuals aged 50 years and older were found to occur in men [4]. The study observed a sex disparity in post-hip fracture treatment, with males having 29.8%–66.5% lower use of anti-osteoporosis medications than females [4]. In a retrospective cohort review of 1171 men aged above 65 with any fracture related to osteoporosis in the US, only 3.3% of the total cohort received a diagnosis of osteoporosis, only

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* Corresponding author. Department of Endocrinology, Singapore General Hospital, Academia, Level 3, 20 College Road, 169856, Singapore.
E-mail address: manju.chandran@singhealth.com.sg (M. Chandran).

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1.1% had a BMD performed, and only 7.1% received anti-osteoporotic treatment within 12 months of index fracture [5] A more recent study performed in a resource-rich Asian country showed that men were less likely to have BMD performed, particularly those under 65 years of age, and significantly less likely to receive antiresorptive therapy, although treatment rates were fairly low both in men and women at 20.1% and 35.7%, respectively [6]. Treatment rates are yet more dismal in less resource-rich settings, with rates of as low as 0.3% reported [7].

This poses a significant problem since osteoporotic fractures are associated with substantial morbidity and increased mortality risk. Though the effect of fracture on utility and recovery of health-related quality -of-life following fragility fractures at any skeletal site is similar between men and women [8], excess mortality after hip fractures is still higher in men than in women at any age, with the highest risk occurring in the 3 months immediately post-fracture (Relative hazard 7.95, 95% CI: 6.13–10.30). This disproportionately increased mortality risk in men is observed at almost all time-bands up to 10 years of observation post-fracture. As expected, mortality increases stepwise with age at time of incident fracture [9].

There is hence an urgent need to increase recognition and treatment of osteoporosis in men. This review aims to expound on the epidemiology of osteoporosis in men with respect to sex and racial/ethnic differences (particularly between Caucasian and Asian), describe the skeletal aging process in men, evaluate some of the controversies in screening and assessment of fracture risk, and summarize current evidence surrounding treatment options.

2. Epidemiology of osteoporosis and osteoporotic fractures in men

Though less often observed in men than in women, osteoporosis is still substantially prevalent in men. A prevalence rate of 4.3% amongst men above the age of 50 years has been reported in the United States [3]. Reported prevalence rates in Asia vary from 1.3% in Taiwan [10], 5.6% in Singapore [11] and 8.8% in South Korea [12]. Variations in reported rates between individual countries may be in part due to different population demographics and study periods, as well as due to differences in genetics, diet, physical activity, health behaviors, and socio-economic factors between populations. Differences in the skeletal site that was used for reporting the BMD may also contribute. In addition, disparities in reported prevalence rates may be because the peak BMD values in the Caucasian population upon which T-scores are derived may not accurately reflect that of Asian populations. Though some of it may be attenuated after adjustments for body size and/or body weight, it is increasingly being reported that differences in peak BMD exist between Asians and Caucasians [13]. The normative data used for the WHO densitometric diagnosis of osteoporosis was from the NHANES reference database on Caucasian women aged 20 to 29. Singaporean men were found to have 10% and 5% lower peak BMD at the lumbar spine and femoral neck respectively when compared to a Caucasian reference population in a study from 2002 [14]. Inter-country differences in BMD have been reported even in populations of similar background ethnicity within Asia, with Young Adult Mean (YAM) BMD observed to be lower in Singaporean Chinese men compared to those residing in mainland China [15]. The T-score depends on both the mean and standard deviation (SD) of the reference population. Therefore, the use of disparate reference populations on different densitometry systems will lead to T-score differences and therefore differences in diagnostic sensitivity, even when the measured BMD is the same. Eighteen percent of men in a study conducted in Chandigarh, India were noted to have BMD T-scores in the osteoporotic range when the NHANES III data base was utilized. However, when a locally derived reference data base was used, only 7.2% of the men had osteoporosis [16]. Similar discrepancies with lower prevalence rates of osteoporosis when local reference data bases were used have been observed in studies conducted in Vietnam [13], China [17], and Singapore [15]. Discrepancies in osteoporosis prevalence based on BMD at the lumbar spine have also been observed amongst different Asian male populations, with one study finding a prevalence rate of 3.2% amongst men in China as compared to a prevalence rate of 6.5% in South Korea. The investigators postulated that this finding was likely due to a greater BMD decline with age and a smaller SD amongst the Koreans [18]. Threshold values for defining osteoporosis specific to Asian male populations are available for Taiwan [19], South Korea [20], China [18], Japan [21], Vietnam [13] and more recently Singapore [15]. Using ethnicity-specific cutoffs based on actual bone mass loss (ie, a cutoff according to a certain decrease (or percentage decrease) from the peak BMD) rather than general statistical comparisons, would lead to a more accurate diagnosis of osteoporosis, and probably help to avoid the paradoxes caused by different SDs among different ethnic populations. It may also aid with better prediction of fractures in different populations. Large longitudinal studies are needed to address this issue.

Differences in osteoporotic fracture incidence are also observed between populations. Although lower rates of osteoporosis are observed in Caucasian men, the age-adjusted hip fracture rates per 100,000 in adults over 50 years of age are significantly higher in Caucasian than in Chinese [22]. Differences in hip geometry have been postulated as a major factor accounting for the ethnic variation in hip fracture incidence noted between Caucasians and East Asians. Longer hip axis lengths are linked to an increased risk of hip fracture [23] and hip axis lengths are reportedly shorter among Asians, even after adjusting for height [24].

Differences in prevalence of osteoporosis and osteoporotic fractures have also been observed between urban and rural populations in both Caucasians and Asians. After adjusting for age, menopause and lean mass, rural subjects were found to have significantly higher femoral neck BMD than urban subjects in a study conducted in Thailand [25]. Some studies from Australia and Japan have reported a higher prevalence of osteoporosis and osteoporotic fractures in urban residents [26, 27], while others from China and Iran have reported the opposite [28–30]. Differences in the prevalence of osteoporosis in urban and rural areas between countries may be related to population structure with areas where the younger and stronger live and work having less prevalence. For instance, in China, an increased prevalence of osteoporosis was observed in rural areas where the population is heavily slanted to older individuals [29]. Other environmental and lifestyle factors including the risk of falls could also contribute to the differences in fracture risks. Despite these extant controversies concerning BMD variations and their impact on the prevalence of osteoporosis, it must be emphatically pointed out that the incidence of osteoporosis and osteoporotic fractures will only continue to increase together with the overall aging trend in populations in the region [11], and that it is a problem common to all populations.

Overall osteoporotic fracture rates are understandably higher in women compared to men, mirroring the higher rates of osteoporosis [31]. In Caucasians, this discrepancy in hip fracture rates between men and women is quite pronounced regardless of the geographical area. However, a blunting of the typical sex ratios has been observed in Latin America and Asia [32]. This blunting has been observed in countries such as India and China. As observed in most European countries, the fracture rates rise similarly in these countries in men and women with advancing age, though they remain lower than that noted in Europe [33, 34].

The distribution of osteoporotic fractures differs slightly between men and women. With regards to incident non-vertebral fractures, men above 55 years of age appear to have similar rates of hip fractures (18.6% vs 17.8%), lower rates of fracture at the wrist (11.7% vs 22.2%) and ankle (18.0% vs 25.4%), but higher rates of rib fractures (20.8% vs 11.4%) [35]. However, the significance of these distributions in non-Caucasian populations is less clear as no good-quality systematic study has evaluated incident non-vertebral fractures in Asian populations. With regards to vertebral fractures, incidence rates of between 2.2 fractures per 1000 person-years in the MrOS study [36] to 5.7

fractures per 1000 person-years in the EPOS study [37] have been reported in Caucasian populations. There is a similar paucity of prospective data on incident vertebral fractures in Asian populations, although a prevalence rates of 10.5% (95% CI: 9.0%–12.0%) and 9.7% (95% CI: 8.2%–11.1%) respectively in men and women above 40 years of age [7] have been reported between men and women aged above forty respectively in a screening study in China.

3. Skeletal aging in men

Bone loss occurs due to the complex interaction of individual and environmental factors, including nutritional deficiencies. Osteoporosis is typically classified as primary and secondary. Some authors have further differentiated primary osteoporosis into two phenotypes. The first is a "post-menopausal" phenotype in which patients are younger (age < 70), genetic factors or undiagnosable secondary factors are often present, trabecular bone loss is greater than cortical bone loss, and vertebral and distal radial fractures predominate as a result. The second is described as "age-related", in which patients are older (age > 70 years) and traditional risk factors are more often present, a stronger relation with sarcopenia or muscle loss exists, trabecular and cortical bone is lost at equal rates, and proximal femur or hip fractures are more common [38]. While useful in terms of understanding the mechanisms of bone loss, a considerable phenotypic overlap likely exists, and there is no evidence that the differences in these groups are clinically significant.

3.1. Patterns of bone loss with aging

The pattern of bone loss that occurs with aging is different in men and women. Loss of trabecular bone in men is primarily due to reduced bone formation and therefore, while trabecular thinning occurs, trabecular number and connectivity remain the same. In women, trabecular bone loss is due to bone resorption, and hence there is a reduction in trabecular number and connectivity, and subsequent perforation [39,40]. At the cortex, both men and women experience similar rates of endosteal resorption. However, men continue to have increased periosteal apposition when compared to women, leading to a lesser decline in overall cortical diameter (Fig. 1 and Table 1). These differences have been demonstrated in various morphometric studies [41,42].

As noted earlier, both Asian men and women have lower peak bone mass than their Caucasian counterparts of the same sex. However, the patterns of bone loss between races appear to be the same. Racial and sex differences in cortical bone traits in aging appear to be mainly due to increased distance of the cortex from the neutral long axis, rather than increased cortical thickness *per se* [41]. In a study involving young adult males, the periosteal diameter of the femoral neck showed no racial differences, but cortical thickness was found to be 0.35 standard deviations lower in Chinese males compared to Caucasians [41]. The study, which included 829 healthy Chinese and 1181 healthy Caucasians aged 18–93 years in Australia, examined various bone parameters such as femoral neck BMD), periosteal and endocortical diameters, cortical thickness, and bone strength indicators like volumetric BMD (vBMD), section modulus, and buckling ratio determined using dual X-ray absorptiometry. Over time, increases in periosteal and endocortical diameters were found to be more in Chinese women than in men, and as a result the sex difference in femur neck periosteal diameter established in young adulthood diminished in old age. Caucasian men experienced a larger increase in periosteal diameter compared to Caucasian women, widening the sex difference in periosteal diameter with age [41]. These racial and sex differences in the behavior of the periosteal and endocortical surfaces contribute to the distinct patterns of femoral neck size, cortical thickness, and bone strength indices observed in old age. In addition, Chinese individuals appear to have a specific pattern of fracturing. As Chinese individuals age, they are more prone to fractures caused by bending forces compared to Caucasians, while they are less likely to fracture due to compressive forces (buckling) than Caucasians. This suggests that the bone structure of older Chinese individuals handles compressive forces better but is weaker when subjected to bending forces. Across both races, women appeared to be generally more susceptible to fractures caused by bending forces

Table 1
Bone aging- men versus women.

Men	Women
Higher peak bone mass and bigger bone structure	Lower peak bone mass and smaller structure
Slow decline in sex steroid levels	Menopause leading to abrupt decline in estrogen concentrations and higher bone turnover
Reduced bone formation	Increased bone resorption
Trabecular thinning	Decrease in trabecular number and connectivity→ Perforation
Endosteal resorption at cortex, but continued periosteal apposition	Lesser periosteal apposition
Lesser decline in overall cortical diameter	More decline in overall cortical diameter

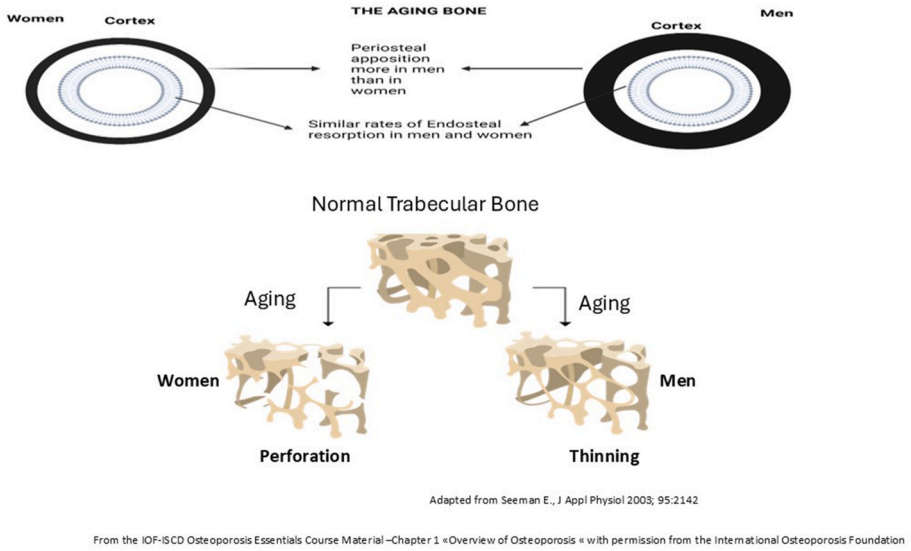

Fig. 1. Changes in cortical and trabecular bone in women and men with aging.

compared to men. The reasons for this could include differences in bone density, structure, or strength between men and women.

4. Sex disparities in BMD

BMD remains a core diagnostic tool in osteoporosis, both in men and women. Historically, sex-specific referent ranges were used to derive BMD T-scores [43]. The original WHO consensus definition delineated osteoporosis as an areal BMD of 2.5 or more standard deviations below the healthy young female mean value, derived from the NHANES III population data base of post-menopausal Caucasian women, leaving questions on applicability to men and pre-menopausal women and other races. Initial studies establishing the strong relationship between BMD T-scores and risk of fracture (in particular, hip fracture) were based on cohorts of post-menopausal women [35]. Further research has subsequently established a significant linear relationship between BMD T-scores and vertebral fractures in men [44].

4.1. Should separate reference ranges be used for men and women?

As mentioned earlier, patterns of bone loss differ between men and women as they age. In addition, given that absolute BMD is higher in men than in women, using the same reference range as in women will lead to a lower prevalence of osteoporosis in men than in women. However, this may be appropriate since men in general have a lower risk of fracture than women. It seems intuitive that since it is a measure based on a normative population database, sex-specific reference ranges should be used to derive the T-score. To evaluate the validity of this assumption, we must answer the underlying question—do men and women fracture at the same BMD?

Studies evaluating this question have had different conclusions. In a cross-sectional study conducted in the UK, men with prevalent vertebral fractures were noted to have a higher absolute BMD at the lumbar spine and femoral neck as compared to women [45]. However, two large contemporaneous observational studies have demonstrated the opposite, with the EPOS study demonstrating the same relationship between lumbar spine BMD and vertebral fractures in men as that observed in women [46] and the Rotterdam Study showing a similar incidence of hip fracture in men and women with the same femoral neck BMD [47].

BMD is typically assessed using dual-energy X-ray absorptiometry (DXA), which is a 2-dimensional measurement that consequently is unable to take into account the dimension of depth. As such, BMD measured by DXA is an "areal" BMD. Areal BMD (aBMD) can differ substantially from volumetric BMD if the depth of the measured bone is significantly higher [48]. Morphometric data is consistent with this, with studies showing that despite a greater areal BMD observed in men compared to women, peak volumetric bone density is actually similar across sexes, and so differences in areal BMD noted between the sexes are likely due to differences in bone size [49].

Conceptually, it may seem therefore that volumetric BMD (vBMD) may be a more accurate measurement of bone strength. However, this requires quantitative CT scanning, which is costly and not available in many practice settings. Moreover, the bulk of evidence demonstrating the relationship between BMD and fracture risk has uniformly used areal BMD, making the clinical relevance of vBMD itself debatable. This remains an area that should be studied further.

A post-hoc analysis of the Canadian Multicentre Osteoporosis Study attempted to address this issue [50]. In this large observational study, it was noted that though mean areal BMD was higher in men who fractured as compared to women, it was also similarly higher in those who did not fracture. After statistical adjustment for age and absolute BMD, gender was not significantly associated with fracture risk. Kanis et al. have elegantly demonstrated that the increase in hip fracture risk is similar in men and women for an equivalent change in BMD T-scores [51]. Put together, these studies suggest that a higher areal BMD in men who fracture may reflect the higher intrinsic areal BMD distribution overall, rather than a true relationship between BMD and fracture risk. Because men on average have higher BMD than women, the use of a male reference group to calculate T-scores results in men being classified as having a T-score < -2.5 at a higher absolute BMD and will likely underestimate their risk of fracture. It is because of this that current guidelines by the ISCD recommend that a "uniform Caucasian (non-race adjusted) female reference be used for men of all ethnic groups" [52].

4.2. The role of sex hormones

The testes release testosterone in response to gonadotropin releasing hormone (GnRH). Testosterone is converted to estradiol via the catalytic effect of the enzyme aromatase. Increasing levels of sex hormone binding globulin and decreasing endogenous sex steroid production with aging results in decreasing availability of free testosterone. It was classically thought that testosterone, as the dominant circulating sex steroid in men, played the same role and that the gradual decline in gonadal function with age in men (as opposed to menopause in women) explained the less precipitous rate of bone decline observed in men [49]. This observation was supported by the findings of the large Dubbo Osteoporosis Epidemiology Study in which testosterone levels after adjustment for SHBG were observed to be inversely associated with fracture risk (HR 1.37 95% CI: 1.11–1.68, $P = 0.003$) [53].

However, in the same study, it was also observed that estradiol was similarly inversely associated with fracture risk (HR 1.25 95% CI: 1.02–1.54, $P = 0.03$). Indeed, increasing evidence suggests that the role of estradiol may be more important than that of testosterone in men. The suggestion that estradiol is the primary sex steroid influencing bone homeostasis even in men, and that it does this by acting on osteoclasts, osteoblasts, and osteocytes was first brought up in two separate case reports. In one of the cases reported by Smith et al. [56], a 28-year-old man with a disruptive estrogen receptor gene mutation was diagnosed with severe osteoporosis on presentation, despite normal serum androgen levels. Morishima et al. [57] reported a second case of aromatase deficiency due to an inactivating mutation in the aromatase gene in a pair of siblings. The 24-year-old male sibling presented with undetectable estradiol levels and was diagnosed with severe bone loss with a distal radius Z-score of −4.7, despite very high androgen levels. Put together, these cases suggest that both serum estradiol levels and the ability for these levels to be sensed by estrogen receptor targets are important in maintaining bone health in men, regardless of androgen levels.

The comparative role of estrogen and testosterone was elegantly elucidated in a physiological study at the Mayo Clinic in which elderly male participants were given a long-acting GnRH agonist and an aromatase inhibitor to suppress endogenous estradiol and testosterone production [54]. Both testosterone and estrogen were then replaced using patches to approximate normal physiological circulating levels of both hormones in men. After a 3-week treatment period, participants were randomized to continue either testosterone, estrogen, both, or neither replacement for another 3 weeks. Estradiol replacement was found to be protective against the potential increase in bone resorption associated with GnRH and aromatase inhibitor administration as evidenced by a dose-dependent decrease in serum levels of the bone resorption marker C-Telopeptide of Collagen, suggesting that estrogen is the dominant contributor to regulating bone resorption.

The quantitative impact of estrogen levels on male bone was also evaluated in the MINOS study, in which 596 men aged 51–85 years were stratified into quartiles of serum estradiol levels. For all 3 outcome measures of total hip BMD, distal forearm BMD and whole-body BMC, there was a significant difference observed between the first quartile of participants and each of the other three quartiles. No significant difference amongst the other three quartiles was observed. This suggests that there may be a threshold level of serum estradiol below which men may be at higher risk of bone loss [55].

Endogenous testosterone levels do however correlate with BMD with

increases in lumbar spine (LS) and total hip (TH) BMD of 1.2% and 0.7%, respectively with higher levels of testosterone noted in one study. In this study, an inverse correlation between testosterone levels and fracture risk was also observed [53]. The risk of fracture was significantly increased in men with reduced testosterone levels (hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.09–1.62). After adjustment for sex hormone-binding globulin, both serum testosterone (HR, 1.48; 95% CI: 1.22–1.78) and serum estradiol (HR, 1.21; 95% CI: 1.00–1.47) levels were associated with overall fracture risk. After further adjustment for major risk factors of fractures (age, weight or BMD, fracture history, smoking status, calcium intake, and sex hormone-binding globulin), lower testosterone levels were still associated with increased risk of fracture, particularly with hip (HR, 1.88; 95% CI: 1.24–2.82) and non-vertebral (HR, 1.32; 95% CI: 1.03–1.68) fractures. It is likely that testosterone levels have a direct effect on fracture risk particularly at very low concentrations [56]. High sex hormone binding globulin concentrations have also been linked to increased fracture risk. In community-dwelling males, higher SHBG levels, independent of the levels of testosterone and estradiol, have been shown to be associated with higher risk of vertebral and nonvertebral fractures [57].

5. Screening for osteoporosis in men

International consensus guidelines on screening for osteoporosis in men vary widely—with one guideline recommending no routine screening [58] and some advocating screening with dual energy x-ray absorptiometry (DXA) scans in individuals with risk factors for osteoporosis [59,60]. Others have suggested universal screening with DXA for all men above 65 years [61] or 70 years of age [62,63]. Though this latter strategy of universal testing might identify all men in these age groups who have WHO BMD T-score criteria based osteoporosis, it is likely to incur considerable cost and the evidence supporting this is acknowledged as “low quality” by the Endocrine Society [62]. The discrepancies between the guidelines cited above may be at least in part explained by differences in regional health care norms. The ideal screening test is one with maximal sensitivity and specificity, which is impossible in the real world. As such, the trade-off between sensitivity and specificity requires a judgement that is particular to that specific practice climate. While there is no clear consensus on the appropriate or ideal age for screening for osteoporosis in Asian men, it may be necessary that screening be considered at even younger ages than 65 or 70 years, in populations with high fracture risk or lower bone mineral densities.

5.1. Screening tools

Whether to implement a universal testing strategy with DXA scan for men above a certain age or to utilize a pre-screening tool to identify men for BMD testing involves several considerations. The Osteoporosis Self-Assessment Tool for Asians (OSTA) was developed in an Asian cohort of post-menopausal women to predict individuals at increased risk of osteoporosis at the femoral neck on DXA scanning. It comprises only two clinical variables—age and body weight [64]. Men were not included in the original development cohort for OSTA. However, since then, several studies in Asian populations have explored the utility of OSTA or OSTA-like tools in men. A clinical risk assessment tool based on only age and weight, similar to OSTA was developed in Hong Kong a few years after the development of the original OSTA [65]. An OSTA value of ≤ -1 had a sensitivity of 81% and specificity of 66% to detect a densitometric diagnosis of osteoporosis in men, and the area under the receiver operating characteristics curve (AUC) was 0.83. The index was validated in another sample of 356 men with similar sensitivities, specificities, and AUC. The usefulness of OSTA was further compared to calcaneal quantitative bone ultrasound (QUS) in the validation sample. The optimal cutoff T-score of −1.2 for QUS yielded sensitivity and specificity values of 75% and 67%, respectively. The AUC for QUS was 0.79. Combining OSTA and QUI gave a sensitivity of 88% and specificity of 66% to identify men with low BMD at the femoral neck, and an AUC of 0.86 which was statistically not different from either OSTA or QUI alone [65]. OSTA has also been validated in Filipino men with sensitivity of 90%, specificity of 66% and area under the curve of 0.847 [66]. A locally developed tool the KORAM-M, also consisting of age and body weight, had a sensitivity of 90.8%, a specificity of 42.4%, and an AUC of 0.666 with a cut-off score of −9 to detect osteoporosis on DXA in South Korean men [67]. Similar results were seen in the validation dataset. Additionally, risk categorization with KORAM-M showed improved reclassification over that of OSTA up to 22.8%.

The Fracture Risk Assessment (FRAX®) algorithm is a widely used tool that gives the probability of hip and major osteoporotic fractures over 10 years. It identifies individuals, both men and women, who may require further investigation with BMD or who would be candidates for pharmacological intervention [51].

Several studies have attempted to compare the performance of the FRAX against that of OSTA and other measures in the diagnosis of osteoporosis in men. Results of such comparisons have been mixed. A study in a cohort of Chinese men reported that OSTA significantly outperformed FRAX (AUC 0.807 vs 0.552 and 0.590 for hip and MOF, respectively) [68]). In a cross-sectional study community-dwelling elderly Han Beijing male population, three clinical tools, OSTA, FRAX without BMD, and body mass index (BMI), for predicting primary osteoporosis (OP) were compared and ideal thresholds which would enable omission of screening BMD were proposed [68]. The AUC of FRAX without BMD ranged from 0.536 to 0.630, which suggested that it had limited predictive value for identifying osteoporosis at least in the elderly Beijing male population the study was conducted on. The AUCs of BMI (0.801–0.880) were slightly better than OSTA (0.722–0.874) in predicting OP at all sites.

A systematic review and meta-analysis (SRM) of the performance of clinical risk assessment tools for screening for DXA-determined osteoporosis or low bone density included tools such as the Osteoporosis Self-Assessment Tool (OST), the Simple Calculated Osteoporosis Risk Estimation (SCORE) instrument, OSTA, the Osteoporosis Risk Assessment Instrument (ORAI), and body weight criteria [69]. The SRM included 30 studies with men representative of both Caucasian and Asian populations. It showed high sensitivity approaching or exceeding 90% for all the tools in various populations but low specificity at thresholds required for high sensitivity. Simpler instruments, such as OST, generally performed as well as or better than more complex ones. Specifically, the meta-analyses of studies evaluating OST using a cutoff threshold value of 3 to identify older US (American) men with osteoporosis at the femoral neck, total hip, or lumbar spine provided summary sensitivity and specificity estimates of 88% (95% CI: 79%–97%) and 55% (95% CI: 42%–68%), respectively. Reported sensitivities and specificities for OSTA for identifying men with osteoporosis at the femoral neck, total hip, or lumbar spine ranged from a high sensitivity of 87.33% and corresponding specificity of 56.20% with use of a threshold of ≤ -1 for Chinese men aged $\geq$ 50 years [70] to a low sensitivity of 38.2% and corresponding specificity of 82.1% with use of a threshold of < 1 for Portuguese men aged $\geq$ 50 years [71]. It is apparent that modifications to the originally proposed index cut-off value of OSTA of < -1 proposed by Koh et al. in postmenopausal Asian women [64] may be necessary to ensure the optimal performance of OSTA in different ethnicities, populations, and in both men and women.

Another SRM that explored the discriminative power of FRAX to identify fracture risk in men and women in Asia had, as its secondary aim, assessment of its discriminative power in identifying a densitometric diagnosis of osteoporosis in Asian populations [72]. The SRM showed that FRAX may exhibit stronger, albeit moderate, predictive capabilities for identifying a densitometric diagnosis of osteoporosis than it does for identifying absolute fracture risk in Asian populations.

While OSTA has only 2 parameters (age and weight) and is much simpler to use, employing a tool such as FRAX that can be added on to

the patient's risk profile and can provide fracture probabilities in addition to just identifying the risk of osteoporosis may provide an additional aid to the physician to discuss options for fracture prevention at the time of initial consultation itself. This may prove to be especially useful in resource-constrained settings with limited availability of DXA machines.

Other osteoporosis risk assessment tools exist. Shepherd et al. [73] developed the Male Osteoporosis Risk Estimation Score (MORES), a predictive tool specific for the diagnosis of osteoporosis in men based on the NHANES III cohort. It is strikingly similar to the OSTA, with the addition of a history of COPD in addition to age and weight. However, validation in other contexts beyond the original development cohort [74] has been limited. The few Asian studies that have attempted to perform such a validation have reported inconsistent results [75,76].

6. Fracture risk estimation in men

Assessing fracture risk plays a pivotal role in the effective management of osteoporosis. The traditional reliance on BMD T-scores alone for treatment decisions has been replaced by a more comprehensive approach that incorporates absolute fracture risk over fixed time frames. This approach integrates clinical risk factors, with or without BMD, into practical fracture risk assessment tools. Such estimation of fracture risk not only helps identify high-risk groups at the health system and population levels enabling targeted allocation of resources but also supports clinicians in engaging patients in shared decision-making for personalized treatment strategies. There is no clear evidence to show that any specific tool outperforms the others and as has been shown with screening tools, more complex tools do not necessarily demonstrate superior performance compared to simpler ones [77]. The scarcity of direct head-to-head comparisons in similar populations, coupled with the limited validation of most tools outside the original cohorts from which they were developed, makes it challenging to establish the superiority of any particular tool. To date, only four fracture risk assessment tools viz Garvan, FRAX, CAROC, and QFracture have undergone validation in a nationally representative, population-based setting [78]. However, even these well validated tools have inherent limitations. For example, a dose response is included for most of the variables in QFracture but not for FRAX. Fewer input parameters are required for FRAX and Garvan than for QFracture. The Garvan tool may be of particular interest in physicians treating elderly patients because it is very simple with only 5 CRFs [78].

FRAX® was developed using data from a WHO collaborating centre at the University of Sheffield and launched in 2008. FRAX can estimate the 10-year fracture probability of a major osteoporotic fracture (MOF) and hip fracture (HF) based on clinical risk factors, with or without BMD [79]. The clinical risk factors include age, gender, weight, height, fracture history, parent fracture history, smoking status, glucocorticoids intake, rheumatoid arthritis, secondary osteoporosis, alcohol intake, and BMD. A recently launched version-the FRAX Plus® allows modification of a probability result obtained from conventional FRAX estimates of probabilities of hip fracture and osteoporotic fracture with knowledge of several other parameters including recency of osteoporotic fracture, higher than average exposure if glucocorticoids, information on Trabecular bone score (TBS), number of falls in the previous year, duration if type 2 diabetes mellitus, concurrent information on lumbar spine BMD and hip axis length [80].

A full discussion of the strengths and weaknesses of FRAX is beyond the scope of this review but have been well summarized elsewhere [81]. Although it was initially developed with several prospective international cohorts, it is recognized that there is great inter-country variation in fracture risk, and therefore it is important to use country-specific models. FRAX enables country-specific calculations of fracture probability. However, it is important to note that its development was primarily based on data from Caucasian populations, and that it was initially validated using 12 cohort studies, of which only one was Asian (11 Caucasian and 1 Japanese), with participants aged between 50 and 65 years [82]. Thus, whether FRAX performs as well in Asian populations as it does in Caucasian ones and whether it performs equally well in very elderly populations as it does in the "young old" is still being debated.

A systematic review encompassing predominantly Caucasian populations had found that the discriminative ability of FRAX-MOF without BMD was 0.77 [95% CI: 0.73–0.80] and with BMD was 0.78 [95% CI: 0.75–0.81] [83]. FRAX-HF, on the other hand, had an AUC of 0.75 [95% CI: 0.72–0.79] without BMD and 0.79 [95% CI: 0.77–0.81] with BMD [83]. A recent SRM explored the discriminative ability of FRAX in predicting major osteoporotic fracture (MOF) and hip fracture (HF) risk in Asian populations [72]. The pooled AUC of FRAX *without* BMD for the prediction of any osteoporotic fracture was 0.72 (95% CI: 0.67–0.77). For MOF prediction *without* BMD the AUC was also 0.72 (95% CI: 0.66–0.77) similar to HF prediction with an AUC of 0.72 (95% CI: 0.65–0.80) [72]. FRAX *with* BMD showed a slightly higher predictive value with a pooled AUC value of 0.74 (95 % CI: 0.71–0.77) for any osteoporotic fracture. an AUC of 0.73 (95% CI: 0.70–0.77) for MOF and 0.77 (95% CI: 0.71–0.83) for HF. The findings from this SRM suggest that FRAX has lower predictive accuracy for fractures in Asian populations compared to what has been observed in Caucasians. The scarcity of FRAX calibration data for Asian populations also highlights potential limitations in its predictive ability across diverse Asian ethnic groups [84].

While the cohorts originally considered for development of FRAX did include men, subsequent studies have called its applicability in male populations into question. In the MrOS cohort, the authors observed a good agreement between FRAX determined risk and observed rate of incident fractures, but it was observed that FRAX tended to overestimate risk of major osteoporotic fractures in men. The AUC C-statistic, a measure of a model's ability to discriminate between those who will experience an event and those who will not, was 0.69 for hip fractures and 0.63 for MOF suggesting that FRAX has a relatively weaker discriminatory performance for MOF compared to HF in men. The inclusion of BMD values improved the discriminatory ability of the test as it appropriately down-classified most men who did not fracture, but this came at the cost of also inappropriately down-classifying the minority who did go on to fracture [85].

It would be timely at this point to remember that rather than fixate on a single best prediction tool, it is more important to understand that these tools can in fact be complementary and not contradictory. FRAX was developed to predict risk of fracture, whilst OSTA and other osteoporosis risk scores more to predict the likelihood of a BMD diagnosis of osteoporosis. Combining the information provided by each tool may offer a more holistic understanding of every male patient that is seen in clinical practice.

7. Management of osteoporosis in men

Specific guidelines for osteoporosis in men such as the Endocrine Society USA 2012 recommendations [86], the 2021 French recommendations from the Groupe de Recherche et D'Information sur les Ostéoporoses (GRIO) in collaboration with La Société Française de Rheumatologie (SFR) [87], the Danish Endocrine Society–National Board of Health 2020 recommendations [88], and most recently the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) guidelines [89] exist. Some of the recommendations made in the above guidelines must be considered in the context of country-specific scenarios before being adapted to the Asian context, though as in women, it is important that patients should be stratified based on fracture risk and treatment should not be a "one size fits all" but be individualized [90].

Secondary osteoporosis is more common in men than women, with a prevalence of 62.5% in men compared to 44.4% in women reported in a study from Singapore [91]. Conditions such as idiopathic

hypercalciuria, vitamin D deficiency and hyperthyroidism are relatively prevalent in men with osteoporosis and should not be ignored in the diagnostic evaluation. Importantly, a substantial proportion of men (9.4% in this report) have hypogonadism, the significance of which will be discussed in the following section. While conventional teaching has often suggested that a Z-score of −2 and below may help to identify patients with disproportionate bone loss for age and hence secondary contributors to osteoporosis, the same study reported very poor performance of the Z-score in identifying secondary osteoporosis at all cut-offs, with a reported AUC of 0.40 (0.213–0.594, P = 0.308). Hence, we suggest that a careful work-up for secondary contributors be considered in all men with a new diagnosis of osteoporosis, regardless of the Z-score.

7.1. The use of bone turnover markers in the management of osteoporosis in men

The association of bone turnover markers (BTMs) with BMD, bone loss, and fracture risk in men, particularly as they age is a subject that has not been well studied. BTMs, including markers of bone formation such as N-terminal extension propeptide of type I collagen (PINP), and osteocalcin, and of resorption such as beta-isomerized C-terminal telopeptide of collagen type I (CTX), have been shown to be weakly associated with BMD in men under 60 [92]. In young adult men, the consolidation and attainment of peak areal BMD (aBMD) is associated with a slowdown of bone turnover. Among middle-aged men, the observed stability in aBMD reflects a balance between periosteal apposition and endosteal bone loss. Since these changes occur gradually, aBMD is likely influenced more by the previously attained peak BMD than by the current rate of bone turnover. In older men, higher BTM levels correlate moderately with lower BMD and increased bone loss, [92]. The value of BTMs when compared to traditional factors such as BMD and history of falls for predicting fracture risk however remains limited in men. with prospective data on any such associations being scanty. Higher BTM levels in men have been shown to be associated with faster bone loss at some skeletal sites such as the hip and distal forearm, but not at other sites like the spine [93]. Factors such as the variability in bone loss across different skeletal sites, and the unreliable assessment of lumbar spine bone loss due to osteoarthritis likely contribute to these disparate results. Additionally, a single BTM measurement may not reflect long-term bone turnover accurately, as it is affected by various factors over time. Endosteal bone loss, the entity that is captured by BTMs, is influenced by the simultaneous occurrence of periosteal apposition. While this process occurs in both older men and women, it may have a more pronounced effect as mentioned earlier in men, who typically experience less endosteal bone loss and more periosteal apposition compared to women [94]. Though bone resorption rate, as measured by CTx has been shown to be an independent predictor of osteoporotic fractures in elderly men [95], and higher levels of both CTX and PINP were associated with hip bone loss and increased fracture risk [93], the association between BTMs and fracture risk in men appears to be less stronger than that observed in women [96].

The role of BTMs in prediction of bone loss and fracture risk in Asian men has been relatively underexplored. A cross-sectional study from China showed that higher levels of undercarboxylated osteocalcin (ucOC)—a marker of bone turnover were associated with lower BMD at the lumbar spine, femoral neck, and total hip [97]. Additionally, the study found a positive correlation between ucOC and other BTMs such as P1NP and b-CTX. A 1- SD increase in ucOC was associated with an odds ratio (OR) of 1.63 and 1.70 for having osteopenia or osteoporosis in men and women, respectively (men, 95% CI: 1.25–2.13, P = 0.004; women, 95% CI: 1.19–2.42, P = 0.004 [97]. Newly discovered BTMs such as the chemokine, CXCL9, may offer fresh insight into the relationship between BTMs and fracture risk in men, with increased levels of the CXCL9 levels shown to be associated with increasing hip fracture risk in elderly Chinese men (but not in women) in a matched case–control study nested in the prospective, population-based Singapore Chinese Health Study [98].

Only small studies have explored the effect of treatment interventions on BTMs in Asian males. A study designed to determine the efficacy and safety of abaloparatide,a Parathyroid Hormone Related Peptide (PTHrP) analogue in increasing BMD in Japanese men and women with osteoporosis at high fracture risk, and that explored the time course changes in BTMs after initiation of abaloparatide showed similar changes in BTMs in men and women [99]. Population and male-specific reference ranges for bone turnover markers must be developed before large scale recommendations on using BTMs to assess fracture risk and to evaluate anti osteoporosis medication treatment effects in Asian men can be made.

7.2. Who to treat and what intervention threshold to use?

Intervention thresholds for osteoporosis in women have in general been based on a specific BMD cut-off value, on whether there is a history of previous fracture or on a fracture probability derived using one of the several fracture risk assessment tools mentioned earlier in this review [78]. Whether the same intervention thresholds can be used in men and women is a subject of debate. Given the dearth of data surrounding this subject, a clear answer to this question cannot be provided. However, most guidelines recommend the approach of using the same intervention thresholds in men and women.

7.3. Non-pharmacological interventions

7.3.1. Exercise

Most studies evaluating the impact of exercise on osteoporosis have been conducted in women. A secondary analysis of an 18-month intervention in men aged 50–79 years examined the association between exercise frequency (average sessions completed per week) and training volume per session [PRT volume (weight lifted, kg), number of impacts (jumps) completed and total training volume (sum of PRT volume and number of impacts) with changes in DXA and QCT-derived femoral neck and lumbar spine bone outcomes over 18 months [100]. Men were allocated to either thrice-weekly progressive resistance plus impact exercise training of 60–75 minutes in duration each or a non-exercising group. The weight-bearing impact exercises were specifically designed to load the lower extremities. The magnitude, rate, and distribution (direction) of impact (jumps applied to the lower body were increased progressively throughout the program by increasing the height of jumps and/or by introducing more complex movement patterns. The total number of impact loads undertaken for each participant was derived from the number of impacts (jumps) completed for each set across all exercises. Average weekly exercise frequency and training volume per session were positively associated with the 18-month changes in femoral neck BMD and lumbar spine trabecular volumetric BMD (vBMD). Men completing on average 1 to < 2 and ≥ 2 sessions/week had a 1.6%–2.2% greater net gain in femoral neck BMD relative to non-exercising men, while those completing ≥ 2 sessions/week had 3.9%–5.2% net gain in lumbar spine trabecular vBMD compared to non-exercising men and those completing < 1 session/week. Further analysis showed that the average number of impact loads per session, but not the average weight-lifted, was positively associated with changes in BMD. Every 10 impact loads per session over 18 months was associated with a 0.3% and 1.3% increase in femoral neck BMD and lumbar spine trabecular vBMD, respectively. Though no reduction in fracture (as an end point) has been demonstrated, international consensus guidelines recommend exercise to men with osteoporosis on the basis of BMD associations and adjunctive benefits across organ systems [89].

7.3.2. Nutritional and supplement intake

An SRM of 53 randomised or quasi-randomised trials that compared vitamin D or related compounds, alone or with calcium, against placebo, no intervention or calcium alone, and reported fracture outcomes in

older people concluded that there is high quality evidence that vitamin D alone is unlikely to be effective in preventing hip fracture or any new fracture. This was corroborated in an ancillary study of the vitamin D and Omega-3 Trial (VITAL) which had 25,871 participants of which 49.4% were generally healthy midlife and older men who were not selected for vitamin D deficiency, low bone mass, or osteoporosis. In this study, vitamin D_3 supplementation did not result in a significantly lower risk of fractures compared to placebo [101] though high quality evidence does exist that vitamin D plus calcium results in a small reduction in hip fracture risk, a statistically significant reduction in incidence of new non-vertebral fractures, and the risk of any type of fracture [102].

7.4. Pharmacological interventions

7.4.1. Testosterone

The T-Trials Bone Trial conducted to determine whether testosterone treatment of older men with low testosterone increases vBMD (determined by quantitative computed tomography) and bone strength (estimated by finite element analysis) demonstrated that testosterone replacement with testosterone gel in addition to calcium and vitamin D supplementation led to significant improvements in lumbar spine trabecular vBMD, with a direct biological relationship observed between serum testosterone levels and vBMD results [103]. While the trial was not powered to evaluate fracture risk and indeed had a very low overall rate of fractures in both arms, it consistently demonstrated improvements in both vBMD and finite element analysis at all sites. Interestingly, improvements in aBMD determined by DXA were only observed in the lumbar spine in this trial—suggesting that a lack of improvement on typical aBMD in patients on testosterone replacement may not represent treatment failure as it does not consider concomitant vBMD improvements—an observation useful for clinical practice. The improvement in lumbar spine BMD alone with testosterone therapy was again observed in a SRM that included observational as well as placebo-controlled or uncontrolled randomized trials [104]. Testosterone improved aBMD at the spine and at the femoral neck in observational studies, whereas placebo controlled RCTs showed a positive effect of testosterone only at lumbar spine and when trials included only hypogonadal patients at baseline (total testosterone < 12 nM). The effects on aBMD were more evident in subjects with lower testosterone levels at baseline and increased as a function of trial duration [104].

In a recent sub-trial of a double-blind, randomized, placebo-controlled trial that assessed the cardiovascular safety of testosterone treatment in middle-aged and older men with hypogonadism, testosterone treatment did not lead to a reduced incidence of fractures compared to placebo [105]. After a median follow-up of 3.19 years, clinical fractures occurred in fact in 91 participants (3.50%) in the testosterone group as opposed to 64 participants (2.46%) in the placebo group, yielding a hazard ratio (HR) of 1.43 (95% CI: 1.04–1.97). The increased fracture incidence in the testosterone group was consistent across various types of fractures, including non-high-impact fractures and fractures in participants not taking osteoporosis medication. The cumulative incidence of clinical fractures at 3 years was 3.8% in the testosterone group and 2.8% in the placebo group. These findings were unexpected, as earlier studies highlighted above suggested improvements in volumetric BMD and trabecular bone strength with testosterone therapy. The discrepancy might arise because improvements in trabecular bone do not necessarily translate into enhanced cortical bone integrity, which is more crucial for fracture prevention in older adults. Testosterone's benefits on bone quality may thus not directly translate into reduced fracture risk, highlighting the need for further investigation into the long-term skeletal effects of testosterone therapy.

A lack of randomized controlled trials on fracture incidence with testosterone therapy and the impracticality of using "bridging" to extrapolate the results from fracture studies in females (since testosterone therapy is specific for males), makes it currently impossible for testosterone therapy to be advocated as a therapy for treating osteoporosis in men. Therefore, other agents with proven anti-fracture efficacy should still be used if fracture risk reduction is the primary aim.

7.4.2. Antiresorptive agents

Only a few studies have evaluated the therapeutic efficacy of antiresorptive agents for osteoporosis in men, and most of these studies have only assessed BMD changes. Therefore, the regulatory approval of these agents for men is often based on "bridging" studies that extrapolate fracture risk reduction correlations with BMD changes observed in women. A 1.83% difference in BMD at the total hip (TH) is required to enable fracture reduction at any site. Additionally, a 1.42% difference in BMD at the TH is necessary for vertebral fracture reduction, while a 3.18% change is needed at the TH to enable hip fracture reduction [106].

7.4.2.1. Bisphosphonates. A recent SRM demonstrated that both alendronate and risedronate have beneficial effects on lumbar spine, femoral neck, and total hip BMD in men [107] Alendronate therapy resulted in a mean difference (MD) of 5.2% at the lumbar spine (95% CI: 2.76–7.64), 2.34% at the total hip (95% CI: 1.66–3.03), and 2.53% at the femoral neck (95% CI: 1.76–3.31) when compared to placebo. Similar improvements in BMD were observed with risedronate, with MDs of 4.39% (95% CI: 3.46–5.31) at the lumbar spine, 2.46% (95% CI: 1.71–3.22) at the total hip, and 1.95% (95% CI: 0.62–3.27) at the femoral neck. Beneficial effects on BMD have also been demonstrated with zoledronic acid therapy in men. Once-yearly IV zoledronic acid (5 mg) increased bone mass at the hip and femoral neck in men within 90 days of low-trauma hip fracture repair, with similar magnitudes of improvement as those observed in women in the same study [108]. In another multicenter, double-blind, placebo-controlled trial, 1199 men aged 50 to 85 with primary or hypogonadism-associated osteoporosis were assigned to receive intravenous infusions of zoledronic acid (5 mg) or placebo at baseline and at 12 months. The primary endpoint was the proportion of participants with one or more new morphometric vertebral fractures over a 24-month period. The rate of any new morphometric vertebral fracture was 1.6% in the zoledronic acid group compared to 4.9% in the placebo group over the 24-month period, representing a 67% risk reduction with zoledronic acid (relative risk, 0.33; 95% CI: 0.16–0.70; $P = 0.002$). Additionally, men receiving zoledronic acid experienced fewer moderate-to-severe vertebral fractures ($P = 0.03$) and less height loss ($P = 0.002$) compared to those in the placebo group [109].

7.4.2.2. Denosumab. Denosumab (60 mg subcutaneously every 6 months) has been shown to be effective in reducing vertebral, non-vertebral, and hip fractures in Caucasian postmenopausal women with osteoporosis [110]. A placebo-controlled, randomized phase 3 study that evaluated the efficacy and safety of denosumab (60 mg every 6 months) in men with low BMD showed significant BMD increases of 5.7% at the lumbar spine, 2.4% at the total hip, 2.1% at the femoral neck, 3.1% at the trochanter, and 0.6% at the one-third radius after 12 months (adjusted $P \leq 0.0144$) [111]. A sensitivity analysis controlling for baseline covariates (including baseline testosterone levels, BMD T-scores, and 10-year osteoporotic fracture risk) confirmed the robustness of these findings. Denosumab also resulted in a significant reduction in bone resorption, with serum CTX levels reduced by day 15 (adjusted $P < 0.0001$). A retrospective cohort study from Taiwan involving 175 male patients receiving annual zoledronic acid treatment and 366 male patients receiving biannual denosumab for 5 years showed significant BMD improvements in both groups. However, BMD improvements were greater with denosumab, especially in patients with T-scores higher than −2.5 [112].

7.4.3. Anabolic agents

7.4.3.1. Teriparatide. Teriparatide treatment has been shown to increase BMD in men. In a study of 437 men with spine or hip BMD T-scores < -2.5, daily injections of either 20 μg or 40 μg teriparatide resulted in lumbar spine BMD increases of 5.9% and 9.0% over baseline with the 20 μg and 40 μg doses respectively by the end of the trial ($P < 0.001$, for both doses vs placebo). In addition, femoral neck BMD increased by 1.5% (20 μg; $P = 0.029$) and 2.9% (40 μg; $P < 0.001$), while whole-body bone mineral content increased by 0.6% (20 μg; $P = 0.021$) and 0.9% (40 μg; $P = 0.005$) above baseline in the teriparatide groups. However, there were no significant changes in radial BMD in the teriparatide groups [113]. PTH was found to be a potent stimulator of skeletal dynamics in men with idiopathic low-turnover osteoporosis, producing significant increases in lumbar spine and hip bone density in an 18-month randomized, double-blind, placebo-controlled trial of 23 men aged 30–68 years (mean age 50 years ± 1.9). PTH (1-34) led to a marked 13.5% increase in lumbar spine BMD, while the control group showed no change ($P < 0.001$). The mean lumbar spine T-score improved from -3.5 ± 0.2 to -2.4 ± 0.4. Femoral neck BMD increased by 2.9% in the PTH-treated group ($P < 0.05$), while the 1/3 site of distal radius showed no change [114]. All bone turnover markers increased in the PTH-treated group, with the largest increases in serum osteocalcin and urinary N-telopeptide (230% and 375% above baseline by 12 months, respectively; $P < 0.001$). A meta-analysis of two RCTs lasting 11 and 18 months, respectively, confirmed BMD improvements at both the lumbar spine and femoral neck with teriparatide therapy in men. A network meta-analysis, which included 13 RCTs and quasi-RCTs, demonstrated that zoledronate had the most significant effect on increasing lumbar spine BMD (SMDs 13.48; 95% credible intervals 11.88–15.08), while teriparatide had the greatest effect in reducing vertebral fractures. The placebo group had an odds ratio of vertebral fractures of 4.04 (95% CI: 1.36–8.49) compared to teriparatide 20 μg and 3.5 (95% CI: 1.14–8.34) compared to teriparatide 40 μg [115].

It is recommended that antiresorptive therapy should follow teriparatide treatment to prevent subsequent bone loss, though this sequential approach is primarily supported by observational studies in women [113,122].

7.4.3.2. Abaloparatide. The Abaloparatide for the Treatment of Men with Osteoporosis (ATOM; NCT03512262) study evaluated abaloparatide's efficacy and safety compared to placebo in men. In this randomized controlled trial, 228 men aged 40–85 years with osteoporosis were randomized in a 2:1 ratio to receive either daily subcutaneous injections of abaloparatide 80 μg or placebo for 12 months. The primary endpoint was the change in lumbar spine BMD from baseline, while key secondary endpoints included BMD changes at the total hip and femoral neck. At 12 months, the BMD gains were significantly greater with abaloparatide compared to placebo at the lumbar spine (least squares mean percentage change [standard error]: 8.48 [0.54] vs 1.17 [0.72]), total hip (2.14 [0.27] vs 0.01 [0.35]), and femoral neck (2.98 [0.34] vs 0.15 [0.45]) (all $P < 0.0001$) [116]. In the phase 3 ACTIVE-J Study conducted in Japan, postmenopausal women and men with osteoporosis at high risk for fractures were treated with daily subcutaneous injections of 80 μg abaloparatide or placebo for 78 weeks [99]. The primary endpoint was the percentage change in lumbar spine BMD at the last visit compared to baseline. Secondary endpoints included time-course changes in BMD at the lumbar spine, total hip, and femoral neck, as well as changes in bone turnover markers and the cumulative number of fractures. Abaloparatide increased BMD at the lumbar spine, total hip, and femoral neck by 12.5% (95% CI: 10.3%–14.8%; $P < 0.001$), 4.3% (95% CI: 3.3%–5.3%), and 4.3% (95% CI: 2.9%–5.6%), respectively, compared to placebo. Markers of bone formation (P1NP) increased rapidly to ~140% above baseline at 6 weeks but gradually decreased, remaining approximately 25% higher than baseline at 78 weeks. Bone resorption markers (serum CTX) gradually increased to 50% above baseline at 24 weeks but decreased to near placebo levels by 60 weeks. Four new vertebral fractures were observed in three participants in the placebo group, but none were observed in the abaloparatide group [99].

7.4.3.3. Romosozumab. Romosozumab is a sclerostin inhibitor that increases bone formation and decreases bone resorption. This dual mechanism leads to rapid and substantial increases in areal bone mineral density (aBMD), as measured by DXA. In a phase 1b, randomized, double-blind, placebo-controlled study, romosozumab or placebo was administered to 32 women and 16 men with low aBMD for 3 months, followed by a 3-month observation period [117]. Quantitative computed tomography (QCT) scans of the lumbar vertebrae (L1-2) and high-resolution QCT (HR-QCT) scans of the thoracic vertebra (T12) were analyzed in a subset of participants at baseline, month 3, and month 6. Linear finite element modeling was used to assess bone stiffness. Compared to placebo, the romosozumab group showed improvements at month 3 in trabecular BMD by QCT and HR-QCT, as well as HR-QCT-derived trabecular bone volume fraction (BV/TV), trabecular separation, density-weighted cortical thickness, and QCT-derived bone stiffness (all $P < 0.05$). At month 6, the romosozumab group exhibited further improvements in QCT-derived trabecular BMD and stiffness, as well as HR-QCT-derived trabecular BV/TV, trabecular separation, density-weighted cortical thickness, and stiffness (all $P < 0.05$). The mean (SE) increase in HR-QCT-derived bone stiffness in the romosozumab group from baseline was 26.9% ± 6.8% at month 3 and 35.0% ± 6.8% at month 6, while placebo-treated participants experienced changes of $-2.7\% \pm 13.4\%$ at month 3 and $-6.4\% \pm 13.4\%$ at month 6. In conclusion, romosozumab administration for 3 months resulted in rapid and substantial improvements in both trabecular and cortical bone mass and structure, as well as whole bone stiffness, which continued for 3 months after the final romosozumab dose [117].

In a European phase 3 randomized, placebo-controlled, double-blind trial evaluating the efficacy and safety of romosozumab in men with osteoporosis, 245 men aged 55–90 years with a BMD T-score of ≤ -2.5 at the lumbar spine, total hip, or femoral neck (or a T-score of ≤ -1.5 with a history of fragility fractures) were randomized in a 2:1 ratio to receive romosozumab (210 mg subcutaneously) or placebo for 12 months [118]. The primary efficacy endpoint was the percentage change in lumbar spine BMD at month 12. BMD increases from baseline was significantly greater in the romosozumab group compared to the placebo group at both the lumbar spine (12.1% vs 1.2%; $P < 0.001$) and total hip (2.5% vs −0.5%; $P < 0.001$). Adverse events and serious adverse events were balanced between the groups, although there was a numerical imbalance in positively adjudicated cardiovascular serious adverse events [romosozumab: 8 events (4.9%) vs placebo: 2 events (2.5%)].

In summary, therapy with antiresorptive agents, including bisphosphonates and denosumab, have shown significant improvements in BMD at multiple sites in men. Zoledronic acid demonstrated a substantial 67% reduction in morphometric vertebral fractures in men with osteoporosis. Denosumab has also proven effective, with biannual therapy with it showing significant BMD improvements in long-term studies, with denosumab providing greater benefits in patients with higher T-scores. Anabolic agents like teriparatide and abaloparatide have shown the most significant increases in BMD, particularly in the lumbar spine, with notable reductions in vertebral fracture risk. Teriparatide is especially potent in men with idiopathic low-turnover osteoporosis, while abaloparatide resulted in marked improvements in BMD at the lumbar spine, hip, and femoral neck. Therapy with romosozumab, has also resulted in rapid and substantial increases in BMD and bone stiffness, demonstrating romosozumab's promise as an effective treatment for male osteoporosis. However, there remains a concern of increased cardiovascular adverse events with this agent and therefore the patient's fracture risk over the next year and their cardiovascular

risk profile should be taken into account before consideration of romosozumab as therapy for osteoporosis.

8. Cost effectiveness of osteoporosis management strategies in men

8.1. Cost effectiveness of screening strategies for osteoporosis and osteoporotic fracture risk

There is ongoing debate regarding the benefits of a widespread systematic screening approach for osteoporosis in men [119]. The healthcare provider must carefully balance the risks and benefits of routine screening. This includes considering the increased demand for DXA scans and their interpretation, the radiation exposure (albeit low doses) from DXA, the higher identification rates of low bone density and osteoporosis, and the greater use of osteoporosis medications with their associated potential side effects against the possible reduction in fracture risk that can be obtained with screening strategies.

A simulation model study conducted in the USA aimed to assess the long-term health and economic impact of DXA screening followed by treatment for osteoporosis in older men with a history of falls [120]. In the base case analysis, it was found that 1876 men would need to be screened to prevent one hip fracture, and 746 men to prevent one major osteoporotic fracture. The screening strategy increased quality-adjusted survival by 0.0026 QALYs, raised costs by 87 USD, and resulted in an ICER of 33,169 USD per QALY gained. Consequently, this strategy would be favoured over usual care at the standard willingness-to-pay threshold of 100,000 USD per QALY. The study concluded that screening with DXA followed by treatment would be reasonably cost-effective for men aged 65 years or older who have experienced a fall within the past year. For men over 77 years, this approach would both improve health outcomes and reduce costs from a societal perspective [120]. These findings suggest that screening could be justified when focused on men at higher risk for osteoporotic fractures. Another study conducted in Germany investigated whether osteoporosis screening using opportunistic Quantitative Computer Tomography (oQCT) is cost-effective for women and men aged 65 years and older and to identify patient-level cost thresholds [121]. Three screening strategies ("no osteoporosis screening", "opportunistic QCT screening", and "DXA screening") after routine CT were simulated in a state transition model for hypothetical cohorts of 1000 patients (women and men aged 65 years) over a follow-up period of 5 years. Compared to DXA screening, opportunistic QCT screening increased QALYs in both sexes (additional 2.40 per 1000 women and 1.44 per 1000 men) and resulted in total costs of 3,199,016 USD and 950,359 USD vs 3,262,934 USD and 933,077 USD for women and men, respectively. The study results suggest that oQCT screening is a cost-effective ancillary approach for osteoporosis screening and has the potential to prevent a substantial number of vertebral fractures if utilized in daily clinical practice.

Though no studies exploring cost effectiveness of osteoporosis screening strategies in men alone have been conducted in Asia, a few have been conducted where populations of both men and women were included. In a study evaluating the cost-effectiveness of selective bone densitometry (SBD) using the Osteoporosis Self-Assessment Tool for Asians (OSTA) as a risk-stratifying method for the three main ethnic groups (Chinese, Malay, and Indian) in Singapore, SBD was compared to no bone densitometry [122]. For men aged 75 to 80, SBD using OSTA would cost between 40,679 USD and 73,909 USD per QALY gained, while for postmenopausal women aged 70 to 80, the cost ranged from 22,386 to 58,185 USD per QALY gained. In contrast, universal bone densitometry for men aged 75 to 80 would cost between 157,955 USD and 177,127 USD per QALY gained, and for postmenopausal women aged 70 to 80, the cost ranged from 40,179 to 66,112 USD per QALY gained, compared to SBD. Osteoporosis screening was the most cost-effective for Malays and the least cost-effective for Indians. Overall, the most cost-effective strategy for males that was found was to use OSTA as a risk-stratifying tool at age 75 in men.

Another study aimed to evaluate the clinical outcomes and cost-effectiveness of dual-energy X-ray absorptiometry (DXA) for osteoporosis screening in Taiwanese women and men (women: men = 63.8%: 36.2%) over a 20-year time horizon [123]. The DXA group had significantly better outcomes than the non-DXA group in terms of fragility fractures (7.6% vs 12.5%, $P < 0.001$) and mortality (0.6% vs 4.3 %, $P < 0.001$). The DXA screening strategy gained an ICER of −2794 USD per quality-adjusted life year (QALY) relative to the non-DXA at the willingness-to-pay threshold of 33,004 USD (Taiwan's per capita gross domestic product). The investigators surmised that using DXA to screen adults aged 50 years or older for osteoporosis resulted in a reduced incidence of fragility fractures, lower mortality rate, and reduced total costs. Screening for osteoporosis was found to be a cost-saving strategy and its effectiveness was found to increase with age. However, these findings should be approached with caution as the study population was predominantly composed of women.

8.2. Cost effectiveness of intervention thresholds and anti-osteoporosis treatment

A study from Portugal determined that treating men aged 50 years and older was cost-effective when the 10-year probability for major osteoporotic fractures (MOF) as estimated using FRAX exceeded 8.8% and for hip fractures (HF) exceeded 2.5%, using generic alendronate as a treatment [124]. A systematic review that specifically explored cost effectiveness of intervention thresholds in men was conducted in 2023. Out of the 25 studies that were included in the SRM, 9 studies included only men and 16 included both men and women. There was one study from Asia. The intervention thresholds at which bisphosphonates were found to be cost effective varied with a 10-year probability of a major osteoporotic fracture that ranged from 8.9% to 34.2% for different age categories [125]. Cost-effectiveness of intervention thresholds were generally similar in those studies in the systematic review conducted in both men and women, with slightly greater incremental cost-effectiveness ratios in men. Denosumab was shown to be cost effective in men aged 75 years and older with osteoporosis compared with bisphosphates and teriparatide in 2 studies that were part of the systematic review [125].

Sequential therapy regimens with an anabolic agent followed by an antiresorptive agent are increasingly being adopted to manage osteoporosis long term and to address very high fracture risk. Therapy with abaloparatide (a PTHrP analogue) followed by alendronate was dominant, (ie, both effective and cost saving) over alendronate monotherapy or biosimilar teriparatide followed by alendronate in a cohort of US men with a BMD T-score ≤ -2.5 and a history of fracture [126]. However, no data on this is available in other populations. At the time of this writing, abaloparatide is available only in 3 countries in Asia and no studies examining cost effectiveness of its use have been conducted.

Most cost-effectiveness analyses in men were based on bridging studies of shorter durations that used BMD as a surrogate endpoint to support an indication in men. In most of these bridging studies, the risk profile of the included study population did not match the fracture risk level in the pivotal trials in postmenopausal women. With the advent and easy availability of potent anti osteoporosis agents it may not be ethical to include men with high fracture risk in a placebo-controlled bridging study. Since more recent phase III studies have included women at lower risk than traditional studies, the data from these studies are more likely to provide a suitable basis for bridging to a male population with a lower risk. When an agent in a bridging study for men increases BMD to a magnitude comparable to that observed in the larger, longer, and more extensive studies required for approval in postmenopausal women, the validation of this treatment in men is considered sufficient [106]. This strategy is accepted both by regulators and payers and is acceptable from a health economics perspective [89].

8.3. Fracture Liaison Services

Fracture Liaison Services (FLSs) have been shown to be universally cost effective in men in Sweden (with zero net costs and 35 quality-adjusted life years gained compared with a 'do nothing' approach) [127] and orthogeriatric services have been shown to be cost effective in the UK in elderly men (at £14,525 per quality-adjusted life years) [128].

8.4. Special causes of secondary osteoporosis in men

Hypogonadism, for instance due to androgen deprivation therapy (ADT) in prostate cancer, and Glucocorticoid Induced Osteoporosis (GIOP) are two main contributors of secondary osteoporosis and fractures in men, and several studies have been conducted in Asia also that corroborates with this [129–134]. Only 2 health economics studies, have been published on cost effectiveness of treatment in these situations, The first of these 2 studies which involved a hypothetical cohort of men aged 70 years with locally advanced or high-risk localized prostate cancer starting a 2-year course of ADT after radiation therapy, found that alendronate therapy in conjunction with BMD testing was cost effective in patients starting adjuvant androgen deprivation therapy for locally advanced or high-risk localized prostate cancer [135]. Routine use of alendronate without a BMD test was found to be justifiable on a health economic basis in patients at higher risk for hip fractures in this study, The second of these 2 studies was conducted in the UK and conducted using an individualized pharmacoeconomic model found that bisphosphates were cost effective in patients using high doses of glucocorticoids ($\geq$ 15 mg of prednisolone or its equivalent daily) [136]. The results of this study suggest that bisphosphonate treatment in elderly GC users is cost-effective, especially in those with a life expectancy over 5 years. They are also cost-effective in younger patients who have a history or develop a clinical fracture during GC therapy. Indeed, recent guidelines on the management of GIOP by the European Calcified Tissue Society recommends anti-osteoporosis treatment regardless of GC dosage, T-score or the underlying disease requiring GCs in post-menopausal women and men $\geq$ 50 years, in the presence of a fragility fracture (vertebral and/or non-vertebral) [137]. Though no studies on cost effectiveness of anti-osteoporosis treatment in GIOP have been published so far in Asians, a SRM that compared the efficacy of oral bisphosphonates, vitamin D and a combination treatment for preventing and managing GIOP in Eastern Asians (from Japan, Korea, and China) had found that compared with vitamin D alone, bisphosphonates alone and combination treatment of bisphosphonates and vitamin D were significantly effective in Eastern Asians with GIOP [134]. The Korean National Guidelines recommend the use of oral bisphosphonates as first line therapy for GIOP in adults $\geq$ 40 years of age [138].

9. Conclusions

Despite it being well recognized that osteoporosis and its associated fragility fractures carry significantly more morbidity and mortality in men, they remain under-recognized and under-treated conditions, particularly in Asian populations, where disparities in diagnostic thresholds and fracture risk stratification persist. This review has highlighted significant differences in skeletal aging and fracture risk between men and women, with critical nuances in ethnic and geographical variations that challenge the application of Western-derived diagnostic criteria. The reliance on Caucasian reference databases for BMD assessment and the absence of specific guidelines tailored for Asian men exacerbates the gap in management. Furthermore, while pharmacological interventions, such as bisphosphonates, denosumab, and newer anabolic agents, demonstrate efficacy in increasing BMD and reducing fractures, their cost-effectiveness and long-term impacts on fracture prevention remain to be rigorously evaluated in diverse male populations. There is an urgent need for larger, longitudinal studies to establish race-specific intervention thresholds and to refine treatment algorithms that integrate fracture risk assessment tools such as FRAX with ethnic and sex-specific considerations. Ultimately, a more individualized approach to the management of male osteoporosis is essential to improve outcomes, reduce morbidity and mortality, and address the growing burden of osteoporotic fractures in aging male populations worldwide.

CRediT author statement

Gerald Gui Ren Sng: Conceptualization, Writing. **Jean-Yves Reginster:** Content Expertise, Editing and Revising. **Majed S Alokail:** Content Expertise. **Manju Chandran:** Conceptualization, Content Expertise, Writing, Editing, and Revising.

Conflicts of interest

The authors declare no competing interests.

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