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Bone health in ageing men

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Abstract

Osteoporosis does not only affect postmenopausal women, but also ageing men. The burden of disease is projected to increase with higher life expectancy both in females and males. Importantly, osteoporotic men remain more often undiagnosed and untreated compared to women. Sex steroid deficiency is associated with bone loss and increased fracture risk, and circulating sex steroid levels have been shown to be associated both with bone mineral density and fracture risk in elderly men. However, in contrast to postmenopausal osteoporosis, the contribution of relatively small decrease of circulating sex steroid concentrations in the ageing male to the development of osteoporosis and related fractures, is probably only minor. In this review we provide several clinical and preclinical arguments in favor of a 'bone threshold' for occurrence of hypogonadal osteoporosis, corresponding to a grade of sex steroid deficiency that in general will not occur in many elderly men. Testosterone replacement therapy has been shown to increase bone mineral density in men, however data in osteoporotic ageing males are scarce, and evidence on fracture risk reduction is lacking. We conclude that testosterone replacement therapy should not be used as a sole bone-specific treatment in osteoporotic elderly men.

Keywords Male osteoporosis · Ageing · Bone health · Sex steroids · Testosterone replacement therapy

Abbreviations

25(OH)D	25-hydroxyvitaminD
aBMD	areal bone mineral density
ADT	androgen deprivation therapy
AR	androgen receptor
BioE2	bioavailable estradiol
BioT	bioavailable testosterone
BMD	bone mineral density
BMI	body mass index
BTM	bone turnover marker
DHT	dihydrotestosterone
DXA	dual X-ray absorptiometry
E1	estrone
E2	estradiol
EMAS	European male ageing study
ERα	estrogen receptor alpha
FN	femoral neck
FRAX	Fracture Risk Assessment Tool
IA	immunoassay
LOH	late onset hypogonadism
LS	lumbar spine
MOF	major osteoporotic fracture
MrOS	osteoporotic fractures in men study
MS	mass spectrometry
PBM	peak bone mass
pQCT	peripheral quantitative computed tomography
QCT	quantitative computed tomography

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RCT	randomized controlled trial
SARM	selective androgen receptor modulator
SD	standard deviation
SERM	selective estrogen receptor modulator
SHBG	sex hormone binding globulin
SNP	single nucleotide polymorphism
T	testosterone
TBS	trabecular bone score
TH	total hip
TRT	testosterone replacement therapy
vBMD	volumetric bone mineral density

1 Epidemiology of osteoporosis and fractures in ageing men

Osteoporosis and subsequent fractures are still often considered to be a female-only disease. Indeed, women have greater risk of developing osteoporosis compared to men. However, the burden of disease in men is still substantial. Moreover, osteoporotic men are more underdiagnosed and more often left untreated. In US adults over 50 years old, the prevalence of osteoporosis, defined as a bone mineral density (BMD) T-score <-2.5 at either femoral neck (FN) or lumbar spine (LS) is 16.5% in women compared to 5.1% in men. [1] Osteopenia, T-score between − 1 and − 2.5, affects even more than half of the female and more than one third of the male population over the age of 50. When expanding the definition of osteoporosis to men with a history of low-impact fracture or high Fracture Risk Assessment Tool (FRAX) score, prevalence of osteoporosis increases to 16%, with rising numbers with increasing age, 5.5% in men aged 50–59 years to 46.3% in men aged 80 years or older, clearly illustrating that osteoporosis is not a female-restricted pathology. [2–4]

In postmenopausal women, each standard deviation (SD) reduction in LS BMD was associated with a 2-fold greater risk of vertebral fracture. Similarly, with every SD decline in hip BMD, risk of hip fracture increased 2.4-fold. [5] This risk may be even higher in older men compared to postmenopausal women, because each SD decrease in total hip (TH) BMD was associated with a 3.2-fold increased risk of hip fracture and 1.6-fold increase in nonvertebral fracture risk. [6] Not only is low BMD as such an important determinant, but also longitudinal changes, as accelerated decrease in BMD at the hip was a strong independent risk factor for hip fracture. [7]

The estimated female-to-male ratio is 1.6 and 2.6 for all osteoporotic fractures and hip fractures respectively. [8] On the other hand, similar prevalence of vertebral fracture in women and men was reported, again with increasing prevalence with increasing age: 11% in 70 to 79-year-olds compared to up to 18% in men and women over 80. [9] Additionally, the absolute risk of subsequent fracture after an initial low-trauma fracture, was similar in men compared to women. [10] In different populations the lifetime risk for a middle-aged man to experience an osteoporotic fracture was estimated to be 20 to 25%. [11–13] For hip fracture this was 6.7%, with a 10-year absolute risk of 4.2% at the age of 65, increasing to 18.6% at the age of 80. [12, 14] Over the last decades there seems to be a decreasing trend in incidence of major osteoporotic fractures (MOF) in middle-aged to older adults, however, the decrease is less pronounced in men compared to women. Hip fracture rates declined with 31% in women but only 19% in men. [15]

Men with low bone mass, accelerated bone loss, or osteoporotic fractures also have increased mortality risk. [16, 17] Older men with accelerated bone loss had 44% greater risk of mortality compared to men with maintained BMD, and this excess mortality was not explained by comorbidity burden, concurrent change in bodyweight, or physical activity. [18] Community-dwelling men had a 2.5-fold increased mortality risk after fracture. [19] Moreover, mortality risk after fracture seemed to be higher in men compared to women. [20–24] Again, this increased mortality risk could not be fully attributed to higher presence of comorbidities in men. [25, 26] After hip fracture, the excess mortality was highest in the first three months, almost 8-fold relative likelihood of death from all causes, and decreased substantially thereafter. Mortality rates did not return to those seen in age-matched controls however, even 10-years post-fracture, mortality rates remained twice as high. [22]

Despite being a very prevalent problem causing major morbidity and mortality, osteoporosis often remains an underdiagnosed and untreated disease. Moreover, this so-called diagnostic and therapeutic gap is greater in men compared to women. [27–33] The proportion of men treated with antiresorptive drugs and having follow-up bone density measurements after suffering from low-energy hip fracture, has been shown to be much less compared to women. [34, 35] Even in men at high risk, such as following chemical castration, both underdiagnosis and undertreatment remain important issues. [36, 37]

Osteoporotic fractures also impose a large economic burden, and costs are projected to only increase with the ageing population in the coming years and decades in both sexes. [38, 39]

In conclusion, osteoporosis and related fractures clearly do not only affect postmenopausal women, but also impose a major health issue in ageing men with even higher risk of mortality compared to women. Despite efforts in the last decades to raise awareness of the importance of bone health in older men, osteoporosis often remains underrecognized and untreated in this population.

2 Male versus female bone (accretion, maintenance, ageing) – structural changes contribute to strength

The main surrogate marker of fracture risk in men as well as women is areal BMD (aBMD) as measured by dual X-ray absorptiometry (DXA). [40] It is important to remind the reader that areal bone density is a two-dimensional projection of a three-dimensional bone. As a result, changes in aBMD may be due to both real changes in volumetric BMD (vBMD), which is real bone density reflecting the amount of calcium per volume bone, as well as alterations in bone structure. Greater bone size, so outer diameter, may therefore lead to greater aBMD without changes in vBMD. Quantitative computed tomography (QCT) is a technique which allows evaluation of size and structure of both the cortical and trabecular compartment separately, but also real density (vBMD). [40] This technique has been extensively used in experimental settings (even in high resolution) but less in clinical practice.

The observed difference in prevalence of osteoporotic fractures in women and men reflects differences in bone strength between sexes. At any age, men have greater bone strength compared to women. [41, 42] This is mainly due to differences in bone structure, characterized by men having wider bones and thus greater cortical bone diameter. [41, 43] Their greater bone diameter provides men with 47% and 37% greater estimated failure load at age 80 compared to women in radius and tibia respectively. [42] Equally, low bone width was associated with increased fracture risk in elderly men, regardless of aBMD. [44]

It is well established that peak bone mass (PBM) accrual is important for future fracture risk. A 10% increase in peak BMD is predicted to delay onset of osteoporosis by 13 years in postmenopausal women. [45] Young men reach their PBM between 18 and 23 years of age and have higher values than women at all sites. [46, 47] In early adulthood, an accelerated bone loss at the femur was observed which is similar in men as in women. [48] 25% of PBM at proximal femur may as such be lost by the age of 50 years in men. [49]

After PBM acquisition, endocortical resorption (and in this way medullary expansion) is greater in women compared to men and exceeds periosteal apposition. [50] Cortical thickness reduces, and cortical porosity increases more in ageing women compared to men. [51–53] Cortical thickness and BMD decrease, whereas medullary area increases in elderly men. [54] Peripheral quantitative computed tomography (pQCT) of the distal radius shows mainly trabecular thinning without change in trabecular number or separation in ageing men, in contrast to women who also lose trabeculae. [51, 55] Whereas substantial cortical bone loss begins in midlife in women, in men this starts mainly after the age of 75. The acceleration of bone loss following menopause in women is clearly related to estrogen deficiency. However, since trabecular bone loss starts earlier and occurs in both women and men, sex steroid deficiency may not be the one and only explanation of age-related bone loss. [56]

Other processes associated with ageing, such as cellular senescence and oxidative stress, also contribute to bone loss in both women and men. [57–59] As mentioned before, even in the absence of sex steroid deficiency, age-related bone loss occurs. Although sex steroids are able to regulate bone cell apoptosis [60, 61], estrogen deficiency and cellular senescence have also been shown to be able to induce bone loss through independent mechanisms. [62, 63] Therefore, age-related bone loss has shifted from an estrogen-centric towards an ageing and oxidative stress perspective. [59]

3 Sex steroids and their impact on bone: is it androgen, estrogen or both?

It is well recognized that sex steroids are essential for the development, as well as maintenance of both bone structure and density. Experimental data suggest a pivotal role for both estrogens and androgens, while in humans, estrogens seem to be the main sex steroids driving bone mass accrual, and similarly for bone maintenance, estrogen deficiency is the most important determinant of sex steroid deficiency-mediated bone loss.

The main circulating androgen in humans, testosterone (T) is being converted into estrogens, mainly into estradiol (E2), in peripheral tissues, such as fat, by the aromatase enzyme. In men, more than 85% of the circulating E2 levels originate from peripheral aromatization of T. [64, 65] As such, T can exert its actions on bone both by stimulating the androgen receptor (AR) directly, or the estrogen receptor alpha (ERα) after aromatization. T is hence the ideal androgen since it integrates both ER and AR actions, which are both important for skeletal development on the one hand, and bone maintenance on the other.

The specific role of both androgens and estrogens and their respective receptors in experimental studies have been reviewed extensively. [43, 66] In summary, AR-related androgen action results in increased cortical apposition, and decreased resorption in the trabecular compartment in male mice. Estrogens, via ERα, also increase periosteal apposition and decrease cortical endosteal bone resorption, while next to decreased trabecular bone resorption, also increase trabecular bone formation. For the normal development of trabecular and periosteal bone growth, both presence of AR and ERα are essential in male mice during puberty. [67]

In humans, overt hypogonadism, and thereby loss of both AR and ER-mediated androgen actions, clearly results in low bone mass, both in regions which are mainly composed of cortical bone, such as the radius, as well as trabecular bone enriched regions, such as the spine. [68, 69] Likewise, men who are deprived of endogenous androgen production, such as prostate cancer patients treated with gonadotropin releasing agonists, suffer from bone loss, as well as structural decay of bone both in the cortical and trabecular compartment, such as decreased cortical vBMD and loss of number of trabeculae. [70–73] Consequently, prostate cancer patients treated with androgen deprivation therapy (ADT) had an increased fracture risk compared to both controls and prostate cancer patients not treated with ADT (Fig. 1). [74–77]

3.1 Aromatization of androgens and impact on bone structure and density

Multiple case reports of men affected by a mutation in the aromatase gene have shown that these men have lower bone mass, and that estrogen replacement therapy was able to increase aBMD. [78–80] Importantly, estrogen therapy in a 17-year-old boy with aromatase deficiency did not show gain in trabecular or cortical vBMD at ultradistal radius as measured by pQCT, indicating that the observed increase in aBMD, measured by DXA was mainly driven by an increase in bone size. Aromatization of androgens into estrogens therefore appears essential for the pubertal periosteal bone expansion typically associated with the male bone phenotype. [81] Men with higher E2 to T ratio, suggestive for high aromatase activity, also have higher BMD at the LS. [82] Additionally, genetic polymorphisms influencing either synthesis (aromatase) or degradation of estrogens (catechol-O-methyltransferase) have been associated with BMD and fracture risk in men. [83–87]

Following treatment of older men with borderline to low T levels with an aromatase inhibitor (AI), which resulted in increased T levels, LS BMD significantly decreased after only one year of treatment compared to placebo. [88] These results were confirmed in another study by treating older men with T levels below 350 ng/dL with either testosterone replacement therapy (TRT), AI or placebo for 12 months. Both TRT and AI increased circulating T levels, but LS BMD increased less in the AI compared to the TRT group, again confirming the essential role of aromatization of androgens for the maintenance of male bone. [89]

Finally, two single nucleotide polymorphisms (SNPs) near the aromatase gene may influence bone effects of TRT in hypogonadal middle-aged to older men. [90]

3.2 AR versus ERα-mediated androgen actions and impact on bone structure and density

Although complete androgen insensitivity syndrome (46XY with a loss of function mutation in the AR) may be associated with some reduction of aBMD, [91, 92] disruptive mutations in the ERα gene clearly cause severely decreased BMD, tall stature, as well as incomplete epiphyseal closure. [93] Genome-wide associations studies showed that polymorphisms near the ESR1 (ERα gene) are associated with quantitative ultrasound parameters and fracture risk in both sexes. [94, 95] Different SNPs in the 6q25 locus, which incorporates the ESR1 gene, correlated with aBMD of the hip, calcaneal ultrasound parameters, and vBMD of the radius. [96] In contrast, CAG repeat length of the AR gene only weakly correlated with ultrasound-estimated calcaneal bone density, which indirectly may even be explained by higher sex steroid concentrations. [97] Moreover, bone turnover markers (BTMs) were not associated with CAG repeat polymorphisms in the AR in healthy elderly men. [98]

Selective estrogen receptor modulators (SERMs) have antiresorptive bone actions, but only in patients with the lowest circulating E2 levels. [99, 100] In contrast, therapy with selective androgen receptor modulators (SARMs) did not show improvement of BMD. [101]

aBMD in gender dysphoric patients treated with cross-hormonal therapy seems to be maintained at least for up to 10 years, indeed suggesting a strong effect of sex steroids on the maintenance of both male and female bone irrespective of sex at birth. [102] Very recently, T therapy was reported to be able to maintain bone structure (pQCT) in female to male transgenders as well, even while suppressing endogenous estrogen production, possibly by important local aromatization effects. [103]

3.3 Experimental evidence for low estrogens as driver of bone resorption in men

In an elegant randomized controlled trial (RCT) landmark study, young adult men were chemically castrated and treated either with or without T in absence or presence of an AI. This study aimed at defining threshold concentrations of T and E2 measured by mass-spectrometry (MS) below which markers of bone resorption and formation increased (CTx and P1NP respectively). [104, 105] According to this study, both androgens and estrogens appeared to independently regulate bone resorption. T deficiency increased bone resorption at levels < 200 ng/dL. Threshold concentrations of E2 levels > 10 pg/mL and T levels > 200 ng/dL appeared to be sufficient to prevent increase in bone resorption. Again, T seemed to have some direct effect in lowering bone resorption, independent of E2. In elderly men, estrogens seemed

Table 1 Association of sex steroid levels and bone mineral density in middle-aged to older men

Study	Study design	Subjects	Hormonal assessment	Endpoint	Results
Greendale et al., 1997 [123]	Cross-sectional (Rancho Bernardo Study)	534 men mean 68.6 +/-9y range 50-89y	Total T (RIA) – BioT measured Total E2 (RIA) – BioE2 measured SHBG	aBMD radius, LS and TH (DXA)	Strongest positive correlations for BioE2 with all sites. Total E2 with LS and TH. BioT with all sites. No association with total T.
Slemenda et al., 1997 [316]	Longitudinal (2.1y)	93 men mean 67.3 +/-4.3y |	Total T (RIA) – freeT measured Total E2 (RIA) – freeE2 measured Total E1 (RIA) SHBG	aBMD LS, FN and trochanter (DXA)	Positive association between total E2 levels and all sites. Weaker negative association between total T levels and BMD LS and trochanter.
Khosla et al., 1998 [115]	Cross-sectional (Rochester)	346 men | range 23-90y	Total T (RIA) – BioT measured E2 (RIA) – BioE2 measured E1 (RIA) – BioE1 measured SHBG	aBMD hip, spine and radius (DXA)	BioE positive predictor of proximal femur BMD
Amin et al., 2000 [129]	Cross sectional (Framingham)	405 men mean 75.7y range 68-96y	Total T (RIA) Total E2 (RIA)	aBMD hip, LS and distal radius (DXA)	Men with highest E2 levels have greater BMD at all sites compared to men with lowest E2 levels No difference for T
Kenny et al., 2000 [124]	Cross-sectional	83 men mean 75 +/-5y ≥ 65y + BioT ≤ 4.44 nmol/L	Total T (RIA) – BioT measured E2 (RIA) E1 (RIA) SHBG	aBMD hip and LS (DXA)	BioT positive correlation with FN BMD.
Khosla et al., 2001 [134]	Longitudinal (4y) (Rochester)	130 men mean 73.7 +/-8.6y range 60-90y	Total T (RIA) – BioT measured E2 (RIA) – BioE2 measured E1 (RIA) SHBG	aBMD hip, spine and forearm (DXA)	Rate of bone loss at forearm associates with BioE2 levels. BioE2 levels below median 40 pmol/L higher rates of bone loss.
Szulc et al., 2003 [138]	Cross-sectional (MINOS)	792 men mean 65 +/-7y range 50-85y	Total T (RIA) – freeT calculated Total E2 (RIA) SHBG	aBMD hip, LS and forearm (DXA)	Positive association between E2 levels and BMD at all sites. No correlation with T.
Gennari et al., 2003 [114]	Longitudinal (4y) (Siena)	200 men mean 64.8 +/- 0.8y range 55-85y	Total T (RIA) –bioT and freeT calculated Total E2 (RIA) – bioE2 and freeE2 calculated SHBG	aBMD hip + LS (DXA)	Total E2, freeE2 and BioE2 positively correlate with aBMD femoral neck + LS. No correlation with T. Lowest E2 levels associate with higher rates of bone loss at FN and LS compared to highest levels of E2.
Van Pottelbergh et al., 2003 [83]	Longitudinal (4y) (Ghent)	214 men mean 75.5 +/-4y range 71-86y	Total T (IA)- BioT calculated Total E2 (CLIA) – BioE2 calculated SHBG	aBMD hip and distal forearm (DXA)	Serum bioE2 associate with baseline BMD and % bone loss at distal forearm and hip.
Khosla et al., 2005 [135]	Cross-sectional (Rochester)	314 men (range 22-91y) of which 140 eldery (≥ 60 years) median 73.6y IQR 66.3-82.5y	Total T (CLIA) – BioT measured E2 (RIA) - BioE2 measured SHBG	vBMD hip, LS, distal radius and tibia (pQCT)	BioE2 association with trabecular vBMD LS, FN, distal radius and tibia. BioE2 association with cortical vBMD FN and distal tibia. Association with different structural parameters as well. At all cortical sites vBMD is associated with bioE2 at low (< 30 pmol/L) levels, but not high levels.
Fink et al., 2006 [127]	Cross-sectional (MrOS USA) Longitudinal (1.8 +/-0.4y) (MrOS USA)	2447 men mean 73 +/-5.6y range 65–99 1227 men (≥ 65y) | |	Total T (RIA) – BioT calculated Total E2 (RIA) – BioE2 calculated SHBG	aBMD hip and LS (DXA)	Total T < 200 ng/dL), total E2 < 10 ng/dL and lowest quintile BioE2 associate with osteoporotic BMD at hip. Total T < 200 ng/dL associates with rapid hip bone loss (≥ 3%/y)

Table 1 (continued)

Study	Study design	Subjects	Hormonal assessment	Endpoint	Results
Mellström et al., 2006 [122]	Cross-sectional (MrOS Sweden)	2908 men mean 75.4y +/-3.2 range 69-80y	Total T (RIA) – freeT calculated Total E2(RIA) – freeE2 calculated SHBG	aBMD total body, TH, femoral trochanter, arm and LS (DXA)	Both free T and free E2 levels correlate with BMD total body, arm, femoral trochanter and TH. Only free E2 correlates with LS.
Bjørnerem et al., 2007 [317]	Longitudinal (6.5 y) (Tromsø)	894 men mean 60 +/-10.1y range 25-80y	Total T (IA) – freeT calculated Total E2 (IA) – freeE2 calculated SHBG	aBMD distal forearm (DXA)	SHBG inversely correlates with bone loss No correlation with T or E2.
Kuchuk et al., 2007 [137]	Cross-sectional (Amsterdam)	623 men mean 75.6 +/-6.6y range 65-88y	Total T (RIA) – bioT calculated Total E2 (RIA) – bioE2 calculated SHBG	aBMD FN and TH (DXA)	Men in lowest quartile of bioE2 levels have lower BMD at TH compared to highest quartile.
Araujo et al., 2008 [132]	Cross sectional (Boston Area Community Health/Bone Survey)	976 men – diverse ethnicity mean 46.7 +/-12y range 30-79y	Total T (CLIA) – freeT calculated Total E2 (LCMS) – free E2 calculated SHBG	aBMD hip, LS and distal radius (DXA)	Total and free E2 levels correlate with FN and TH. No correlations with T.
Cauley et al., 2010 [128]	Cross-sectional (MrOS USA) Longitudinal (4.6y) (MrOS USA)	1238 men Mean 73.5 +/- 5.8y | 969 men (≥ 65y) | |	Total T (LCMS) – BioT calculated Total E2 (LCMS) – BioE2 calculated SHBG	aBMD TH (DXA)	Total E2 and BioE2 positive correlation with BMD TH. SHBG negative correlation with BMD TH. Low BioE2 levels and high SHBG levels associate with faster annualized bone loss at the hip
Cauley et al., 2010 [121]	Cross-sectional (MrOS USA)	3670 men mean 73.6y +/- 5.9y | (only 978 men with sex steroid measurements)	Total T (LCMS) – BioT calculated Total E2 (LCMS) – BioE2 calculated SHBG	vBMD FN and LS (QCT)	BioE2 and BioT positive correlation with trabecular vBMD LS. SHBG negative correlation with trabecular vBMD LS.
Vanderschueren et al., 2010 [139]	Cross-sectional (EMAS)	3141 men mean 59.7 +/- 10.9y |	Total T (GCMS) – freeT and bioT calculated Total E2 (GCMS) – freeE2 and bioE2 calculated SHBG	Quantitative ultrasound of the heel (BUA / SOS / QUI)	Free and total E2 positive association with all QUS readings.
Ward et al., 2011 [54]	Cross-sectional (EMAS Manchester) (EMAS Leuven)	339 men mean 60.2 +/-11.1y | 389 men mean 60.0 +/-11.1y |	Total T (GCMS) – freeT and bioT calculated Total E2 (GCMS) – freeE2 and bioE2 calculated SHBG	vBMD radius (pQCT)	BioE2 levels positive association with cortical and trabecular vBMD in the Leuven, but not the Manchester cohort.
Woo et al., 2012 [131]	Cross-sectional (MrOS Hong Kong) Longitudinal (4y) (MrOS Hong Kong)	1489 men mean 72.5 +/-5y |	Total T (GCMS) – freeT and bioT calculated Total E2 (GCMS) – freeE2 and bio E2 calculated SHBG	aBMD TH and FN (DXA)	FreeT (weak), total E2, BioE2 (strongest) positive association with BMD TH and FN. SHBG negative correlation with TH. FreeT (weak), total E2, BioE2 (strongest) positive association with change in BMD/year at TH; for bioE2 also at FN. SHBG negative association with BMD loss at FN.
Vandenput et al., 2014 [130]	Cross-sectional (MrOS Sweden)	440 men mean 80.1 +/- 3.5y |	Total T (GCMS) – freeT calculated Total E2 (GCMS) – freeE2 calculated SHBG	vBMD distal tibia (pQCT)	Inverse association between total and free E2 levels and cortical porosity and pore diameter. No association trabecular parameters. No associations with T

Table 1 (continued)

Study	Study design	Subjects	Hormonal assessment	Endpoint	Results
Hsu et al., 2015/2016 [154] [155]	Longitudinal (5y) (CHAMP)	1705 men mean 76.9 +/-5.5y range 70-97y	Total T (LCMS) – freeT calculated DHT (LCMS) Total E2 (LCMS) Total E1 (LCMS) SHBG	aBMD hip (DXA)	SHBG negative correlation with hip BMD loss. E1 positive correlation with hip BMD loss. No association E2, T or DHT. Temporal increase in SHBG, and decrease in E1 and freeT associates with hip BMD loss.
Pye et al., 2017 [281]	Longitudinal (4.3 y) (EMAS Leuven + Manchester)	514 men mean 59.6 +/-10.5 y range 40-79y	Total T (GCMS) – freeT and bioT calculated Total E2 (GCMS) – freeE2 and bioE2 calculated SHBG	vBMD distal and midshaft radius (pQCT)	No association between sex steroids and changes in pQCT parameters in adjusted models.
Kong et al., 2019 [125]	Cross-sectional (Ansung)	922 men mean 70.2 +/-6.8y |	Free T (RIA) measured E2 (CLIA)	aBMD FN, LS and TBS (DXA).	Men in lowest tertile of free T levels have higher odds of low TBS.
Piot et al., 2019 [126]	Longitudinal (8y) (STRAMBO)	820 men (> 60y) Mean +/- 72y |	Total T (RIA) – freeT calculated Total E2 (RIA) – bioE2 calculated SHBG	vBMD distal radius and tibia (pQCT)	Lowest quartile bioE2 faster decrease at tibia of BMC, total vBMD, cortical thickness and area, and increased Trabecular area versus highest quartile. Lowest quartile freeT faster decrease at tibia of cortical thickness and increase of trabecular area. Combination of both low bioE2 (< 28.2 pg/mL) and low freeT (< 19.2 ng/dL) faster decrease at distal tibia of total vBMD, cortical thickness, area and vBMD, and increase trabecular area versus all other patients.
Guebeli et al., 2020 [133]	Cross-sectional (NHANES 1999–2004)	806 men mean 42.96 y 47% of men < 40y	Total T (CLIA) – freeT calculated Total E2 (CLIA) – freeE2 calculated SHBG	aBMD LS (DXA)	Lower E2 levels associate with greater odds of osteopenia at LS. No association with T.

Abbreviations: T = testosterone, BioT = bioavailable testosterone, FreeT = free testosterone, DHT = dihydrotestosterone, E2 = estradiol, BioE2 = bioavailable estradiol, FreeE2 = free estradiol, E1 = estrone, BioE1 = bioavailable estrone, SHBG = sex hormone binding globulin, IA = immunoassay, RIA = radio-immunoassay, CLIA = chemiluminescent immunoassay, LCMS = liquid chromatography mass-spectrometry, GCMS = gas chromatography mass-spectrometry, DXA = dual X-ray absorptiometry, aBMD = areal bone mineral density, pQCT = peripheral quantitative computed tomography, vBMD = volumetric bone mineral density, LS = lumbar spine, FN = femoral neck and TH = total hip, TBS = trabecular bone score.

to be the dominant sex steroid regulating bone resorption, whereas T could stimulate bone formation either directly or after aromatization. [106, 107] The threshold of T levels of 200 ng/dL as seen in younger men, has not been well established in older men, where bone resorption markers were already modestly increased < 500 ng/dL, though marked increase was only observed < 100 ng/dL and decrease in trabecular vBMD of the L4 vertebra was only seen < 200 ng/dL. [108] Together, this suggests that sex steroid levels have to substantially decline before resulting in bone loss, suggesting a 'bone threshold'. Even so, in an early preclinical aged rat model by our group, a similar threshold has been demonstrated. In line with the human observations, bone resorption was already prevented in presence of T replacement dosage not able yet to restore androgen sensitive organ weights. Moreover, loss of aBMD was prevented in these 'undertreated' animals as well. [109]

In conclusion, reductions of sex steroids in men in the castrate range have major impact on bone resorption which are clearly not only related to loss of AR-, but also loss of ERα-stimulation. This raises the question whether sex steroid changes in ageing men, are sufficient to contribute to bone resorption and thereby bone loss. The threshold of T needed to substantially increase bone resorption may indeed only be present in a small subset of elderly men.

Table 2 Association of sex steroid levels and fracture risk in middle-aged to older men

Study	Study design	Subjects	Hormonal assessment	Endpoint/n° fractures	Results
Nyguist et al., 1998 [144]	Longitudinal (7y) (Malmö)	242 men mean 67 +/-10.1y range 50-80y	Total T (RIA) SHBG	Prevalent and incident fractures N = 91 and N = 31	No association T and fracture risk
Goderie-Plomp et al., 2004 [143]	Longitudinal (6.5y) – case-control (Rotterdam)	178 men (1:3 age and BMI matched controls) ≥ 55y mean 66.1 +/- 6.3y	Total T (RIA) Total E2 (RIA) SHBG	Incident vertebral fracture N = 45	No correlation with T or E2 levels and incident vertebral fracture.
Amin et al., 2006 [149]	Longitudinal (18y) (Framingham)	793 men mean 71y range 61-92y	Total T (RIA) Total E2 (RIA)	Hip fracture incidence N = 39 with fracture	Men with low E2 (< 18.2 pg/mL) have increased risk for hip fracture (HR 3.1 95%CI 1.4–6.9) Low T (< 385 ng/dL) no association. Both low E2 and low T have highest risk (HR 6.5 95%CI 2.9–14.3).
Mellström et al., 2006 [122]	Cross-sectional (MrOS Sweden)	2908 men mean 75.4y +/-3.2 range 69-80y 907 men with vertebral X-ray (Malmö)	Total T (RIA) – freeT calculated Total E2 (RIA) – freeE2 calculated SHBG	Prevalent osteoporotic related fracture N = 193 X-ray confirmed vertebral fracture N = 161	Free T levels are associated with prevalent osteoporotic related fracture (OR 1.56 95%CI 1.14–2.14) Free T levels are associated with prevalent vertebral fracture (OR 2.0 95%CI 1.34–2.86)
Bjørnerem et al., 2007 [141]	Longitudinal (8.4y) (Tromsø)	1364 men | range 50-84y	Total T (IA) – free T calculated Total E2 (IA) – free E2 calculated SHBG	Non-vertebral fracture N = 105 with fracture	Higher SHBG levels association with increased non-vertebral fracture risk (each SD increase in SHBG, HR 1.25 95% 1.03–1.54), but after adjustment for BMD not significant any more. No correlation T or E2
Meier et al., 2008 [147]	Longitudinal (5.8y) (Dubbo Osteoporosis Epidemiology Study)	609 men mean 72.6+/-5.7y |	Total T (LCMS) Total E2 (LCMS) SHBG	Incident low-impact fracture (all) N = 113	T levels correlate with fracture risk at hip (HR 1.88 95%CI 1.24–2.82) and non-vertebral (HR 1.32 95%CI 1.03–1.68). After correction for FN BMD not significant anymore.
Mellström et al., 2008 [146]	Longitudinal (3.3y) (MrOS Sweden)	2639 men mean 75.4y +/-3.2y range 60-80y	Total T (GCMS) – freeT calculated Total E2 (GCMS) – freeE2 calculated SHBG	Incident osteoporotic fractures N = 209	FreeE2 and SHBG independently associate with fracture risk, but not freeT. Per SD decrease of freeE2 and adjusted for BMD: non-vertebral osteoporotic fracture (HR 1.36 95%CI 1.16–1.58), hip fractures (HR 1.31 95%CI 1.05–1.63) and clinical vertebral fracture (HR 1.47 95%CI 1.26–1.71)
Tuck et al., 2008 [142]	Case-control (Newcastle)	57 cases mean 59.8 +/- 12.67y 57 controls mean 59.7 +/- 12.6y	Total T (RIA) – freeT and bioT calculated E2 (RIA) SHBG	Case-control: symptomatic low-trauma vertebral fracture: n = 57	No association with sex steroids. SHBG levels higher in patients with fracture.
LeBlanc et al., 2009 [150]	Longitudinal (4.7y) (MrOS US – case-cohort)	342 cases mean 75.2 +/-6.4y 1636 controls Mean 73.2 +/-5.8y	Total T (GCMS) – BioT calculated Total E2 (GCMS) – BioE2 calculated SHBG	Incident fracture (all) N = 342	Men in lowest quartile of bioE2 (< 11.4 pg/mL) or highest quartile SHBG (≥ 59.1 nmol/L) are at higher risk for non-vertebral fracture (HR 1.29 (95% CI 1.01–1.64) and HR 1.36 (95% CI 1.07–1.72) respectively)
Roddam et al., 2009 [151]	Case-control (EPIC-Oxford)	155 cases mean 50.9 +/- 12.7y 309 controls mean 51 +/- 12.4y	Total T (RIA) – freeT calculated Total E2 (RIA) – freeE2 calculated SHBG	Case-control: any prevalent fracture N = 155	Inverse association between total E2 and fracture risk (RR 0.65 95%CI 0.44–0.96) and freeE2 and fracture risk (RR 0.64 95%CI 0.42–0.96)

Table 2 (continued)

Study	Study design	Subjects	Hormonal assessment	Endpoint/n° fractures	Results
Woo et al., 2012 [131]	Longitudinal (4y) (MrOS Hong Kong)	1489 men mean 72.5 +/-5y |	Total T (GCMS) – freeT and bioT calculated Total E2 (GCMS) – freeE2 and bio E2 calculated SHBG	Incident fractures N = 108 (of which 59 non-vertebral fracture)	Men in lowest quartile of BioE2 or E2 vs. 3 other quartiles have higher risk of all fracture and nonvertebral fracture respectively, but no longer present after correction for BMD.
Hsu et al., 2015/2016 [154] [155]	Longitudinal (6y) (CHAMP)	1705 men mean 76.9 +/-5.5 range 70-97y	Total T (LCMS) – freeT calculated DHT (LCMS) Total E2 (LCMS) Total E1 (LCMS) SHBG	Incident fracture (all) N = 171	No correlation baseline measurements with incident fracture. Temporal increase in SHBG was associated with any fracture and hip fracture.
Cawthon et al., 2016 [140]	Cross sectional (MrOS USA) Longitudinal (4.6 y) (MrOS USA)	1463 men ≥ 65y 1053 men ≥ 65y	Total T (GCMS) – BioT calculated Total E2 (GCMS) – BioE2 calculated SHBG	Prevalent vertebral fracture N = 140 Incident vertebral fracture N = 55	SHBG correlates with higher risk of radiographic vertebral fracture. (each SD increase in SHBG, OR 1.38 95%CI 1.11–1.72). No correlation with T or E2. SHBG associates with increased likelihood of new or worsening radiographic vertebral fracture (each SD increase in SHBG, OR 1.42 95%CI 1.03–1.95) No correlation with T or E2.
Vandenput et al., 2016 [145]	Longitudinal (9.1y) (MrOS Sweden + Hong Kong)	4324 men mean 74.4 +/-4.1 y |	Total T (GCMS) – bioT calculated Total E2 (GCMS) – bioE2 calculated SHBG	Incident clinical vertebral fractures N = 242 Incident radiographic vertebral fractures N = 157 (subset of 2256 men with FU 4.3y)	No association with sex steroids. High SHBG levels associates with increased fracture risk (per SD increase SHBG 24% and 23% increased risk for clinical and radiographic vertebral fracture respectively)
Yeap et al., 2020 [157]	Longitudinal (10.6 y) (Health In Men Study (HIMS – Australia)	3307 men mean 76.8 +/-3.5y |	Total T (LCMS) – freeT calculated Total E2 (LCMS) SHBG	Incident fractures N = 330 (also hand/foot-non-osteoporotic fractures) (of which 144 hip fracture)	Midrange total T is associated with lower incidence of any fracture and hip fracture. Midrange freeT levels are associated with any fracture. U-shaped relation. Higher SHBG levels associated with increased risk for hip fracture, no association with E2 levels.
Rosenberg et al., 2021 [148]	Longitudinal (Cardiovascular Health Study) (10.2y)	1128 men mean 76.5 +/- 5.1y |	Total T (LCMS) DHT (LCMS) SHBG	Incident hip fractures N = 102	Inverse association between DHT levels and fracture risk (HR 0.74, 95%CI 0.55-1). No association with T levels.

Abbreviations: T = testosterone, BioT = bioavailable testosterone, FreeT = free testosterone, DHT = dihydrotestosterone, E2 = estradiol, BioE2 = bioavailable estradiol, FreeE2 = free estradiol, E1 = estrone, BioE1 = bioavailable estrone, SHBG = sex hormone binding globulin, IA = immunoassay, RIA = radio-immunoassay, CLIA = chemiluminescent immunoassay, LCMS = liquid chromatography mass-spectrometry and GCMS = gas chromatography mass-spectrometry.

4 Impact of decreasing circulating sex steroid concentration on bone structure and density in ageing men

The term postmenopausal osteoporosis clearly indicates the dominant role of estrogen deficiency in the pathophysiology of bone loss in ageing women. In contrast, ageing men do not experience similar absolute sex steroid deficiency. Nevertheless, serum total T levels decline approximately with 0.8% per year in middle-aged men, while free T levels even decrease about 2% per year. [110] Total E2 levels however, remain unchanged or even slightly increase in elderly men. But as sex hormone binding globulin (SHBG) levels rise, free and bioavailable levels of T as well as E2 decline substantially more than total levels. [111–114] A more than 2-fold increase in SHBG levels over the life span in men may even reduce bioavailable T (bioT) levels with 64% and bioavailable estrogen (bioE) levels with 47%. [115] Not all studies confirm the decline of total T levels while ageing, in contrast to decline of calculated free T levels which seems to be consistent. [116]

However, even though free and bioavailable sex steroid levels decline while ageing, the percentage of men experiencing hypogonadal symptoms remains rather low. Late onset hypogonadism (LOH) defined as low T levels (total T < 320 ng/dL and free T < 6.3 ng/dL) and presence of three sexual symptoms (decreased sexual interest, decreased morning erections, and erectile dysfunction) affects only 2.1% of community-dwelling men aged 40–79 in Europe. [117, 118] Only about half of these men with LOH have total T levels below 230 ng/dL, close to the 'bone threshold' for increased bone resorption as discussed earlier.

In contrast to healthy older community-dwelling men, patients with underlying comorbidities, such as, but not limited to cancer or chronic kidney disease, are at increased risk of developing hypogonadism and may exhibit accelerated and/or greater decline in sex steroid levels while ageing. [119, 120] However, the impact of low sex steroid concentrations on bone health in these specific populations are underexplored. Even so, strong evidence on effects of TRT on bone in these patients is lacking.

5 Association of bone mineral density and/or fracture risk in elderly men with their circulating sex steroid levels

Although the percentage of middle-aged to older men suffering from osteoporosis and related fractures is substantially larger than the percentage of ageing men which have low T levels and associated symptoms, many studies have shown associations between circulating sex steroid concentrations and bone related endpoints in healthy community-dwelling men (summarized in Tables 1 and 2).

The relevance of determination of free and/or bioavailable fraction versus total concentration of sex steroids remains controversial. Nevertheless, associations between serum T and BMD levels, albeit still rather weak, were greater with the free or bioavailable fraction of the hormone. [121–126] The Osteoporotic Fractures in Men (MrOS) study in the US also suggested a 'bone threshold' of total T levels. The odds of having osteoporosis at the hip tripled, as did the odds of experiencing rapid hip bone loss in men with T levels < 200 ng/dL compared to men having 500 ng/dL or higher. [127] In contrast with T, more studies consistently showed a correlation between estrogen levels, again especially free and bioavailable levels, with BMD and bone loss in elderly men. [54, 83, 112, 115, 121–123, 126, 128–139] In the US cohort of MrOS, 1SD increase in bioE2 levels was associated with 6% higher vBMD at the hip. [121] In the Sweden cohort, E2 levels negatively correlated with cortical porosity in older men. [130] In the Leuven cohort of the European Male Ageing Study (EMAS), bioE2 levels were associated with both cortical and trabecular vBMD at the radius, and also with cortical thickness and medullary area. [54] Moreover, these associations were only present in men > 60 years old. The combination of low BioE2, low BioT and high SHBG was also related with the fastest rates of BMD loss. [128] Likewise for E2 levels a 'bone threshold' seemed to be present in older men. Men with bioE2 levels < 11 pg/mL had significantly higher rates of bone loss over 4 years, compared to men with concentrations above this level. [134] When addressing pQCT measurements, vBMD and structural parameters were not related to sex steroid levels in young men, whereas bioE2 levels were associated with vBMD in elder men. At all cortical sites vBMD was associated with bioE2 at low (< 8 pg/mL) but not at high levels. Such clear threshold was not visible at trabecular sites, where bone loss seemed to be more gradual, already present at normal E2 levels. [135]

Whereas multiple studies showed a correlation between circulating sex steroid levels and bone density, many studies failed to show an association with fracture risk. [131, 140–145] In contrast, in the MrOS Sweden study free T levels below the median were associated with prevalent osteoporotic and radiographic fractures, but not with incident fractures. [122, 146] Additionally, low total T levels were associated with increased risk of overall incident osteoporotic fracture in the Dubbo Osteoporosis Epidemiology Study. [11, 147] Yet, low T increased incident osteoporotic fracture risk only by 33% while age and history of prior fracture increased the risk by 76% and 83% respectively. Finally, the Cardiovascular Health Trial showed an inverse relationship between dihydrotestosterone (DHT) levels and hip fracture risk, but not with T. [148] Also, both free and bioE2 have been shown to be negatively associated with incident fracture risk in older men. [137, 146, 149–151] Using a Mendelian randomization approach a 9.6 pg/mL genetically instrumented decrease in serum E2 levels was associated with an increased risk of any fracture of 35% and nonvertebral MOF of 75% [152] Similarly for fracture risk, there seems to be a 'bone threshold' of sex steroid levels. In the MrOS Sweden cohort higher fracture risk was clear when total E2 and freeE2 were below 16 pg/mL and 0.27 pg/mL, respectively. [146]

Multiple studies also showed a correlation between SHBG levels and BMD and/or fracture risk in elderly men, sometimes independent of sex steroid levels. [121, 128, 131, 140–142, 145, 146, 148, 150, 153–157] According to a meta-analysis, each increase of 1 µg/dL SHBG increases fracture risk with 22%. [158] Moreover, polymorphisms in the SHBG promotor gene are able to predict serum SHBG levels and BMD at the hip. [159]

This raises the question whether measurement of T, E2 and/or SHBG may improve fracture risk prediction in men.

This question was addressed in the MrOS studies, in which both T and E2 were measured by accurate and precise MS. [160] Neither T, E2 nor SHBG however, improved a fracture risk discrimination model, for example when added to FRAX with BMD. [160] Hence, the clinical utility of these markers is limited in the evaluation of osteoporosis in ageing men.

In conclusion, sex steroids, usually free or bioavailable fractions, have been shown to be associated with BMD, BMD loss and both prevalent and incident fracture risk in older men. However, studies are rather inconsistent with respect to which sex steroid is independently related, and the relatively small associations suggest that the influence of decline in sex steroid levels during ageing on bone is limited, and only partially contributing to the age-related bone loss and increased fracture risk in elderly community-dwelling men (Fig. 1). Most importantly, determination of sex steroid concentrations, even by accurate methodology, does not improve fracture risk prediction in elderly men.

6 Importance of calcium and vitamin D

Adequate vitamin D and calcium levels are essential for development as well as maintenance of bone. Supplementation of both has been one of the cornerstones of treatment of osteoporosis, still certain issues remain unresolved. Calcium supplementation has been associated with increased cardiovascular risk by some but not all studies, and target range of 25-hydroxyvitaminD (25(OH)D) levels is not completely clear, though levels of 20 ng/mL are generally accepted as sufficient for bone health. [161]

Higher dietary calcium intake is associated with lower rates of bone loss. [162] The importance of sufficient dietary intake of calcium has been recently investigated in institutionalized older adults. Providing vitamin D replete residents with additional calcium and proteins in the diet reduced risk of falls with 11% and fractures with 33%. [163]

Low 25(OH)D levels in older men have been associated with lower BMD, higher rates of bone loss, and increased fracture risk. [164–170] The combination of vitamin D deficiency and low bioE2 and/or high SHBG levels resulted in even higher rates of hip bone loss than abnormalities in sex hormones alone. Additionally, incident non-spine fracture risk was higher as well. [171] Moreover, hypogonadism in older men seems to be associated with vitamin D deficiency. [172] Very low levels of 25(OH)D (< 10 ng/mL) were associated with increased risk of falling in older people, adding up to increased risk of fractures. [173] No benefit was shown of supplementation with vitamin D and/or omega-3 fatty acids on BMD after 2 years, nor on risk of falls in middle-aged to older men and women with mean vitamin D levels of 30 ng/mL. [174, 175] Likewise, a monthly high-dose of vitamin D supplementation did not reduce the risk of falls. [176] Therefore, vitamin D alone, is unlikely to be effective in preventing hip fracture or any new fracture in elderly people. However, vitamin D plus calcium substitution results in a small reduction in hip fracture and non-vertebral fracture risk, without increasing overall mortality. [177, 178] Still further investigation is warranted, because vitamin D supplementation may even have adverse effects on muscle health. [179]

In conclusion, sex steroid and vitamin D deficiency seem to be associated in elderly men, and the combination of both may further increase bone loss and fracture risk. There seems to be no benefit of supplementation with vitamin D in older men without vitamin D deficiency; however, when 25(OH)D levels are < 20 ng/mL substitution remains important, as is sufficient calcium intake, preferably via the diet.

7 Physical activity and muscle strength

In the last decades, the interest in muscle health in the ageing population has increased. Terminology such as sarcopenia and osteosarcopenia has been introduced. [180] While the importance of muscle strength and functioning for both the maintenance of bone mass, and reduction of risk of falls, is theoretically obvious, current data remain often conflicting or inconclusive.

For an extensive overview on sarcopenia, physical function and frailty in elderly men we refer to the next chapter of these series on male gonadal function and ageing . The molecular mechanisms involved in the muscle-bone interaction are reviewed elsewhere [181]. Lean body mass has been associated with FN BMD. [182] A variety of studies show the importance of physical activity and/or muscle mass and strength on fracture risk. In community-dwelling men, decline in gait speed was associated with fracture risk, as were quadricep strength and 5 times repeated sit-to-stand. [183] Even so, in MrOS several measures of physical performance predicted incident fracture independently of FRAX probability. Greater time for five chair stands was also related with greater risk, while greater walking speed and grip strength were associated with lower risk of incident MOF. [184] In the same cohort sarcopenia status, defined by different definitions, correlated with incident MOF, although predictive value was reduced by adjustment for FN BMD. [185] The presence of dysmobility syndrome, which combines lean mass, body fat%, BMD, grip strength, gait speed and recent falls, also confers higher risk for MOF. [186] In contrast, the recent Concord Health and Ageing in Men project (CHAMP) showed that greater physical activity, self-reported by the patient, was associated with

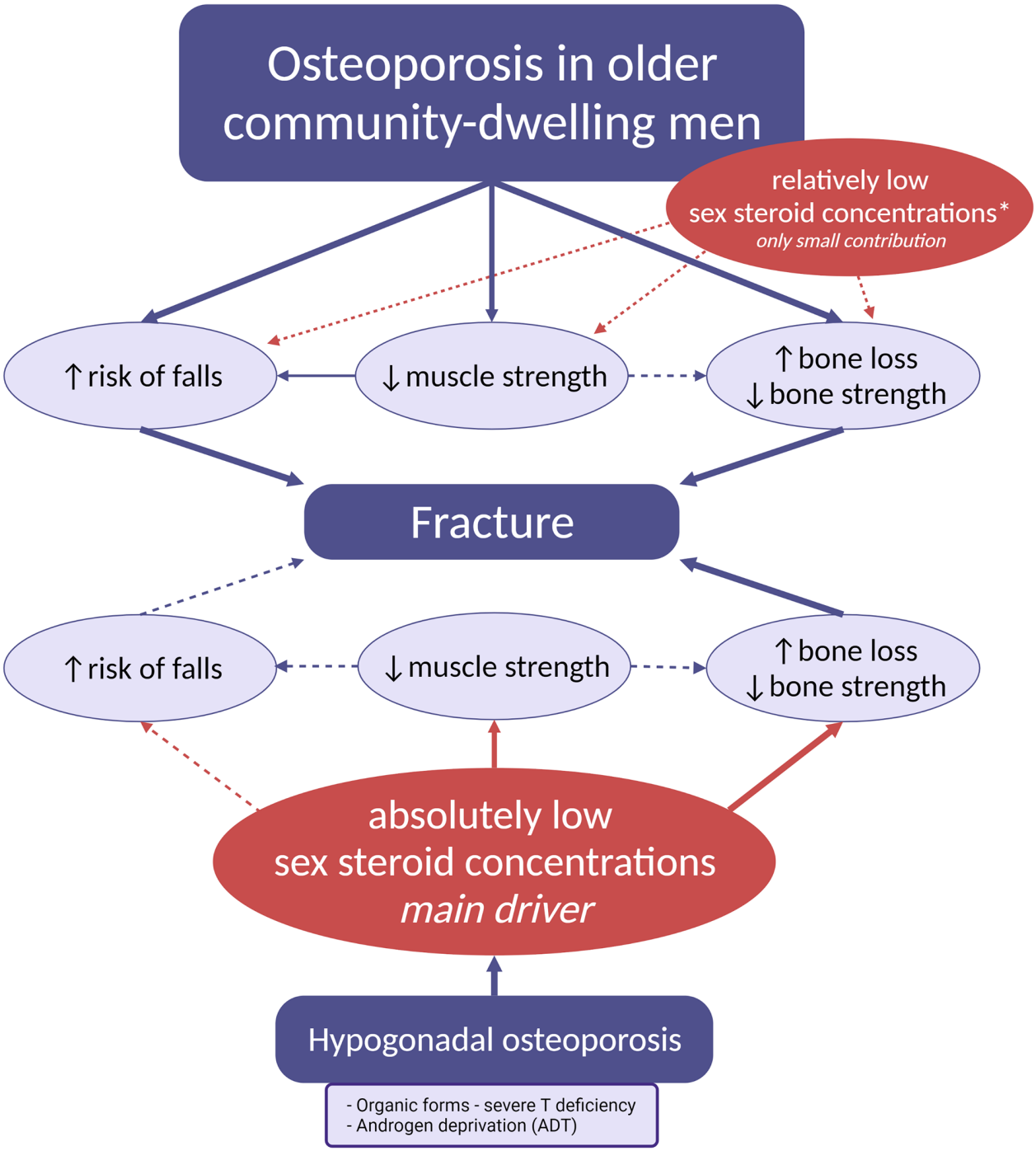

Fig. 1 Impact of sex steroids on fracture development in older community-dwelling men versus hypogonadal men. Several arguments favoring a 'bone threshold' of T levels in age-related bone loss in men are available. In ageing rats, TRT which is not sufficient for restoring androgen sensitive organs weights, is effective in maintaining BMD and preventing bone resorption [109]. In healthy men whom are sex steroid deprived and subsequently treated with different doses of TRT, increased bone resorption is only present when T levels are < 200 ng/dL. [104] A similar experiment in older men shows loss in vBMD at the spine only to occur when T levels are < 200 ng/dL. [108] In an observational study in elderly men, the odds of having osteoporosis at the hip triples, as does the odds of experiencing rapid hip bone loss in men with baseline T levels < 200 ng/dL compared to men with T levels > 500 ng/dL. [127] Finally, the results of TRT on BMD increase are more pronounced in patients with T levels < 200 ng/dL than in patients with higher levels. [258] [259] These data suggest that the relatively small decline in sex steroid concentrations in older community-dwelling men only limitedly contributes to the pathogenesis of osteoporosis, while in hypogonadal osteoporosis the severe sex steroid deficiency is considered to be the main driver of increased fracture risk. (*) In patients with underlying comorbidities such as cancer, decline in sex steroid levels may be accelerated compared to 'healthy' community-dwelling men. If this greater decline in sex steroid levels negatively impacts bone health in these patients with this 'pathological ageing'-phenotype remains to be elucidated. The effects of TRT on BMD in this population are underexplored as well. Dotted arrows indicate rather weak or uncertain effects. Created with BioRender.com

Table 3 Effect of anti-osteoporotic treatment on bone mineral density and fracture risk in middle-aged to older men in randomized controlled trials

Study	Subjects	Inclusion criteria	Men with low T levels included	Treatment and primary endpoint	Effects on BMD	Effects on fracture
Bisphosphonates						
Orwoll et al., 2000 [216]	241 men mean 63 +/-13y in alendronate group mean 63 +/-12y in placebo group	BMD T-score FN ≤-2 and LS ≤-1 or FN ≤-1 and history of fracture	Yes	Alendronate 10 mg/day or placebo and 500 mg calcium and 400IU vitamin D Prim endpoint: BMD at lumbar spine after 24 months	Increase in LS BMD from baseline (7.1% vs. 1.8%). Increase in BMD TH (2.53.1% vs. 0.6%) and FN (2.5% vs. -0.1%)	Decrease in incident radiographic vertebral fracture (0.8 vs. 7.1%)
Ringe et al., 2006 [219] Ringe et al., 2009 [220] (extension to 24 months FU)	316 men mean 55.8 +/-10y in risedronate group mean 58 +/-10.3y in control group)	BMD T-score LS ≤ -2.5 and FN ≤ -2 Remark: high baseline incidence of vertebral fractures > 50%)	?	Risedronate 5 mg/day and calcium 1000 mg and vitamin D 800 IU or calcium 1000 mg and vitamin D 800 IU alone or calcium 1500 mg and alfacalcidol 1 µg/d alone in case of vertebral fracture at baseline in control group Prim endpoint: BMD at LS after 12 months	Increase in LS BMD from baseline (4.7 vs. 1%), TH (2.7 vs. 0.4%) and FN neck (1.8 vs. 0.2%) Increase in LS BMD from baseline (6.5 vs. 2.2%), TH (4.4 vs. 0.4%) and FN (3.2 vs. 0.6%)	Reduction of incident radiographic vertebral fractures with 60% (5.1 vs. 12.7%) Non-significant reduction in nonvertebral fractures of 42% (6.3 vs. 10.8%) Reduction of incident radiographic vertebral fractures with 61% (9.2 vs. 23.6%) Significant reduction in nonvertebral fractures of 47% (11.8 vs. 22.3%)
Boonen et al., 2009 [217]	284 men mean 60 +/-11y in risedronate group mean 62 +/-11y in placebo group	T score LS ≤-2.5 and FN ≤-1 or T score LS ≤-1 and FN ≤-2	Yes	35 mg risedronate 1x/week or placebo and calcium 1000 mg and 400–500 IU vit D Prim endpoint: BMD at LS after 24 months	4.5% increase LS BMD compared to placebo (95% CI 3.5–5.6%) Increase TH and FN (exact % not reported – only graphically)	Not significant
Boonen et al., 2011 [221]	508 men mean 72.5 +/-10.3y in zoledronic acid group mean 72.6 +/-10.4y in placebo group	Low trauma hip fracture within 90 days after surgical repair	Yes	1x/year zoledronic acid 5 mg IV or placebo and loading dose vitamin D and daily calcium 1000–1500 mg and vitamin D 400–800 IU Prim endpoint: Changes BMD non-fractured hip after 24 months	Total hip BMD increases vs. placebo (3.8% 95%CI 2.2–5.4) and femoral neck (3.1% 95% CI 1.2-5)	Not significant
Boonen et al., 2012 [222]	1119 men median 66y range 50-85y	BMD T score ≤-1.5 TH or FN and prevalent vertebral fractures or BMD T score ≤-2.5 at TH, FN or LS without fracture	Yes	1x/year zoledronic acid 5 mg IV or placebo Prim endpoint: incident vertebral fracture after 24 months	Higher increase in LS BMD from baseline vs. placebo (7.7 vs. 1.6%)	67% reduction in vertebral fracture (1.6% vs. 4.9%) (RR 0.33, 95% CI 0.16–0.70) at 24 months compared to placebo

Table 3 (continued)

Study	Subjects	Inclusion criteria	Men with low T levels included	Treatment and primary endpoint	Effects on BMD	Effects on fracture
Denosumab						
Orwoll et al., 2012 [228]	242 men mean 64 +/-10.5y in denosumab group mean 65 +/-9.1y in placebo group	BMD T-score at LS or FN ≤-2 and ≥-3.5 or previous MOF and T-score ≤-1 and ≥-3.5	Yes	Denosumab 60 mg 1x/6 months or placebo and calcium ≥ 1000 mg/d and vitamin D ≥ 800IU/d Prim endpoint: BMD at LS after 12 months	Increase in LS BMD from baseline (5.7% vs. 0.9%). Increase in BMD TH (2.4 vs. 0.3%) and FN (2.1 vs. 0%).	Not significant
Teriparatide						
Orwoll et al., 2003 [232]	437 men mean 58 +/-13y in teriparatide 40 µg group mean 59 +/-13y in teriparatide 20 µg group mean 59 +/-13y in placebo group	BMD T-score LS or hip ≤-2	Yes	Teriparatide 40 µg SC 1x/d or Teriparatide 20 µg 1x/d or placebo and 1000 mg calcium and 400-1200IU vitamin D Prim endpoint: BMD at LS after 24 months (trial stopped early because of warnings osteosarcoma rat – median FU 11 months)	Increase in LS BMD from baseline (9 vs. 5.9 vs. 0.5%). Increase in BMD TH (2.3 vs. 1.2 vs. 0.5%) and FN (2.9 vs. 1.5 vs. 0.3%)	Not significant
Romosozumab						
Lewiecki et al., 2018 [235]	245 men mean 72.4 +/- 7.4y in romosozumab group mean 71.5 +/- 6.9y in placebo group	BMD T-score LS, TH or FN ≤-2.5 or ≤-1.5 with fragility fracture (male ref pop)	Yes	Romosozumab 210 mg 1x/month or placebo and 500-1000 mg calcium and 600–800 IU vitamin D Prim endpoint: BMD at LS after 12 months	Increase in LS BMD from baseline (12.1% vs. 1.2%). Increase in BMD TH (2.5% vs. -0.5%) and FN (2.2% vs. -0.2%).	Not significant

Abbreviations: BMD = bone mineral density, LS = lumbar spine, FN = femoral neck and TH = total hip, MOF = major osteoporotic fracture. All BMD was assessed by DXA (Dual X-ray absorptiometry) and reported T-scores are based on male reference population values.

maintenance of BMD at LS and hip, but not with reduction of incident falls and fractures in multivariate analysis. [187] In the same cohort, patients with osteosarcopenia did not have an increased risk of falls or fracture compared to patients with either condition alone. They did have a 41% increase in risk of fall and 87% increase in risk of fracture compared to men without osteopenia/osteoporosis or sarcopenia. [188] The prevalence of sarcopenia highly depends on the used definition, but seems to be more prevalent in people with a fragility facture, especially in men. [189]

The anabolic effects of androgens on muscle are well established [190], and severe androgen deficiency rapidly results in decreased lean mass, muscle size and strength. [191, 192] Again the question arises if the relatively small decrease in circulating sex steroids in older men contributes to age-related decline in lean mass and muscle strength. In the aforementioned experimental study investigating threshold levels of TRT in ageing men [108], lean mass only seemed to decline when T concentrations were < 200 ng/dL. Even so, in an earlier preclinical study we showed that although partial androgen deficiency was still present by 'undertreating' with TRT, BMD as well as lean body mass seemed to be preserved. [109] In older men, T levels were also associated with higher grip strength and less decline in lean body mass. [125, 193] On the other hand, older men having low T levels with high body mass index (BMI) had higher bone density than men with BMI < 30 kg/m^2, while they also had lower % lean mass and muscle density. [194]

Interventional studies investigating either the effects of recreational physical activity, aerobic training or resistance training showed diverse results. Some did not show any effect on BMD [195, 196], others were able to prevent BMD loss [197–199], whilst some even showed improvement of BMD. [200–204] A recent meta-analysis of RCTs investigating effects of different forms of exercise on BMD showed a significant benefit from exercise on FN BMD, but no effect on LS. So importantly, even though exercise may potentially be beneficial for some parts of the skeleton, it does not protect against bone loss at other sites. [205] Furthermore, effects of exercise on BMD may also depend on ERα gene polymorphisms, while CAG-repeat length of the AR gene and TTTA repeat of the aromatase gene do not seem to influence the BMD response. [206]

In conclusion, whether the effects of a relative decrease in T levels observed in ageing men on muscle is sufficient to increase fracture risk remains uncertain.

8 Risk of falls and prevention

Falls are common in the elderly population and obviously impose a risk for development of fractures. Falls from less than 1-meter height are considered to be a low-energy trauma and cause 53% of all fractures above 50 years old, and at age 75 or older this accounts even for more than 80% of fractures. [207] The importance of tackling falls in older men is further illustrated by the higher risk of non-spine fracture in men who suffered from a fall in the previous year, which is independent of hip BMD. [208] Additionally, history of past falls predicts incident fracture at any site independently of FRAX: 63% increased risk of any fracture, 51% increased risk of MOF, and 54% increased risk of hip fracture. [209] As mentioned before, physical activity may be important for risk of falling, with community-dwelling men with lowest activity/worst physical performance having high risk of falls, however, fall risk in men with better activity and performance was also substantial. [210]

Low T levels in older men have also been associated with increased risk of falls. [138, 211, 212] Nevertheless, although improving self-reported walking ability and modestly improved 6-minute-walk test, TRT did not decrease frequency of falls. [213]

Several interventions aiming to prevent falls in older people have been shown to be effective. Multifactorial (exercise, nutrition therapy, knowledge, drug management, urinary incontinency management, environmental modifications…) and exercise interventions (gait, balance, functional training) show fall-related benefit, but evidence is most consistent across multiple fall-related outcomes for exercise. [214] Vitamin D supplementation interventions show mixed results, with a high dose being associated with higher rates of fall-related outcomes. Little evidence exists however on fall-related fractures, with some evidence showing reduction by exercise. [214]

In conclusion, the contribution of relatively lower sex steroid concentrations in the ageing men to falls as well as the role of TRT remains to be demonstrated.

9 Bone-specific treatment of osteoporosis

The most important RCTs investigating bone-specific treatments in male osteoporosis are summarized in Table 3. Initial approval of all of these therapies was based on studies in postmenopausal osteoporosis. These trials typically have a duration of about 3 years, with reduction of vertebral fractures as primary outcome and other fractures as secondary endpoint. For approval in other populations, such as osteoporosis in men, so-called bridging studies were sufficient. These studies were often too small and too short to show fracture risk reduction but similar gains in BMD as in postmenopausal osteoporosis were needed for approval of the drug. [215]

Bisphosphonates are the best studied anti-osteoporotic drug in the treatment of male osteoporosis and often first choice of treatment in clinical practice. Oral alendronate and risedronate improved BMD at LS, FN and TH. [216–218] Therapy was as efficient in men with low T levels compared to men with normal levels. [217] These drugs also have shown to reduce the occurrence of radiographic incident vertebral fractures. [216, 219] An extension trial of risedronate with an additional year was also able to show a reduction in nonvertebral fracture risk. [220] Intravenous administration of zoledronic acid increased BMD levels in men who suffered from osteoporotic fracture of the hip, and this effect was comparable to what is observed in women. [221] This therapy also reduced vertebral fracture risk (-67%) after 24 months of therapy in osteoporotic men. [222] Of note, effects in this latter study on BMD and fracture risk were similar in men with total T levels below or above 350 ng/dL. Moreover, annual infusion of zoledronic acid within 90 days of repair of low-impact hip fracture reduced the rate of any new clinical fracture with 35% and decreased mortality risk with 28%. [223] Bisphosphonates have also been shown to be effective in bone loss induced by ADT in prostate cancer patients. [224] Fracture risk reduction with bisphosphonates in male osteoporosis was also confirmed in several meta-analyses. [225–227]

Denosumab, a RANKL inhibitor, increased BMD at LS, TH and FN following 1 year of therapy. [228] This was further confirmed in the 12-month open label phase after the initial RCT. [229] An RCT in Japanese patients (with about 23% of the patients being men but the majority suffering from postmenopausal osteoporosis) showed a reduction of risk of new or worsening vertebral fracture by 65.7% after 24 months of treatment with denosumab compared to placebo. [230] However, best evidence for denosumab in treatment of male osteoporosis was observed in prostate cancer patients treated with ADT, where 36 months of therapy reduced vertebral fracture risk with 62%. [231]

While bisphosphonates and denosumab reduce bone resorption, teriparatide also has osteoanabolic effects. The RCT investigating a teriparatide dose of 20 and 40 μg versus placebo has been stopped in advance at 11 months because of initial reports of development of osteosarcoma in rats. Primary endpoint was LS BMD after 24 months, but after 11 months, an increase in BMD at LS, TH and FN was already observed. [232] The follow-up study showed that antiresorptive treatment after initial treatment with teriparatide prevented decline in BMD and decreased risk of incident vertebral fractures. [233] Real life data showed

no safety issue relating to the possible associations with osteosarcoma. [234]

Romosozumab is a monoclonal antisclerostin antibody. Sclerostin is an inhibitor of the Wnt pathway and hereby inhibits bone formation and stimulates bone resorption. The BRIDGE study evaluated safety and efficacy of romosozumab in men with osteoporosis. This study showed an increase in BMD at LS, TH and FN after 12 months of therapy. [235]

In conclusion, bone-specific drugs, which were first evaluated in postmenopausal osteoporosis, appear to increase BMD and to some extent also decrease fracture risk in men. Moreover, bisphosphonates and denosumab have also been proven to be effective in osteoporotic men with low T levels or who are treated with ADT.

10 Testosterone replacement therapy and bone

Trials investigating the effect of TRT on bone density in middle-aged to older men are shown in Table 4. The interpretation of these TRT studies on bone outcome needs some caution. Firstly, not all of these studies make the distinction between eugonadal and hypogonadal men. In the latter group, the severity of the hypogonadism may be of major importance to the outcome if not taken into consideration. As discussed earlier, the 'bone threshold' of about 200 ng/dL may be indeed lower than the more conservative 'hypogonadism threshold' of 300 ng/dL that is often used. In patients with very low T levels, improvement of BMD upon TRT is to be expected, as prior bone loss was probably in a large part mediated by sex steroid deficiency. However, in patients with only slightly low or normal T levels as is the case in the majority of elderly men suffering from osteoporosis, sex steroid deficiency may not be the main driver of the age-related bone loss. As a result, the expected effects of TRT will be much smaller. Secondly, the definition of hypogonadism or low T levels highly differs between studies, making it difficult to draw firm conclusions with respect to impact of hypogonadism or TRT. Finally, the bone status of patients before starting TRT is essential for the interpretation of results. If participants do not have low bone density or high fracture risk at baseline which is often the case, any increase in BMD may not be that easily transferable to patients suffering from osteoporosis. Moreover, the improvement of BMD in men with normal baseline values may result from (even slightly) supraphysiological T levels following TRT. Indeed, in preclinical rodent studies increase in particularly trabecular bone mass due to further reduction of bone resorption is always observed following even discrete supraphysiological TRT. [67]

In patients suffering from well-defined organic forms of hypogonadism, such as congenital hypogonadotropic hypogonadism or Klinefelter syndrome with T deficiency, both aBMD and vBMD increase early after starting TRT. [236–242] These studies are however uncontrolled, as all patients are severely androgen deficient, and therefore requiring T substitution irrespective of their bone status. However, despite increase in BMD, these patients often remain in the osteopenic or osteoporotic range. [243] If they have high risk of fracture, at elderly age for instance, treatment with bone-specific agent, in addition to TRT, may therefore still be indicated.

Nevertheless, multiple trials using different modes of T administration showed a beneficial effect of TRT on BMD in middle-aged to older men with low T levels, mostly at the LS. [244–249] The spine is rich in trabecular bone, which may be most responsive to T, at least in preclinical models. However, in these trials, participants often have normal baseline bone density levels. Again, also in accordance with preclinical models, response to T is observed also with normal baseline bone density. Transdermal application of non-aromatizable DHT on the other hand decreased LS BMD after 2 years of treatment, again indicating the importance of T, which is aromatizable into estrogens, for maintenance of male bone. [250] Only few studies included patients with osteopenia/osteoporosis or history of fracture. In a small study including eugonadal men with vertebral fracture, intramuscular TRT for 6 months resulted in increase in LS BMD. [251] However, in another study in older frail patients with low T levels and history of fracture or T score < -2, only modest effect of TRT on LS BMD was observed. [252] Moreover, a Japanese trial, with improvement of quality of life as primary endpoint, did not show a significant improvement of LS BMD after treatment of 52 weeks compared to no treatment in older, hypogonadal men. [253] A subanalysis however, only focusing on hypogonadal men also suffering from osteopenia or osteoporosis, showed that TRT could improve BMD at the LS to a higher extent compared to non-treated men. [254] Another study confirmed that TRT was able to increase BMD at both LS and FN in osteoporotic elderly men with T levels < 300 ng/dL. [255] A meta-analysis in middle-aged or ageing men with low T levels did not find a beneficial effect of TRT on total aBMD or LS aBMD [256], although one negative study in particular was given a lot of weight in the analysis. [89] Very recently, another meta-analysis did show beneficial effects of TRT on LS aBMD in subjects with LOH. [257] Importantly, confirming the discussion above, the effects were more evident in subjects with lower T levels at baseline. Additionally, the duration of therapy and higher prevalence of diabetic patients increased beneficial effect of TRT on aBMD of LS.

Table 4 Effect of testosterone replacement therapy on bone mineral density in middle-aged to older men

Study	Subjects and treatment	Inclusion criteria (Hormonal / Bone)	Hormonal assessment	Primary end-point	Effects
Anderson et al., 1997 [251]	21 men mean 58y range 34-73y Sustanon 250 mg/2w for 6 months	Eugonadal men (mean total T 19.36 +/-2.56 nnmol/L) Idiopathic vertebral fracture	Total T (RIA) Total E2 (RIA) SHBG	aBMD LS and hip (DXA)	Significant improvement of LS BMD (+ 5%), no changes in hip Improvement of LS positively correlates with increase in serum E2, not T levels
Snyder et al., 1999 [258] RCT	108 men mean 73.1 +/-5.8y in TRT group mean 73 +/-5.9y in placebo group T transdermal 6 mg/d scrotal patch or placebo and calcium 500 mg/d and vitamin D 125 IU/d for 36 months	Total T < 475 ng/dL BMD LS T-score < -1	Total T (RIA) – free T calculated SHBG	aBMD at LS and hip (DXA)	No significant improvement at evolution LS (4.2 vs. 2.5%). In patients with pretreatment T levels of 400 ng/dL, improvement LS 0.9% vs. placebo while 5.9% improvement vs. placebo in patients with pretreatment T levels of 200 ng/dL
Kenny et al., 2001 [248] RCT	44 men mean 76 +/-4y in TRT group mean 75 +/-5y in placebo group T transdermal 5 mg/d or placebo and 500mgCa/400IU vit D for 12 months	BioT levels ≤ 4.4 nmol/L Bone no criteria	Total T (RIA) – BioT measured Total E2 (RIA) Total E1 (RIA) SHBG	aBMD LS and hip (DXA)	Higher BMD at FN compared to placebo (0.3% gain vs. 1.6% loss)
Christmas et al., 2002 [318] RCT	36 men mean 70 +/-0.7y in TRT group mean 70 +/-1.1 in placebo group T enanthate 100 mg IM/2 weeks or placebo for 6 months (additional to groups receiving growth hormone +/- TRT)	65y or older and IGF1 levels ≥ 1SD below the mean T or bone no criteria	Total T (RIA) Total E2 (RIA)	Primary endpoint not defined	No effect of TRT on aBMD measurements (LS, hip and radius).
Amory et al., 2004 [244] RCT	70 men mean 71 +/-4y in TRT group mean 71 +/-5y in placebo group T enanthate 200 mg/2w or placebo for 36 months	T < 349 ng/dL Bone no criteria	Total T (IA) Total E2 (IA) SHBG	aBMD LS and hip (DXA)	Increased BMD at LS, TH and FN compared to placebo.

Table 4 (continued)

Study	Subjects and treatment	Inclusion criteria (Hormonal / Bone)	Hormonal assessment	Primary end-point	Effects
Merza et al., 2006 [319] RCT	39 men mean 63 +/-9y in TRT group mean 59.7 +/-10.2y in placebo group Testosterone transdermal 5 mg/d or placebo for 6 months	Total T < 10 nmol/L or FAI < 30% Bone no criteria	Total T (RIA) – FAI Total E2 (CLIA) SHBG	Primary endpoint: bone turnover Secondary endpoint: aBMD hip and LS (DXA)	No difference in BMD between TRT and placebo
Basurto et al., 2008 [320] RCT	48 men mean age 63.2 +/- 8.5y in TRT group mean age 63.1 +/- 7.7y in placebo group T enanthate 250 mg/3w IM or placebo for 12 months	≥ 60 y and total T ≤ 320 ng/dL Bone no criteria	Total T (RIA) Total E2 (RIA)	aBMD at LS and hip (DXA)	Greater increase in BMD LS compared to placebo (3.5% vs. ?).
Emmelot-Vonk et al., 2008 [321] RCT	223 men mean 67.1 +/- 5y in TRT group mean 67.4 +/- 4.9y in placebo group T undecanoate 160 mg/d oral or placebo for 6 months	Total T < 13.7 nmol/L Bone no criteria	Total T (IA) – freeT and bioT calculated SHBG	aBMD LS and hip (DXA)	No effect on BMD
Svartberg et al., 2008 [322] RCT	35 men mean 69 +/-5y in TRT group mean 69 +/- 5y in placebo group T undecanoate IM 1000 mg/12 weeks or placebo for 12 months	Total T ≤ 11 nmol/L Bone no criteria	Total T (IA) Total E2 (IA) SHBG	aBMD LS and hip (DXA)	Higher BMD at TH compared to placebo (1.4% increase vs. 0%).
Kenny et al., 2010 [252] RCT	131 men mean 77.9 +/- 7.3y in TRT group mean 76.3 +/- 8y in placebo group T transdermal 5 mg/d or placebo and 1500mgCa/1000IU vit D for 12 to 24 months	Total T < 350 ng/dL or bioT <-1.5 SD below 95 ng/dL History of fracture or T-score < -2 and frailty	Total T (RIA) – BioT measured Total E2 (RIA) Total E1 (RIA) SHBG	aBMD LS, hip and forearm (DXA)	Greater increase BMD at LS vs. placebo (3.07 vs. 0.2%), but greater decrease BMD at forearm mid-radius vs. placebo (-1.29 vs. -0.2%). No difference at the hip.
Aversa et al., 2012 [245]	20 men mean 57y +/-10y T undecanoate 1000 mg/12w IM for 36 months	Total T < 320 ng/dL with metabolic syndrome Bone no criteria	Total T (IA) – freeT calculated Total E2 (assay?) SHBG	aBMD LS and hip (DXA)	Significant increase in BMD both at LS and femur.
Bouloux et al., 2013 [246] RCT	322 men ≥ 50 years mean 58.7 +/- 5.8y Oral T undecanoate in different doses (80-160-240 mg/d) or placebo for 12 months	Free T < 7.5 ng/dL AND symptoms of T deficiency according to questionnaire (ADAMS) Bone no criteria	Total T (IA) – freeT calculated SHBG	aBMD LS and hip (DXA)	Significant increase in BMD at LS 2.7% in highest TRT group vs. placebo 1.12% and at total hip 0.84% vs. -0.44%.

Table 4 (continued)

Study	Subjects and treatment	Inclusion criteria (Hormonal / Bone)	Hormonal assessment	Primary end-point	Effects
Rodriguez-Tolra et al., 2013 [249]	50 men mean 59.14 +/-5.6y T transdermal 50 mg/d for 12 months followed by T undecanoate 1000 mg/2-3mo IM for another 12 months (total FU 24 months)	Free T < 7.2 ng/dL Bone no criteria	Total T (RIA) – free T calculated SHBG	Primary endpoints: biochemical measurement: safety, total T, SHBG and free T aBMD (DXA) as secondary endpoint	Improvement of BMD LS with 4.5%, TH 3% and FN 2.5% compared to baseline.
Wang et al., 2013 [255] RCT	186 men mean 68.1 +/-5.4y in 40 mg group mean 68.4 +/- 5.5y in 20 mg group mean 68 +/-4.8y in placebo group T undecanoate 40 mg oral or T undecanoate 20 mg oral or placebo and 600 mg calcium and 125 IU vitamin D for 24 months	Total T < 300 ng/dL BMD T-score ≤ -2.5 without vertebral fracture or T-score ≤ -2 and presence of vertebral fracture	Total T (IA) – freeT calculated Total E2 (IA)	Primary endpoint not defined	TRT results in greater increase in aBMD LS and FN in both low and high dose group compared to placebo.
Dias et al., 2016 [89] RCT	43 men mean 72 +/- 1y in TRT group mean 72 +/-1 in AI group mean 70 +/-1 in placebo group T transdermal 5 g/d or anastrozole 1 mg/d or placebo for 12 months	Total T < 350 ng/dL Bone no criteria	T (LCMS) E2 (LCMS) SHGB	aBMD LS and FN (DXA)	Increase in BMD LS compared to baseline in TRT group but not significantly different from placebo treated group.
Permpongkosol et al., 2016 [323] Observational	120 men mean age 65.6 +/- 8.9y T undecanoate IM 1000 mg 1x/10-14w for 72 months	Total T levels < 300 ng/dL and symptoms of hypogonadism Bone no criteria	Total T (IA) SHBG	aBMD LS and FN (BMD)	Improvement of T-score LS (0.06 to 0.85) and FN (-0.55 to -0.31).
Konaka et al., 2016 [253] RCT (EARTH study) Shigehara et al., 2017 [254] Subanalysis	334 men mean 65.7 +/-9y in TRT group mean 67.6 +/- 9.4y in control group T enanthate 250 mg IM/4w or no treatment for 52 weeks 69 men mean 67.9+/-8.6y	Free T levels < 11.8 pg/mL Bone no criteria Free T levels < 11.8 pg/mL T-score < -1	Free T measured (RIA)	aBMD LS (DXA) as secondary endpoint	No improvement of BMD LS after TRT. TRT improves BMD LS significantly more compared to no treatment.

Table 4 (continued)

Study	Subjects and treatment	Inclusion criteria (Hormonal / Bone)	Hormonal assessment	Primary end-point	Effects
Snyder et al., 2017 [259] RCT (Bone Trial of T Trials)	211 men mean 72.3 +/-6.3y in TRT group mean 72.4 +/-5y in placebo group T transdermal 5 g/d or placebo and calcium 600 mg and 800 IU vitamin D for 12 months	Total T < 275 ng/dL Bone no criteria	Total T (LCMS) – freeT measured (EQD) Total E2 (LCMS)	Primary endpoint: trabecular vBMD at LS (QCT) Secondary: vBMD hip (QCT) and aBMD LS and hip (DXA)	TRT results in greater increase trabecular vBMD LS (7.5% vs. 0.8%) and trabecular vBMD hip (1.6% vs. 0.1%). Effect does not vary according to baseline sex steroid levels, but increase in LS trabecular vBMD is associated with increase in total T and E2. Greater increase aBMD LS (3.3 vs. 2.1%).
Ng Tang Fui et al., 2018 [324]	100 obese men median age 54.2y IQR 46.9-59.3y in TRT group median age 52.8y IQR 47.4-60.1y in placebo group T undecanoate 1000 mg/10w or placebo and diet and exercise for 56 weeks	BMI > 30 kg/m^2 and total T levels ≤ 12 nmol/L Bone no criteria	Total T (CLIA) – freeT calculated Total E2 (CLIA) SHBG	Primary endpoint: change in fat mass Secondary endpoint: aBMD hip, LS (DXA)	No difference in BMD between TRT and placebo
Colleluori et al., 2021 [325]	105 men mean 53+/- 5.9y for type 2 diabetes patients mean 56+/-9.5y for non-diabetic patients T cypionate 200 mg/2w IM For 18 months	T < 300 ng/dL Bone no criteria	Total T (LCMS) Total E2 (LCMS)	aBMD LS, FN and TH (DXA) vBMD tibia (pQCT)	Increase in aBMD LS 4.5% vs. 3.2% in T2D patients vs. nonT2D. Decrease in vBMD, but increase in total mineral content, total area and endosteal and periosteal circumference in T2D vs. non T2D
Ng Tang Fui et al., 2021 [247] RCT	136 men for vBMD mean 60 +/- 6.6y for TRT group mean 60.3 +/-6.5y for placebo group 601 men for aBMD T undecanoate 1000 mg/3m IM or placebo for 2 years	Total T levels < 403 ng/dL (IA) (but when remeasured with LCMS mean T levels increased from 10 nmol/L to 14 nmol/L) Bone no criteria	T (IA + LCMS) E2 (LCMS) SHBG	Primary: cortical vBMD distal tibia (pQCT) Secondary: vBMD tibia, radius (pQCT) and aBMD hip + LS (DXA)	Increase in tibial and radial total + cortical vBMD and cortical area + cortical thickness. Trabecular much less effect. Increase aBMD all sites, biggest increase at LS.

Abbreviations: T = testosterone, BioT = bioavailable testosterone, FreeT = free testosterone, FAI = free androgen index, DHT = dihydrotestosterone, E2 = estradiol, BioE2 = bioavailable estradiol, FreeE2 = free estradiol, E1 = estrone, BioE1 = bioavailable estrone, SHBG = sex hormone binding globulin, IA = immunoassay, RIA = radio-immunoassay, CLIA = chemiluminescent immunoassay, LCMS = liquid chromatography mass-spectrometry and GCMS = gas chromatography mass-spectrometry, DXA = dual X-ray absorptiometry, aBMD = areal bone mineral density, pQCT = peripheral quantitative computed tomography, vBMD = volumetric bone mineral density, LS = lumbar spine, FN = femoral neck and TH = total hip, TBS = trabecular bone score.

One of the earlier trials by Snyder et al. already suggested importance of the baseline severity of sex steroid deficiency for improvement of bone health upon TRT. In men aged 65 years or older, with baseline T levels below 475 ng/dL and having at least osteopenia at the LS, transdermal TRT did not significantly increase LS aBMD compared to placebo when evaluating the group as a whole. However, regression model showed a significant inverse correlation between the effect of TRT on LS aBMD and pretreatment serum T levels. For pretreatment T of 400 ng/dL, TRT increased LS BMD only by 0.9% versus placebo, in contrast to pretreatment values of 200 ng/dL, where TRT resulted in an increase of 5.9%. [258] The same group, more recently contributed to 'the bone trial' of the T-trials. [259] In this trial in addition to DXA, BMD was also evaluated using QCT. Older, hypogonadal men (T < 275 ng/dL) received TRT or placebo transdermally for 12 months. TRT significantly increased trabecular LS vBMD (7.5% vs. 0.8%). Importantly, increase in vBMD was associated with increases in total T and E2, again suggesting that lower baseline levels of sex steroids resulted in greater potential gain following TRT. The effect on aBMD was only modest and trabecular bone score (TBS), a relatively new marker of skeletal integrity, was not increased in these patients. [260]

No studies have compared TRT with bone-specific treatment for osteoporosis such as bisphosphonates in a head-to-head trial. The bone T trial suggests however that TRT has an impact on vBMD following one year of treatment similar to the effects of bisphosphonates on vBMD. Nevertheless, men in the T-trial did not have low aBMD and therefore results cannot be extrapolated to patients with osteoporosis. The effect of TRT on aBMD overall seems similar than that of anti-osteoporotic drug in osteoporosis. [261, 262] Actually, no TRT study was powered sufficiently to evaluate the effects on incident fracture, so in contrast to approved bone-specific treatment of osteoporosis such as bisphosphonates, TRT has not been shown to be able to reduce fracture risk in osteoporotic men, hereby severely limiting its use in clinical practice in men at high risk of fracture.

Moreover, TRT in elderly men with high risk for osteoporosis may not be without side effects. Despite beneficial effects of TRT, mainly on cortical bone in middle-aged to older men, up to 20% of the participants experienced raised hematocrit levels compared to only 1% in the placebo group in a recent trial. [247] Another cardiovascular safety issue was raised from 'the cardiovascular trial' of the T-Trials, where treated patients had greater increase in noncalcified coronary artery plaque volume compared to placebo. [261] This surrogate outcome measure does not reflect cardiovascular mortality, but remains concerning. Larger trials specifically aimed at investigating cardiovascular safety of TRT are therefore highly needed and results of the currently ongoing TRAVERSE trial (NCT03518034) are eagerly awaited.

Currently, guidelines do not support the sole use of TRT as a bone-health agent. [263–266] TRT is not recommended in the absence of hypogonadism. In younger hypogonadal men, not at high risk of fracture, treatment with anti-osteoporotic therapy can be deferred until an effect of TRT on BMD is evident. [263, 266] In contrast, in middle-aged to older men with both hypogonadism and established osteoporosis or high risk of fracture, bone-specific treatment should be started in addition to therapy with TRT. These bone-specific treatments have been shown to be effective, not only in increasing bone density but also in reducing fracture risk, both in men with normal and lower T levels. Only in a minority of cases where patients at high risk for fractures and low T levels (< 200 ng/dL) who lack standard indication of TRT, but who have contra-indications to approved bone-specific drugs, TRT may still be considered as an alternative for bone health. [264]

11 Evaluation of male osteoporosis

11.1 Case history and physical examination

The evaluation of a patient with osteoporosis starts with a thorough medical history and physical examination (Fig. 2). [215, 267, 268] History of prior fracture is a key predictor of future fractures in women as well as in men. Interestingly, rib fractures have been identified as the most common incident clinical fracture in older men and were associated with classic risk factors for osteoporosis such as old age, low hip BMD and history of fracture. [269] Additionally, patients should be inquired for fracture history among relatives. In older patients, fall risk should be evaluated as well as certain risk factors such as alcohol intake, smoking, sedentary lifestyle, low dietary calcium intake or undernutrition should be screened and consequently addressed. Current or past use of drugs such as glucocorticoids, ADT, chemotherapeutics and anticonvulsants that are known to increase fracture risk should be recorded. Secondary causes or concomitant diseases such as HIV infection, chronic obstructive pulmonary disease, renal insufficiency, liver disease, cancer, rheumatoid arthritis, malabsorption syndromes and others may predispose patients to higher risk of fracture. At physical examination the clinician should consider height and presence of kyphosis. Older men with height loss ≥ 3 cm had a nearly twofold higher risk of hip fracture and 1.4-fold increased risk of any clinical fracture compared to men with height loss < 1 cm during a mean follow-up of 7 years. [270] Clinical suspicion of secondary causes should guide the

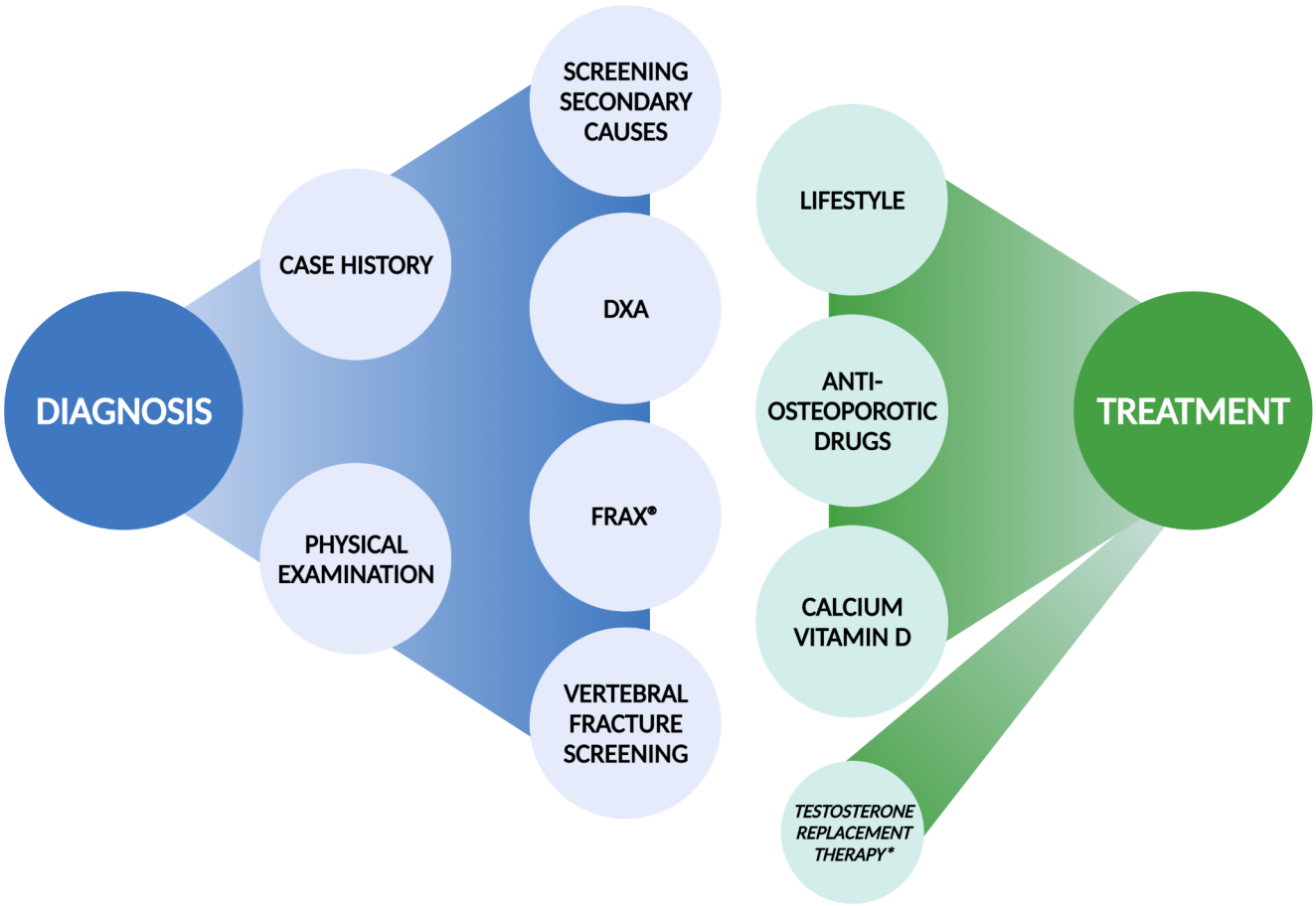

Fig. 2 Diagnosis and treatment of osteoporosis in men is similar to diagnostic and therapeutic approach in postmenopausal osteoporosis. Diagnosis consists of thorough medical history and physical examination. Screening of secondary causes is mainly needed in men below 70 years. DXA is the preferred technical examination for screening of osteoporosis. FRAX calculation is useful to assess fracture risk. Screening for vertebral fractures is indicated, due to their prevalence and often asymptomatic character. In the treatment of male osteoporosis lifestyle factors should be addressed and calcium and vitamin D supplementation should be provided when deficient. In patients at high fracture risk bone-specific anti-osteoporotic treatment is indicated. If hypogonadism is present, TRT should be provided, but bone-health therapy should not be restricted to TRT alone as it has not been able to show fracture risk reduction. It can however be used in addition to a bone-specific anti-osteoporotic treatment in hypogonadal men (*). DXA = dual X-ray absorptiometry; FRAX = Fracture Risk Assessment Tool. Created with BioRender.com

physician towards additional investigations such as laboratory assessment.

11.2 Laboratory assessment and screening for secondary causes: is this needed in the elderly population?

Secondary osteoporosis and potential contributing factors are found in up to 60% of men with osteoporosis. [271–273] This high percentage may be potentially biased however, because a large proportion of men are not evaluated for osteoporosis. Moreover, evaluation is mostly performed in younger men, not in older men who usually suffer from primary age-related bone loss. Routinely advised laboratory testing for screening of secondary causes include complete blood count, metabolic panel (calcium, phosphorus, creatinine, alkaline phosphatase, liver function tests), 25(OH)D, total T and free T, TSH, PTH, 24-h urine calcium, sodium and creatinine. [215, 274] However, in older men with osteoporosis, only 25(OH)D and alkaline phosphatase were found to be more frequently abnormal than in men without osteoporosis. [275] Hence, the benefit of more extensive laboratory testing in order to identify secondary causes in older osteoporotic men is less well established. In earlier studies a distinction was often made between potential secondary osteoporosis versus so-called 'senile or primary osteoporosis' in men aged 70 or higher. [276, 277]

Although measurement of T with MS is more accurate than immunoassay (IA), the latter may be sufficient for screening in case of suspicion of hypogonadal osteoporosis. On a cohort level, fundamental relationships between BMD and sex steroid levels have been shown to be largely

unaffected by the method of measurement. [112, 135, 136, 278] Although the correlation of estrogens with BMD and/or fracture risk in older men seems to be stronger than with T, there is no indication for measurement of E2 on top of T. Not only is correct measurement (LCMS vs. IA) of E2 difficult in the male low normal range [112, 268, 279, 280], but also neither E2 nor T improved fracture risk discrimination model as mentioned before. [160] Therefore, measurement of T is sufficient to discriminate between men with severe sex steroid deficiency and eugonadal men. Additionally, because of the limited therapeutic implications, the value of measurement of sex steroids in the evaluation of older men (> 70y) with osteoporosis is rather small.

The utility of BTM measurements in routine clinical practice remains limited as well. Increase in BTMs was associated with faster bone loss but not with increased fracture risk in older men. [281–283] Currently, measurement of BTMs is only advised to monitor response and compliance to anti-resorptive treatment in postmenopausal women but not for diagnosis of osteoporosis or fracture risk assessment. [284, 285]

11.3 Dual X-ray absorptiometry: is it as useful in men as in women?

While multiple different imaging techniques for evaluating male bone health are available [40], DXA measurement remains the cornerstone of diagnosis for osteoporosis in men and women. QCT measurements have been associated with fracture risk of multiple sites in older men, but with the exception of vertebral fractures, this technique does not appear to add additional information to fracture risk assessment on top of aBMD measured by DXA. Additionally, DXA is cheaper and more widely available, making it still the preferred screening tool for osteoporosis in older men similar to postmenopausal osteoporosis. [286] Finally, other imaging methods have not been validated in clinical trials evaluating effects of bone-specific treatments for osteoporosis.

Different guidelines propose slightly different criteria for BMD testing for evaluation of male bone health. [264, 268, 287] As mentioned before, osteoporosis is present when T-score is ≤ -2.5 and diagnosis of osteopenia is made when T-score is between − 1 and − 2.5. Whether to use male or female reference ranges for diagnosis of osteoporosis by BMD testing, the so-called T-score debate, remains controversial. [39, 264, 287–289] When male reference ranges are used, more men will be identified as osteoporotic, but on average with a lower fracture risk. In contrast, when using female reference ranges, more fractures will occur in men with still normal BMD levels. [290–292] Importantly, approval of bone-specific treatments has been based on trials (Table 3) using male reference ranges to identify individuals with osteoporosis.

In general, universal DXA screening is advised in men > 70 years old and in men younger than 70 years with presence of risk factors such as prior fracture, and diseases and drugs associated with bone loss. [264, 287] Specifically, in hypogonadal patients, DXA testing is recommended in every patient with T levels < 200 ng/dL, and also strongly advised when T levels are between 200 and 300 ng/dL. [268] Some propose to further refine criteria before submitting men to DXA evaluation, for example by prior osteoporosis self-assessment tool, while others propose to even lower the age of universal DXA screening to 60 years of age instead of 70. [293, 294]

However, although low BMD and age are important predictors of future fracture, only about 15 to 20% of fractures occur in men with T-score in the osteoporotic range. [295, 296] In combination with advanced age (> 70 years), T-scores in the osteoporotic range account for 35% of all fractures. [295] Although DXA measurement is important, other possible risks for fracture should be considered, for example by use of risk calculators such as FRAX.

11.4 Fracture risk Assessment Tool: in men as well?

The most often used risk calculator, FRAX, does not only include BMD but also other factors such as age, personal and family history of prior fracture, smoking and drinking status, use of glucocorticoids as well as presence of secondary causes. [297, 298] Falls however, are not included in this risk profile, but the FRAX score itself has been shown to predict risk of incident falls in older men. [299] Several studies show good performance of FRAX in older men to predict fracture risk, with variable results on additive value of BMD in this calculation. [300–303] Still, certain factors such as comorbidities (e.g. diabetes mellitus, chronic kidney disease), drugs, and behavioral aspects are not included in this calculator, and may compel to higher fracture risk estimation [304, 305], which will be mainly based on clinical judgement. Finally, adjusting FRAX score with TBS improves fracture prediction but the effect is often small, and does not seem to contribute significantly to the prediction of incident fracture. [306–309]

11.5 Vertebral fracture screening: also relevant in men

Vertebral fracture screening by X-ray of the spine or vertebral fracture assessment by DXA is important since the majority of spine fractures occurs unnoticed in men as well as in women. [9] Although incident radiographic vertebral fractures are often symptomatic and associated with new

and worsening back pain, less than 15% are also clinically diagnosed. [310, 311] Diagnosis of osteoporosis has to be made even when BMD levels are still in the osteopenic range when the patient has a history of low-impact vertebral fracture as well. [4]

12 Management and treatment: are they different in men compared to women?

Treatment of male osteoporosis is similar to postmenopausal osteoporosis. [277] It should include lifestyle changes, calcium and vitamin D substitution, as well as use of bone-specific treatments (Fig. 2). First, certain lifestyle factors such as smoking and alcohol intake should be addressed. Patients should be advised to regularly exercise to improve strength and balance, hereby reducing risk of falls. [287] Secondly, the advised intake of calcium is 1000–1200 mg daily, preferably via diet, if not with supplementation. [312] 25(OH)D levels of >20 ng/mL should be targeted, mostly vitamin D intake of 800 IU daily is sufficient to attain this goal. [161, 287, 313–315] Finally, the use of TRT alone as anti-osteoporotic drug is not recommended, similar to the advice against the use of hormonal replacement therapy as sole agent for osteoporosis in postmenopausal women. Specific bone-targeted therapies are recommended if fracture risk is high. Bisphosphonates are still the most commonly used therapy, due to their wide availability and low cost; however, first-line treatment might also differ due to country-specific reimbursement criteria. Guidelines support the use of bone-specific treatment in men with history of low-impact fracture of the vertebrae and hip, men with T-score $\leq$-2.5, and older men with a combination of osteopenia on BMD and FRAX derived 10-year hip fracture probability of $\geq 3\%$ or 10-year MOF probability of $\geq 20\%$. [264, 287] Finally, in addition to TRT, hypogonadal osteoporosis should be treated with anti-osteoporotic drugs similar to primary age-related osteoporosis without severe underlying hypogonadism and not left untreated since it is a well-recognized additional risk factor for fractures.

13 Conclusion

Osteoporosis imposes a major health burden which is expected only to increase with higher life expectancies. It is a condition not limited to postmenopausal women, but also affecting ageing men, and the diagnostic and therapeutic gap in male osteoporosis is large and remains larger compared to women. In humans, estrogens are the main drivers of hypogonadism-associated bone loss as seen in postmenopausal osteoporosis and severely androgen-deprived men; therefore, aromatization of T seems to be important for maintenance of male bone. Although positive correlations between declining sex steroid levels, mainly free and bioavailable fractions, and decline in bone density and increase in fracture risk in older men have been demonstrated, the contribution of sex steroid deficiency to age-related bone loss seems to be small in community-dwelling men (Fig. 1). Determination of circulating sex steroid levels in older men does not improve fracture risk prediction. TRT is able to increase BMD in hypogonadal men, especially when T levels are <200 ng/dL. In this review, we have discussed several clinical as well as preclinical arguments in favor of a 'bone threshold' for hypogonadal osteoporosis, corresponding to a grade of sex steroid deficiency that in general will not occur in many elderly men. Data on BMD evolution in osteoporotic older men treated with TRT are scarce, and TRT is still without evidence for fracture risk reduction. Hence, TRT is not recommended as a bone-specific treatment of male osteoporosis. The diagnosis and treatment of male osteoporosis is therefore largely similar to postmenopausal osteoporosis (Fig. 2). Bone-specific treatments have been shown to increase bone mineral density, and for some also fracture risk reduction in both primary male osteoporosis and hypogonadism-related osteoporosis in men.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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