MANAGEMENT OF ENDOCRINE DISEASE

Male osteoporosis: diagnosis and management - should the treatment and the target be the same as for female osteoporosis?

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Abstract

Male osteoporosis has been neglected for too long time and there is need for a change. This condition is clearly underestimated, under-diagnosed and under-treated. The diagnosis is often made late in the natural history of the pathology or even after a fracture event. Guidelines on screening politics do not agree whether and when men should be considered, and clinical trials are far less performed in men with respect to women. Actually, most of our knowledge on male osteoporosis, especially regarding treatment, is extrapolate from the female counterpart. Male osteoporosis is frequently secondary to other conditions and often associated with comorbidities. Therefore, identification of specific causes of male osteoporosis is essential to drive a correct and personalized treatment. Moreover, men have more osteoporosis-related complications and higher mortality rate associated with fractures. Furthermore, not only fewer men receive a correct and timely diagnosis, but also fewer men receive adequate treatment, and adherence to therapy is far less in men than in women. Of note, very few studies assessed the effect of antiosteoporotic treatments in men and most of them considered only bone density as primary endpoint. This review focuses on the areas that are still nebulous in male osteoporosis field, from identification of subjects who need to be evaluated for osteoporosis and screening programs dealing with primary prevention to diagnostic procedures for good estimates of bone quantity and quality and precise calculation of fracture risk and personalized treatment that take into account the pathophysiology of osteoporosis.

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Invited Author's profile

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Introduction: gender differences in osteoporosis

Health disparities exist in the osteoporosis field. For too long time this pathology and its complications have been regarded as a typical female condition, whereas male osteoporosis has been neglected or under considered. In women, researches in the past decades clearly indicated the best strategies for prevention, screening, risk factor management, clinical management and treatment, and novel drugs have been developed to manage osteoporosis, fracture risk and complications, with many clinical trials performed (1, 2, 3). In contrast, very little has been done dealing with these aspects for osteoporosis in the male.

While effectively less common in men than in women, osteoporosis affects both genders, but in men it is clearly under-estimated, under-diagnosed and under-treated. The diagnosis, when even done, is often made late in the natural history of the pathology or even after a fracture event. Guidelines on screening politics do not agree whether and when men should be considered, and clinical trials are far less performed in men with respect to women. Actually, male osteoporosis is frequently secondary to other conditions and men tend to have more comorbidities (4). As a consequence, identification of specific causes of male osteoporosis is essential to drive the correct treatment, and specific diagnostic procedures are needed in the management of osteoporosis in men. Indeed, evidence indicates that men tend to have more osteoporosis-related complications and the mortality rate associated with fractures is higher in men than in women (5, 6, 7, 8). Furthermore, not only fewer men receive a correct and timely diagnosis of osteoporosis with respect to women, but also fewer men receive adequate treatment: antiresorptive therapy after a fracture has been reported for 4.5% of men with respect to 49.5% of women (9, 10).

Of note, very few studies assessed the effect of drugs for osteoporosis in men and only one large randomized controlled trial (RCT) provided data on fractures as primary endpoint (11). Although the main goal of treating men with osteoporosis is to decrease the risk of osteoporotic fractures, there is actually very limited evidence about the effects of therapies for osteoporosis in the male population. Indeed, vertebral fractures (VFs) were also reported in other trials (see subsequently), supporting the use of these drugs also in men.

Thereby, further studies are needed to better understand the pathogenesis of male osteoporosis, define proper diagnostic criteria, and clarify the long-term anti-fracture potential of pharmacological agents.

This is also important because, in secondary osteoporosis and osteoporosis associated with other comorbidities, rational and combined treatments could be offered (e.g. testosterone plus antiresorptive treatment in hypogonadal men). Again, no studies addressed this point especially in terms of fracture prevention (12).

Therefore, it is evident that male osteoporosis deserves more attention and it is not correct to directly extrapolate and translate to the male what is known for females.

Epidemiology of male osteoporosis and fractures

Osteoporosis is as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of the bone tissue, leading to bone fragility and fracture susceptibility (13). It represents a major cause of fractures in individuals over the age of 50 years, with potentially serious and complex sequelae and an associated increased mortality. Osteoporosis is a silent disease with no symptoms until a fracture occurs and this contributes to make it under-recognized and under-treated.

Osteoporosis is widely considered to be much more prevalent in women, even though approximately 39% of new osteoporotic fractures estimated to have occurred worldwide in the year 2000 were in men (14). The prevalence of osteoporosis in the US has been estimated in 3–6% in men >50 years and in 13–18% in women >50 years (15). However, a study showed a comparable prevalence of osteoporosis for men aged 70 years or older and women aged 65 years (16). In 2010 in Europe, there were 22 million women and 5.5 million men with osteoporosis and almost 1.2 million had suffered fragility fractures, accounting for 2% of the overall burden of non-communicable diseases (17, 18). However, these figures might not be accurate, as debate still exists on whether female or male bone mineral density (BMD) reference ranges should be applied to men (see subsequently). For example, in the population-based cohort of MrOs, the proportion of men with osteoporosis was 2.2% using the female reference BMD and 9.4% using the male specific BMD reference (19).

Although estimates of lifetime fracture risk in men is indeed lower than women (13–25% compared to almost 50%) (20), projections suggest that with population aging the total number of fractures will increase by 34% by 2025 to almost 1.6 million cases per year, with an attendant cost of 15.5 billion euros ((18); International Osteoporosis Foundation. Osteoporosis in men: why change needs to

Box 1: Physiological roles of sex steroids in bone metabolism

- Sex steroids are essential for skeletal development during puberty and bone health maintenance throughout adult life, both in men and women.
- Estrogens and androgens effects on bone occur following binding to the estrogen receptor (ER) α and β and the androgen receptor (AR), respectively. Osteoblasts, osteoclasts, osteocytes and marrow stromal cells express ER and AR (23). Furthermore, in men estrogens come from testosterone aromatization through the activity of the CYP19A1 enzyme (aromatase), which is expressed in many tissues, including the bone (24).
- Before pubertal growth spurt there is little difference between sexes in bone modeling. During puberty the concomitant increase of testosterone, estradiol, GH, and IGF-1 represents a complex hormonal milieu for bone anabolism (25). During puberty, in men androgens stimulate periosteal apposition, whereas in women estrogens inhibit periosteal apposition. Interestingly, in men estrogens seem to be even more important than androgens for cortical bone, whereas androgens are solely responsible for normal trabecular bone growth (26).
- After puberty, estrogens in females inhibit periosteal bone formation, thereby limiting the diameter of the bone and increasing the endocortical surface. In men, androgens enhance both the periosteal apposition and the endocortical bone resorption, therefore leading to the development of wider bones with thicker cortex as compared to women. The final result is that men reach higher peak bone mass and have a bigger, though not a denser, skeleton (25, 27).
- Once the peak bone mass has been achieved, sex steroids help to maintain bone density and strength, by slowing bone remodeling rate and by maintaining a balance between resorption and formation, through effects on RANKL/RANK/OPG axis and on osteoclasts lifespan (25). Therefore, changes in sex steroids levels and/or balance during adulthood and senescence might affect bone metabolism in both sexes.

happen, 2014, www.iofbonehealth.org/data-publications/reports/osteoporosis-men-why-change-needs-happen, accessed 20 Dec 2019).

In men, as in women, the incidence of fractures increases exponentially with age, although the increase begins approximately 10 years later in men (21). A 60-year-old man has an approximately 25% chance of having an osteoporotic fracture during his lifetime, and at 90 years of age, one in every six men will have a hip fracture. In absolute numbers, the prevalence of vertebral or hip fracture in older men is approximately one-third of that in women, but the mortality rate associated with hip fractures, as well as vertebral and other major fractures, is higher in men than in women (5, 6, 7, 8). Compared with women, men are about two times more likely to die in the hospital after a hip fracture.

Aetiology of male osteoporosis

Two main phases during life are fundamental for the development of osteoporosis: achievement of peak bone mass and bone turnover during aging. The first is a major determinant of bone mass in later life and can be affected by different conditions and pathologies, the second as well might be accelerated by numerous disorders, lifestyle behaviours, comorbidities, and drug treatments. Estimates

of the timing of peak bone mass of the spine and hip vary, but bone accrual in men is probably complete by the end of the third decade (22). Important influences on peak bone mass for young males include: hormones (especially the growth hormone axis and sex steroids, Box 1), exercise and body weight, calcium intake, vitamin D level, protein intake and genetic predisposition. Other factors that can adversely affect peak bone mass in young males include smoking, alcohol consumption, certain childhood diseases, and medications such as glucocorticoids or anti-epileptic drugs.

The skeleton renews every 10 years through a process called bone remodeling by which the old bone is replaced by the new one. Ageing in men (Box 2) is associated with increased rates of bone turnover, leading to imbalance of bone resorption relative to formation. This imbalance leads to decreases in BMD of about 1% per year, which can begin soon after peak bone mass, at about the age of 40 years. In addition to decrease in BMD and alterations in bone geometry, microarchitecture deteriorates with ageing (Box 2). This physiological deterioration in bone quantity and quality might be accelerated without apparent causes or secondarily to many conditions. However, males acquire skeletal advantage with respect to women also during midlife, in particular at the cortical level. In this phase (typically 45–55 years) men experience a more gradual decrease in sex steroid levels than women,

Box 2: Age-related changes in bone remodeling and microarchitecture in males

- Age-related bone loss is a universal phenomenon affecting both men and women and is associated with reduced bone strength and increased fracture risk (27).
- As the skeleton ages, it becomes less responsive to hormonal and local regulators, as well as mechanical load, and the final common pathway is an unbalance between bone formation and resorption, generally characterized by an increase in bone resorption with no change or decrease in bone formation.
- Age-related BMD loss is gender different, affecting lesser men than women because men do not undergo a strong reduction in sex hormone levels as observed during menopause. Consequently, the increased rates for both vertebral and hip fractures in men are delayed by about 10 years with respect to women (21).
- The trabecular BMD loss seems to begin in the third decade of life in both sexes, independently from gonadal function. The lifetime loss of the trabecular bone at spine has been calculated in 55% in women and 45% in men (28) and it is greatly accelerated in women at menopause (29). Since men do not experience this rapid decline in sex hormones, the loss of trabecular bone loss is attenuated.
- On the contrary, the cortical bone is substantially maintained in both sexes until around the sixth decade. Thereafter, there is a slow decline that is slightly higher in women (28%) than in men (18%) due to the greater cortical bone loss that occurs in women in the peri-menopausal and early postmenopausal period (28).
- Although the rate of resorption at the endocortical surface is partially compensated by an increase in periosteal circumference, which increases bone size and bone strength, a net decrease in cortical thickness occurs reducing bone strength and increasing fracture risk (30).
- Besides bone mass, bone microarchitecture in males deteriorates with aging: cortical porosity increases, endocortical resorption reduces cortical bone width, and trabecular thickness decreases (31, 32). These changes are related to decreased testosterone levels and increased SHBG levels during aging which lower bioavailable testosterone and estrogen levels. Moreover, changes in GH-IGF1 are involved in bone loss in both sexes (33).

with less severe decrease in bone strength. Trabecular surface decreases as in women, but there is greater degree of periosteal thickening leading to a greater cortical thickness and increased cross-sectional diameter of long bones that increases the bending strength (30).

Male osteoporosis is typically classified into primary and secondary forms (Table 1). Types of primary male osteoporosis include the age-related osteoporosis (>60 years) and the idiopathic forms observed in young and middle-aged men. Male osteoporosis that results from specific, well-defined clinical disorders or medical treatment is classified as secondary osteoporosis. Although the prevalence of secondary osteoporosis is widely debated (34, 35, 36, 37, 38, 39, 40), it is generally assumed that up to 40% of postmenopausal women and 60% of men have factors contributing to osteoporosis when evaluated for underlying causes of the disease (4). Indeed, the relative percentage of primary and secondary forms depends on the clinical approach and depth of diagnostic work up. For example, one study showed that subclinical contributors to low BMD and/or fragility fractures besides hypovitaminosis D (that was present in 70% of cases) were present in more than 40% of the subjects with apparent primary osteoporosis,

without difference between gender (40). Based also on clinical experience, about two thirds of men have factors contributing to osteoporosis, and this figure is probably slightly higher with respect to women in which it is prevalent in the primary, postmenopausal or idiopathic forms.

The most common secondary causes and risk factors of osteoporosis in men (Table 1) include different endocrine conditions (especially hypogonadism – Box 3, diabetes mellitus and vitamin D deficiency), lifestyle (especially excessive alcohol intake, smoking, lack of exercise or excessive exercise, low calcium intake), medications (especially chronic corticosteroid therapy, androgen deprivation therapy (ADT), chemotherapeutics, and treatments for HIV), and a number of other diseases (especially malabsorption syndromes, rheumatoid arthritis and ankylosing spondylosis, chronic liver or kidney disease, HIV infection, chronic obstructive pulmonary disease). It is therefore evident that an accurate diagnostic work up is needed to understand the aetiology of male osteoporosis, identify modifiable and non-modifiable risk factors, and assess associated comorbidities, to finally adequately consider the most appropriate therapeutic approach.

Screening guidelines for male osteoporosis

At present, there is no universally accepted policy for screening of male population to identify individuals with osteoporosis or those at high risk of fracture (Table 2). Indeed, osteoporosis may be defined simply by the occurrence of a low-trauma fracture, by a BMD of 2.5 or more s.d. below the normal young mean as suggested by WHO, or by calculation of fracture risk (see subsequently).

Assessment of risk factors for osteoporosis and Dual energy X-ray Absorptiometry (DXA) are recommended in men >65–70 years from some endocrine and osteoporosis scientific societies (International Society for Clinical Densitometry www.iscd.org/official-positions/2019-iscd-official-positions-adult/, accessed 20 Dec 2019, National Osteoporosis Foundation 2014 clinician's guide to prevention and treatment of osteoporosis, www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international, accessed 20 Dec 2019, (58, 59)). The American College of Physician suggests performing DXA in men >65 years only when risk factors are documented to increase the risk for osteoporosis and/or are candidates for drug therapy (57).

In middle-aged men (>50 years) DXA is suggested for men with risk factors (National Osteoporosis Foundation 2014 clinician's guide to prevention and treatment of osteoporosis, www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international, accessed 20 Dec 2019, (58, 59, 60)), but a detailed list of risk factors is not provided in some cases (National Osteoporosis Foundation 2014 clinician's guide to prevention and treatment of osteoporosis, www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international, accessed 20 Dec 2019, (58, 60)).

For younger men (<50 years), only the Canadian Osteoporosis Society (52) made recommendations for DXA screening, highlighting the most frequent conditions that are associated with accelerated bone loss and/or fracture, such as prolonged use of glucocorticoids, hypogonadism (including ADT) and malabsorption syndrome. The International Society for Clinical Densitometry (www.iscd.org/official-positions/2019-iscd-official-positions-adult/, accessed 20 Dec 2019) makes no age limitations for DXA screening in men with risk factors for low BMD, being recommended in all men <70 years.

Interestingly, the United States Preventive Services Task Force (61) does not recommend osteoporosis screening in men justified by insufficient evidence. However, it clearly states that this recommendation applies

Table 1 Etiology and risk factors of male osteoporosis.

Primary osteoporosis (30–35%)
Idiopathic in young and middle-aged men
Age related (>60 years)
Secondary osteoporosis (65–70%)
Endocrine diseases
Hypogonadism
Cushing syndrome
Acromegaly
Hyperparathyroidism
Hyperthyroidism
Diabetes mellitus
Delayed puberty
Growth hormone deficiency
Estrogen deficiency
Vitamin D deficiency
Lifestyle
Alcohol intake
Sedentary lifestyle
Smoking
Undernutrition
Inadequate calcium intake
Medications
Glucocorticoids
Androgen deprivation therapy (ADT)
Antiepileptics
Immunosuppressants
Chemotherapeutics
Treatments for HIV
Other diseases
Malabsorption syndromes (celiac disease, inflammatory bowel diseases, bariatric surgery)
Low BMI (BMI <20)
Rheumatoid arthritis and ankylosing spondylosis
Chronic liver or kidney disease
HIV infection
Chronic obstructive pulmonary disease
Neoplastic diseases
Idiopathic hypercalciuria
Multiple myeloma
Mastocytosis
Osteogenesis imperfecta
Neuromuscular diseases
Ehlers-Danlos syndrome

to older adults without a history of low-trauma fractures, conditions that may cause secondary osteoporosis, conditions that may increase the risk of falls, and does not apply to persons who take long-term medications that may cause secondary osteoporosis.

A specific guideline for osteoporosis screening has been published for men with hypogonadism from the European Academy of Andrology (12). In this specific population, DXA is recommended in all cases when testosterone levels are <300 ng/dL (10.4 nmol/L), when patients are candidate to ADT and when history of hypogonadism is documented, especially if occurred during puberty or early adult life.

Box 3: Testicular function and bone metabolism beyond testosterone (Fig. 1)

- Testosterone is clearly the major testicular factor influencing bone metabolism. It allows for skeletal growth and bone mass accrual during development and puberty and for maintaining bone metabolism during adulthood by acting on bone cells (osteoblasts, osteoclasts, osteocytes) directly through AR and indirectly through ER after transformation to estradiol by aromatase enzyme.
- However, other functions of the Leydig cells are important in the testis-bone crosstalk: they produce the peptide hormone INSL3 and express CYP2R1, a 25-hydroxylase enzyme that converts the inactive cholecalciferol to 25OH-D3 (calcifediol), which can be further hydroxylated to the active form 1,25(OH)₂-D3 by renal 1-hydroxylase (41). Therefore, part of the 25OH-D3 derives from correct testis function other than classical 25OH-activation from the liver.
- INSL3 and vitamin D have an anabolic role acting on osteoblasts and osteocytes through the G-protein coupled receptor RXFP2 and VDR, respectively (42, 43, 44, 45, 46).
- All these functions of the Leydig cells are under the control of LH/hCG. Disturbed Leydig cell function, as observed in primary and secondary hypogonadism, is associated with reduction of INSL3, 25OH-D3 and testosterone levels, all contributing to the increased risk of osteoporosis (41, 47).
- Interestingly, mild Leydig cell impairment (as observed for example in subclinical hypogonadism) is associated with reduction of INSL3 and vitamin D levels with still normal concentrations of testosterone (41, 47, 48, 49), suggesting that steroidogenesis is compromised only in more severe forms of testiculopathy.
- Leydig cell function is also regulated by the skeleton, as osteocalcin produced by osteoblasts acts in parallel to LH to stimulate testosterone and 25OH-D3 production through its receptor GPRC6A (50, 51, 52).
- The testis-bone crosstalk is also linked to skeletal muscle function, as both testosterone and INSL3 increase muscle mass and strength (46, 53).
- Implications also for treatment are derived from these novel physiologic axes. For example, hypovitaminosis D in hypogonadal men should be better treated with calcifediol rather than cholecalciferol (54, 55). Furthermore, testosterone replacement therapy in hypogonadal men, by suppressing LH, does not maintain the full function of the Leydig cells, further reducing INSL3 and vitamin D levels. Therefore, at least patients with hypogonadotropic hypogonadism should theoretically benefit from stimulation of the Leydig cell function by hCG (or by increased LH levels induced by clomiphene), thus allowing to maintain testosterone (and estradiol), INSL3 and 25OH-D3 levels (56). Studies dealing with these aspects are needed.

A recent study (62) showed that DXA screening on all men aged >65 years was not associated with a decrease in fractures during a mean follow-up time of 4.7 years (153 311 men tested by DXA and 390 158 controls). However, targeted DXA screening in prespecified subgroups (ADT, glucocorticoids, age 80 years and older, one or more risk factors, and high Fracture Risk Assessment Tool (FRAX)) was associated with a lower risk of fracture.

Based on clinical experience, published guidelines and epidemiology of secondary causes and risk factor for osteoporosis in men (2, 3, 63), we suggest that osteoporosis should be considered in all men when risk factors for low BMD and fractures are present, independently from age. Age *per se* is sufficient for screening after the age of 65–70 years. Indeed, if clinicians just better consider bone health in their male patients bearing in mind the tens of conditions, risk factors, life style behaviours, and drugs able to deteriorate bone mass and quality, osteoporosis in men could be less ignored than in the past.

Of particular note, BMD does not always correlate with fracture risk and a fraction of fractures happen in men with normal BMD or BMD in the range of osteopenia, especially in some population such as men with HIV, diabetes or endocrine-related forms, because the fracture risk in these patients is related more to bone quality than bone mass (2, 3, 4, 63, 64). Therefore, it would be advisable to correctly diagnose osteoporosis, and in particular fracture risk and usefulness of therapy, also with tools other than DXA, such as FRAX algorithm or other risk calculators (3, 63, 65) and vertebral morphometric assay (see subsequently).

Diagnosis and management of male osteoporosis and fracture risk assessment

Although diagnosis of low bone mass and fracture risk is relatively simple, some aspects merit particular attention. First of all, osteoporosis is widely defined as a silent

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Table 2 Summary of main recommendations for osteoporosis screening in men.

Organization	Recommendations for DXA screening men
American College of Physician (2008) (57)	Assess risk factors for osteoporosis men >65 years and perform DXA in men who are at increased risk for osteoporosis and are candidates for drug therapy
International Society for Clinical Densitometry (2008) (www.iscd.org/official-positions/2019-iscd-official-positions-adult , accessed 20 Dec 2019)	Men >70 years Men <70 years with risk factors for low BMD (low body weight, prior fracture, high risk medication use, disease or condition associated with bone loss)
Canadian Osteoporosis Society (2010) (58)	Men ≥65 years Men 50–64 years with risk factors Men <50 years with fragility fracture, prolonged use of glucocorticoids, use of other high-risk medications (for example, aromatase inhibitors or androgen deprivation therapy), hypogonadism, malabsorption syndrome, primary hyperparathyroidism, other disorders strongly associated with rapid bone loss and/or fracture
Endocrine Society (2012) (59)	Men ≥70 years Men 50–69 years with risk factors (history of fracture after age 50, diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis)
National Osteoporosis Foundation (2014) (www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international , accessed 20 Dec 2019.)	Men >70 years Men 50–69 years based on risk factors profile
UK National Osteoporosis Guideline Group (2017) (60)	Assess fracture probability in men > 50 years who have risk factors for fracture
United States Preventive Services Task Force (2018) (61)	In individuals at intermediate risk, DXA should be performed No recommendation. Grade: I (insufficient evidence) This recommendation applies to older adults without a history of low-trauma fractures and without conditions that may cause secondary osteoporosis and patients without conditions that may increase their risk of falls. This recommendation does not apply to persons who take long-term medications that may cause secondary osteoporosis
European Academy of Andrology (2018) (12)	Specific guidelines for osteoporosis in male hypogonadism Hypogonadal patients with serum testosterone <300 ng/dL (10.4 nmol/L) Patients who need androgen deprivation therapy (ADT). Men with a well-documented history of hypogonadism

condition, meaning that in the early stages there are no symptoms until a fracture occurs. Therefore, particular attention should be made to the conditions (Table 1) that higher the risk of osteoporosis and fractures and to the identification of men who need assessment for an early diagnosis. Second, as already said, osteoporosis in men is frequently secondary. As a consequence, diagnosis should take into consideration a careful history and biochemical/instrumental assessment to confirm or exclude all the different aetiologies. It is evident that the identification of the correct diagnosis underlying osteoporosis and fracture risk is essential also to drive the correct therapeutic approach. Third, global assessment of the skeletal muscle-bone unit might be considered, as it could be useful for a more precise definition of the condition, fall prevention and fracture risk. Of particular note is that many of the causes that induce osteoporosis in men are also involved

in the development of sarcopenia (e.g. hypogonadism), defined as reduced skeletal muscle mass and strength (66). Furthermore, sarcopenia is a relatively frequent condition also in age-related osteoporosis and is part of the frailty syndrome (66). The diagnosis of sarcopenia is relatively simple (66), involving mainly the use of questionnaire (such as the SARC-F), strength assessment (such as the gait speed and hand grip tests), and determination of skeletal muscle mass by non invasive methods, such as DXA and bioimpedance (BIA) (66). Table 3 summarizes the different methods used for the assessment of osteosarcopenia.

The gold standard for the diagnosis of osteoporosis according to WHO threshold values and for fracture risk assessment is DXA, and this is the far most used method worldwide for diagnosis, follow-up and monitoring of treatment. However, DXA determines areal density (g/cm^2) and not volumetric bone density (g/cm^3) (vBMD) and

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Table 3 Summary and main characteristics of the different methods for the assessment of osteosarcopenia.

	Osteoporosis		Sarcopenia	
	Pros	Cons	Pros	Cons
Conventional radiography	<ul style="list-style-type: none"> Findings suggestive of osteoporosis are frequently encountered on radiographs ↑ bone radiolucency ↑ cortical thinning changes in the trabecular pattern Detection of morphometric vertebral fractures 	<ul style="list-style-type: none"> Osteoporosis detectable only in the advanced stages of the disease (bone loss at least 30%) Low sensitivity for diagnosing low BMD 	-	-
DXA	<ul style="list-style-type: none"> Gold standard for diagnosis and monitoring of osteoporosis and low BMD conditions WHO definition of osteoporosis is based on DXA Input for FRAX Detection of vertebral fractures Measurement of TBS Wide availability, low cost, and minimal radiation exposure 	<ul style="list-style-type: none"> Inability to detect bone strength as: bone microarchitecture geometry mineralization bone turnover 	<ul style="list-style-type: none"> Standardized method for diagnosing sarcopenia Assessment of muscle mass both at whole body and regional level Assessment of regional body composition and nutritional status in disease states and growth disorders Good accuracy and reproducibility Wide availability, low cost, and minimal radiation exposure 	<ul style="list-style-type: none"> Indirect assessment of muscle mass through X-ray attenuation Lean mass assessed with DXA includes all soft tissues (skeletal muscle, organs, connective tissue, and skin) Time of scanning Weight/height limits
QUS	<ul style="list-style-type: none"> No exposure to radiations Wide availability, low cost, portable Could be used for population-based screening and large cohort studies 	<ul style="list-style-type: none"> Indirect quantification of BMD Not recommended for diagnosing osteoporosis and monitoring treatment 	-	-
BIA	-	-	<ul style="list-style-type: none"> Standardized method for diagnosing sarcopenia and body composition No exposure to radiations Safe, fast, non-invasive, low-cost, reproducible, portable Wide availability 	<ul style="list-style-type: none"> Contraindicated in patients with pacemakers and in pregnant women The validity of the result depends on the correct state of hydration of the subject (problems in severely obese or malnourished subjects)
CT/QCT	<ul style="list-style-type: none"> Ability to measure BMD in a chosen volume (vBMD) Evaluation of cortical and trabecular bone separately Differential diagnosis of fractures (osteoporotic vs malignant) Estimation of bone strength 	<ul style="list-style-type: none"> High radiation exposure High costs Not for bone monitoring (lack of a strictly standardized acquisition protocol) Reproducibility Low availability For research purpose only 	<ul style="list-style-type: none"> Standardized method for diagnosing sarcopenia Gold standard in assessing muscle mass and quality in research setting CT scan can differentiate between fat and fat-free mass Dedicated algorithms for quantification of skeletal muscle composition/adipose tissue distribution in different body segments 	<ul style="list-style-type: none"> High radiation exposure High costs Operational complexity Low availability

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Table 3 Continued.

	Osteoporosis		Sarcopenia	
	Pros	Cons	Pros	Cons
MRI	<ul style="list-style-type: none"> • High resolution discrimination of normal and pathologic body tissues • Assessment of bone microarchitecture • Assessment of the features of trabecular bone and its biomechanical proprieties • Discrimination between acute and chronic vertebral fractures • Estimation of bone strength • No X-ray exposure 	<ul style="list-style-type: none"> • Osteoporosis screening challenging, time-consuming, and high costs • Lack of MRI protocols suited for the study of trabecular bone • Low availability • For research purpose only 	<ul style="list-style-type: none"> • Standardized method for diagnosing sarcopenia • Quantification of muscle size and assessment of muscle quality • Gold standard in assessing muscle mass and quality in research setting • No X-ray exposure • Ability to detect changes in the muscle occurring with aging and disease progression 	<ul style="list-style-type: none"> • Lack of a standardized assessment protocol in image analysis • Time-consuming • High costs • Limited comparison between the results of different studies • Tissue segmentation algorithms can vary a lot ranging from a manual segmentation technique to a fully automated method

BIA, bioimpedance; BMD, bone mineral density; DXA, dual-X-ray absorptiometry; QCT, quantitative CT; QUS, quantitative ultrasound; TBS, trabecular bone score.

does not give accurate information on bone quality. The areal BMD (aBMD) does not consider the third dimension of depth, so that larger bones, having greater depth, will have a greater density as measured by DXA. Thus, men, having larger bones compared to women, will have higher aBMD even if the vBMD is identical. Although it is clear that there is an inverse association between BMD and fracture risk, the specifics of the relationship are not well established in men as in women. Furthermore, as said, debate still exists whether to use female or male reference values when performing DXA in men. Therefore, the bone density criteria that should be used to identify men with high fracture risk and, thus, in need of intervention are still controversial. The adoption of the T-score threshold for men is based on the assumption that, for any given level of BMD, the absolute risk of fracture is similar between men and women (67). However, direct translation of data from women to men is not so evident, as older men have, on average, a higher BMD and a lower rate of bone loss than women and have a lower absolute risk of fracture at a later age (68).

Software has been developed to evaluate geometric parameters related to bone strength, such as the Trabecular Bone Score (TBS). TBS is a gray-level textural metric that can be extracted from the 2D lumbar spine. TBS relates to trabecular bone microarchitecture as an overall quality score computed from the difference of a pixel by pixel projection of 3D gray-level texture variation onto a 2D plane. A high TBS reflects a strong, fracture-resistant microarchitecture, whereas a low TBS is associated with an increase in both prevalent and incident fractures, in part,

independently from both clinical risk factors and aBMD at the lumbar spine and femoral neck. TBS progressively decreases with advancing age (69) and increases after osteoporosis treatments. The association of BMD and TBS provides greater information than BMD alone. The use of TBS appears particularly useful in the classification of subjects at risk for fragility fracture with normal BMD values and both primary and secondary osteoporosis (e.g. diabetes, hyperparathyroidism and chronic glucocorticoid therapy) (70). Indeed, according to the International Society for Clinical Densitometry guidelines, TBS should not be used alone in clinical practice, but rather in combination with BMD and algorithms for fracture risk assessment (71). In fact, many clinical factors despite BMD and TBS contribute to the occurrence of fragility fracture in non-osteoporotic patients (7).

Of particular help, not only for the diagnosis of osteoporosis, but above all for the assessment of the risk of fracture are algorithms, such as the FRAX. It allows fracture risk assessment over a period of 10 years considering several clinical risk factors (age, gender, ethnic and geographic region, smoking, alcohol intake, previous low-trauma fracture, parental hip fracture, oral glucocorticoid therapy, rheumatoid arthritis and secondary causes of osteoporosis), with or without femoral neck BMD. FRAX uses femoral neck BMD because it represents the best predictor of hip fractures, which are the osteoporotic fractures associated with the worst impact on survival in men. It has to be noted that some variables in FRAX are not graduated, but only dichotomic (yes/no, with no indication on location and number of

previous fractures, severity of comorbidity, number of cigarettes, dose and duration of corticosteroids), and that other clinical risk factors are not considered (e.g. other osteopenic drugs, comorbidities such as diabetes mellitus, vertebral BMD). In summary, DXA is particularly useful for identification of men at the highest risk, represented by those with osteoporosis by T-score, whereas FRAX might be useful for the identification of those men at risk despite normal BMD or T-score in the range of osteopenia. Indeed, fracture risk calculated by FRAX can be underestimated in men, especially those with secondary causes of bone fragility, such as diabetes (2).

Finally, in most conditions the definition of osteoporosis in men should consider VF assessment (72). Fractures of the hip and wrist usually occur after a fall, resulting in severe pain that motivates patients to seek immediate medical attention. On the contrary, VFs commonly occur with no recognizable trauma and may not cause pain of sufficient magnitude to arouse the concern of the patient or physician. Only about one-third of all radiographic VFs come to clinical attention, more commonly in men (42%) than women (22%) (72). The mortality rate 5 years after a clinical VF is about 20% greater than expected, with mortality rates higher for men than women. Moreover, mortality rates increase with the number of VFs. The two most widely used methods to determine the presence and degree of VFs are the semiquantitative assessment and the morphometric quantitative approach, involving the measurements of vertebral body heights. The measurements are generally made on conventional spinal radiographs (MRX: morphometric X-ray radiography) or on images obtained from DXA scans (MXA: morphometric X-ray absorptiometry). Therefore, the availability of a rapid, low-dose method for assessment of VFs, using advanced DXA devices, provides a practical method for integrated assessment of BMD and VFs status and, in our opinion, should be performed in all men at diagnosis.

It is quite clear that, although the determination of BMD, fracture risk, eventual sarcopenia and VFs with these methods allows for a careful management of men with osteoporosis, we are still far from a detailed analysis of bone structure and strength and that follow-up during treatment is still based on rough markers. In fact, not only accurate biomarkers of osteoporosis and response to treatment are still undefined, but also the resolution of DXA is insufficient in distinguishing between the cortical and trabecular framework and is not sensitive enough to detect cortical bone loss. Furthermore, DXA might be inadequate for establishing fracture risk in conditions

characterized mainly by loss of bone quality rather than quantity, such as the endocrine-related forms (4).

Compared to DXA, quantitative CT (QCT) has the advantage to measure vBMD and trabecular tissue, providing pertinent information on bone strength (Table 3). MRI has also proved to be an accurate method to obtain microarchitectural data of trabecular bone, particularly in the peripheral appendicular skeleton (distal radius and calcaneus). Also high-resolution peripheral quantitative CT (HRp-QCT) performed at distal bones is able to provide reliable data on bone microarchitecture with high image resolution. Studies conducted in men have provided novel insights in understanding the biological, aetiopathogenetic and biomechanical processes that occur within the skeleton (73). For example, in men, trabecular number is preserved while trabecular thickness decreases with ageing, whereas in women trabecular number decreases significantly. Despite the undoubted advantages, the HRp-QCT is limited by the relatively high radiation dose and the difficulty in predicting bone quality and osteoporotic fractures other than distal bones (i.e. VFs). Similarly, the QCT resolution is limited by safe radiation exposure dosages and MRI struggles with the signal-to-noise ratio and scanning time. Furthermore, high costs and the expertise level required to handle these techniques has limited their application to few research centres, but the continuous and significant improvements in computational power in the next decade will probably allow the development of more powerful and elaborate 3D morphological analysis techniques.

Therapeutic approach to male osteoporosis and target of treatment

General considerations

Many issues are still relatively undefined in the treatment approach to male osteoporosis. Although the target of treatment is, similarly to women, the reduction of fracture risk, some considerations merit attention before examining the data available on specific drugs used to treat osteoporosis. First of all, we all should better consider male osteoporosis in our clinical practice and screening for male osteoporosis should be more adopted than today. Secondly, we should put great effort in convincing men (especially those at risk) to screening and early diagnosis and convincing national health systems to definitely eliminate the gender disparities in offering osteoporosis screening. Hopefully, these efforts could lead in the future to more diagnosis of osteoporosis in men,

and especially in more diagnosis at early stages, before fracture risk is too high or fractures have already occurred. Thirdly, osteoporosis in men is frequently secondary, and obviously the first step in the therapeutic approach is the elimination and treatment of the trigger cause, where possible. Furthermore, great efforts should be made also to increase the percentage of men receiving a treatment, because osteoporosis in men is undoubtedly under-treated other than under-diagnosed. Finally, consideration should be given on how to achieve greater adherence to treatment. Adherence, in fact, considered as both compliance and persistence, is the pivotal element to obtain a successful treatment, to prevent complications and to reduce healthcare costs. Unfortunately, not only adherence to treatment in men is low, but also its assessment is under-estimated in clinical practice and in trials. For example, studies have found non-adherence to bisphosphonates in men ranging from one-third to two-thirds, with subsequent increased fracture risk (74). Therefore, therapeutic success of osteoporosis treatment in men can be measured by different methods, such as absence of fractures, increment or maintaining BMD, compliance with therapy (75).

Following precise diagnosis, adequate management of male osteoporosis requires a careful selection of patients candidates to receive specific treatment, life style interventions, treatment of underlying conditions, and decision on which drug to use. According to guidelines ((12, 58, 59, 60), National Osteoporosis Foundation 2014 clinician's guide to prevention and treatment of osteoporosis, www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international, accessed 20 Dec 2019) pharmacological therapy in men is recommended for men with hip and/or vertebral fragility fracture, men with a T-score (spine, hip) lower than -2.5 s.d., and men with T-score between -1 and -2.5 (spine, hip) and fracture risk over 20% or hip fracture risk in 10 years $\geq 3\%$ according to FRAX. Furthermore, men receiving chronic therapy with high dosage glucocorticoids and men receiving ADT for prostatic cancer are also candidates to antiosteoporotic drugs.

Non-pharmacological approach

Non-pharmacological approach, mainly based on lifestyle behaviours, is suggested for osteoporosis in men, as for women. Lifestyle education is the basis also for osteoporosis prevention. Since early infancy, in fact, it is important to have a healthy diet (especially regarding

adequate calcium intake) and regular physical activity, in order to reach adequate bone mass peak. Maintaining a healthy lifestyle is essential also during adulthood, with adequate sun exposition, normal body weight, avoiding excessive alcohol intake and smoking. Physical activity and targeted exercises could improve muscular mass, strength and resistance and therefore reduce falls risk (76). Although there is no strong evidence that physical activity might prevent fractures, observational studies found that the physical activity-related BMD increase is approximately 2% in older men (77, 78) and that it helps maintaining muscle mass and strength. In elderly men, home safety should be improved to prevent falls and fractures.

Supplement and replacement therapy

Although calcium and vitamin D are well known regulators of bone health, there are few published studies on calcium and vitamin D supplementation in men, and they are often controversial. Anyway, based on evidence derived from studies in postmenopausal osteoporotic women, the same therapeutic approach is commonly applied in men. A daily calcium intake of 1000 mg for men under 70 years and 1200 mg for men over 70 years is generally suggested, and calcium supplementation should be prescribed only if dietary intake is inadequate (79).

Vitamin D supplementation is often necessary, as hypovitaminosis D is common in the elderly mainly as a result of reduced sunlight exposure and a decreased functional capacity of the skin. Furthermore, many conditions (Table 1) associated with osteoporosis are characterized by low levels of vitamin D. Dietetic supplementation of vitamin D is not able to restore normal levels of 25-hydroxy vitamin D, therefore, aside with adequate sun exposure, guidelines suggest supplementation in an individualized dose, based on serum 25-hydroxy vitamin D levels, starting from 800 UI/day (79). Although treatment of hypovitaminosis D is not under the scope of this review, an important point to highlight is that the choice to supplement with the inactivated form of vitamin D (cholecalciferol) or with the 25-hydroxylated form (calcifediol) should consider also the pathogenesis of hypovitaminosis. For example, men with hypogonadism could better benefit from treatment with calcifediol because the testis participates with the liver in the 25 hydroxylation of cholecalciferol (35) (Box 3, Fig. 1) and this approach allows for rapid restoring of 25-hydroxy vitamin D levels (48), as for men

Figure 1

The testis-bone crosstalk. AR, androgen receptor; E2, estradiol; ER, estrogen receptor; GPRC6A, G-protein-coupled receptor family C group 6 member A; INSL3, insulin like factor 3; LH, luteinizing hormone; LHR, luteinizing hormone receptor, OC, osteocalcin; RXFP2, relaxin family peptide receptor 2; T, testosterone; uOC, uncarboxylated osteocalcin; VDR, vitamin D receptor.

with liver dysfunction. Similarly, obese men might also benefit from supplementation with calcifediol because cholecalciferol is more sequestered in the adipose tissue than calcifediol (80). Nevertheless, guidelines on vitamin D supplementation generally suggest treatment with cholecalciferol or simply do not differentiate between cholecalciferol and calcifediol, or distinguish the pathophysiologic mechanism leading to hypovitaminosis.

Although it is necessary to restore vitamin D levels and maintain an optimal calcium homeostasis, the efficacy of calcium and vitamin D supplementation alone in reducing fracture risk is controversial, but it could indeed improve BMD (81). Of note, calcium and vitamin D supplementation is always recommended before starting antiosteoporotic treatment when there is a deficiency condition, and it should be maintained during treatment.

Hypogonadism, both in the young men (for example Klinefelter syndrome) and in aging (late onset hypogonadism – LOH), is a major cause of osteoporosis. Importantly, both the reduction of testosterone and estradiol are important for bone loss (Box 1). Many conditions associate with low testosterone in the setting of male osteoporosis (Table 1) such as ADT, HIV infection and its treatment, obesity, diabetes, metabolic syndrome, liver and renal dysfunction, or chronic obstructive pulmonary disease. Therefore, hypogonadism should always be considered during the clinical workup of male osteoporosis and it should be carefully diagnosed and eventually treated (12). Testosterone replacement therapy (TRT) in the setting of male osteoporosis is particularly recommended in young adult hypogonadal men to prevent bone loss and help acquiring peak bone mass

(12, 82). In the other groups of patients, mainly older men with functional hypogonadism, the benefits and risks of TRT should be accurately discussed with the patients, contraindications to testosterone treatment should be identified and therapy should be monitored. Nevertheless, TRT alone is not recommended and should be associated with antiresorptive drugs when fracture risk is high (12). Actually, the effect of TRT alone on bone health in hypogonadal men is still not well defined (75), and no studies with fractures as primary end point have been performed. Indeed, TRT can improve BMD, particularly at the vertebral level and when testosterone levels are very low (12, 83). The Bone Trial of the Testosterone Trials (T-Trials) showed that testosterone treatment for 1 year in older men with low testosterone significantly increased vBMD and estimated bone strength, more in trabecular than peripheral bone and more in the spine than hip (84). The association of TRT with antiosteoporotic drugs has not been investigated, as well as the combined effects of TRT on bone and skeletal muscle has not been taken into consideration. Nonetheless, the association of TRT with vitamin D (calcifediol) and calcium seems more effective in increasing BMD than TRT alone, at least in men with Klinefelter syndrome (55).

Antiestrogenic drugs

The antiresorptive and anabolic drugs approved for osteoporosis in men in Europe and USA and their effects in male osteoporosis are summarized in Table 4 and are represented by bisphosphonates, denosumab, and teriparatide. Compared to osteoporosis in the female, the data from clinical trials are incredibly few for male osteoporosis, and the few randomized controlled studies published included frequently a limited number of men. Of note, almost all of our knowledge on the effects of antiosteoporotic drugs are derived from studies in women. Furthermore, no study, except one with zoledronic acid (11), had fracture risk as primary end point. Indeed, antiresorptive treatment (bisphosphonates and denosumab) increases bone density in osteoporotic men (11, 85, 86, 87, 88, 89, 90).

First-line treatment is represented by bisphosphonates, which act through inhibition of osteoclastic bone resorption. Randomized controlled studies in men with osteoporosis have been performed with alendronate, risidronate and zoledronic acid (Table 4). They all increased femoral and vertebral BMD (the primary endpoint) after 2–3 years. Alendronate also reduced VFs (secondary endpoint) in the two studies published (85,

86), while risidronate reduced VFs in one study (88), but not in another study (87). Both drugs did not reduce non-vertebral fractures. The efficacy of zoledronate i.v. was assessed in one large study (11) and showed efficacy on BMD (lumbar spine, total hip, femoral neck) and VFs (primary endpoint) in 2 years of treatment in men with idiopathic and glucocorticoid-induced osteoporosis. Despite these few data, a meta-analysis showed that alendronate and risidronate significantly reduced risk of VFs and that bisphosphonates as a treatment group reduced also non-VFs (93). Actually, all the studies included in the meta-analysis were assessed as at risk of bias (93).

Bisphosphonates are suggested for men with osteoporosis and increased fracture risk, including those with secondary osteoporosis, such as hypogonadism (12). Adverse effects of oral bisphosphonate in men are comparable to those described in trials in postmenopausal women. The most commonly referred is esophageal irritation, which can be reduced by administration 30 min before eating, maintaining upright posture, and with a large glass of water. A possible limitation of daily or weekly oral therapy in male osteoporosis (as for alendronate and risidronate) could be the poor adherence. Compliance could be improved with longer half-life drugs, for example, zoledronate i.v. once/year.

The duration of bisphosphonate treatment is not well determined. Nevertheless, since the occurrence of rare cases of osteonecrosis of the jaw and atypical femoral fractures, a 'therapeutic holiday' from oral bisphosphonate after 5 years of administration and after 3 years for i.v. bisphosphonates could be considered with reassessment at 2 to 3 years for patients not at high fracture risk and without fractures antecedent to treatment or in early treatment phase (3). However, the evidence on fracture risk reduction obtained by drug holiday, in particular for risidronate, and on fracture risk for continued drug efficacy for prolonged periods is limited and controversial (94), and data on men are even weaker.

The data on denosumab (a MAB, which neutralizes RANK-L activity) in male osteoporosis are even more limited (80, 81), but showed positive effect on vertebral BMD (primary endpoint) and femoral BMD in the first year of treatment and VFs in the second year. No data are available for non-vertebral fractures. Denosumab finds best indication to treat bone loss in patients with primary osteoporosis, those receiving ADT for prostate cancer and hypogonadal men (12). Adverse effects of denosumab are hypocalcaemia, osteonecrosis of the jaw, and atypical femoral fracture. There are no data about therapeutic adherence in male population. However, based on the

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Table 4 Summary of the evidence on the different treatment for male osteoporosis based on available RCTs.

Treatment	Study	Dose/ regimen	No. of patients (drug/placebo)	Primary end-point	Effects on			Adverse effects
					BMD	VFs	NVFs	
Alendronate	Orwoll <i>et al.</i> (85)	10 mg daily, oral	241 (146/95)	Effect of 2 years alendronate treatment on BMD	+	±	NS	<ul style="list-style-type: none"> Gastrointestinal disorders (mainly reflux) Muscle and joint pain Osteonecrosis of the jaw Atypical femoral fracture
	Ringe <i>et al.</i> (86)	10 mg daily, oral	134 (68/66)	Effect of 3 years alendronate treatment on BMD	+	±	NS	<ul style="list-style-type: none"> Muscle and joint pain Osteonecrosis of the jaw Atypical femoral fracture
Risedronate	Boonen <i>et al.</i> (87)	35 mg weekly, oral	284 (191/93)	Effect of 2 years risedronate treatment on spinal BMD	+	NS	NS	<ul style="list-style-type: none"> Gastrointestinal disorders (mainly reflux) Headache Muscle and joint pain Osteonecrosis of the jaw Atypical femoral fracture
	Ringe <i>et al.</i> (88)	5 mg daily, oral	316 (158/158)	Effect of 2 years risedronate treatment on BMD	+	±	NS	<ul style="list-style-type: none"> Muscle and joint pain Osteonecrosis of the jaw Atypical femoral fracture
Zoledronate	Boonen <i>et al.</i> (11)	5 mg yearly, i.v.	1199 (588/611)	Effect of 2 years zoledronate treatment on morphometric vertebral fractures	+	+	NS	<ul style="list-style-type: none"> Fever after infusion Muscle and joint pain Hypocalcemia Osteonecrosis of the jaw Atypical femoral fracture
Denosumab	Orwoll <i>et al.</i> (89) Langdahl <i>et al.</i> (90)	60 mg every 6 months, SC	242 (121/121)	Effect of 1 year (80) and 2 years (81) denosumab treatment on spinal BMD	+	±	NA	<ul style="list-style-type: none"> Hypocalcemia Hypersensitivity reactions Osteonecrosis of the jaw Atypical femoral fracture
Teriparatide	Orwoll <i>et al.</i> (91) Kaufman <i>et al.</i> (92)	20 or 40 µg daily, SC	437 (139 + 151/147)	Effect of 11 months teriparatide treatment on BMD (a)	+	± (b)	NA	<ul style="list-style-type: none"> Nausea, headache, dizziness Muscle pain Hypercalcemia Nephrolithiasis

+ indicates significant improvement with respect to placebo as result of primary end point; ± indicates significant or near significant finding obtained from secondary end-point or from subsequent meta-analysis; (a) This trial (91) was stopped after 11 months because of a finding of osteosarcomas in rats in toxicology studies; (b) Data obtained from the post-trial observational study through 30 months of post-treatment follow-up (92). BMD, bone mineral density; µg, micrograms; NA, data not acquired; NS, not significant between-group differences; NVFs, non-vertebral fractures; VFs, vertebral fractures.

Denosumab Adherence Preference Satisfaction (DAPS) study, it could be supposed to be higher with respect to oral bisphosphonates, since it is subcutaneously injected every 6 months. (95). Unlike bisphosphonates, the beneficial effects of denosumab on bone is rapidly reversible, since an increase in osteoclastogenesis occurs early after withdrawal. In phase II and III trials, denosumab discontinuation was associated with an increase of the bone turnover markers and a decrease of BMD (96). Subsequent case reports and cases series described the occurrence of multiple spontaneous clinical VFs after stopping denosumab, but a post-hoc analysis of the FREEDOM and FREEDOM Extension trial concluded that VFs risk was similar after denosumab or placebo

discontinuation (96). No data have been published regarding gender difference in rebound-associated VFs, even if a theoretical risk could be hypothesized mainly for hypogonadal men, because low testosterone (and estradiol) is associated with high bone turnover (97). Therefore, it has not yet been established how long the patients should be treated with denosumab, or whether and when it should be discontinued. Generally, denosumab is mostly discontinued when patients have reached a target T-score outside the osteoporosis zone. In addition, the risk, although low, of osteonecrosis of the jaw and atypical femoral fracture increases with denosumab treatment duration, and the risk-benefit ratio can favor the decision to stop the treatment in those with

low fracture risk (96). Bisphosphonates are suggested after stopping denosumab to reduce the increased risk of rebound-associated fractures (98).

Teriparatide is the only anabolic agent approved for male osteoporosis and reported in randomized controlled studies. The intermittent administration of teriparatide, which represents the 1–34 amino-terminal fragment of PTH, has an anabolic action on bone, both through direct effects on the osteoblasts and indirect ones, through IGF-I induction and sclerostin suppression (99). In women, it increases both lumbar and femoral BMD and reduces fracture risk. Furthermore, it seems to be more effective than bisphosphonates in glucocorticoid-induced osteoporosis. One study in men (91) showed a beneficial effect on BMD after 11 months and a reduction in VFs in a post-trial observational study through 30 months of post-treatment follow-up (92). It is administered s.c. at a daily dose of 20 µg, for a maximum period of 24 months, because its safety and efficacy have not been evaluated over 2 years. Teriparatide is generally well tolerated. Possible post-dose adverse effects are hypercalcemia and hypercalciuria, nausea, arthralgia, and headache. Teriparatide is contraindicated in patients with pre-existing hypercalcemia, with bone malignancies or other neoplasms with potential bone involvement including multiple myeloma, in those with bone metastasis, in children, and in patients at risk to develop osteosarcoma.

More recently, new therapeutic possibilities are emerging in the management of osteoporotic patient, represented by romosozumab and abaloparatide. Romosozumab is a monoclonal humanized antibody that neutralizes the effects of sclerostin, a protein produced by osteocytes, and has therefore a dual action, by increasing bone formation and reducing bone resorption (99). In a phase III trial on the efficacy and safety of romosozumab in males (BRIDGE Trial), an increase in BMD at both spinal and femoral level was observed, comparable to what was previously found in the female population after 12 months of treatment (100). The positive effects of romosozumab seem to be related to action on both cortical and trabecular bone compartments at the spine and hip. Abaloparatide is a synthetic agonist of the PTH type I receptor approved for postmenopausal women at high fracture risk. It increases BMD both at spinal and femoral level more than teriparatide and reduces vertebral- and non-vertebral fracture incidence, with no evident difference with teriparatide (99). It works as an anabolic agent, by stimulating periosteal expansion and endocortical apposition, determining a cortical bone volume increase.

Conclusion and perspectives

Although many gender disparities exist in the field of osteoporosis, with the male being the weaker sex, progresses have been made in last years and hopefully will be made in a near future to fill this gap. Male osteoporosis has been neglected for too long time and there is need for a change. Many areas are still nebulous, ranging from clear identification of subjects who need to be evaluated for osteoporosis, health programs focused on primary prevention (screening), diagnostic procedures for good estimates of bone quality and precise calculation of fracture risk, personalized treatment that take into account the pathophysiology of osteoporosis. Comorbidities are very frequent in men with osteoporosis (such as hypogonadism, obesity, diabetes) and lifestyle influences bone health from the very young age, when peak bone mass is reached. However, we too often still continue to consider male osteoporosis as a single disease and treat it consequently, and prevention during the different phases of life is not adequate.

Men with osteoporosis not only are under-diagnosed, but treatment is under-utilized. Importantly, adherence to therapy and compliance are far less than women and the disparity in the number of clinical trials involving males with respect to women is incredible. Hopefully, the new drugs that are available now in the market will be tested also in large, multicentre, randomized, controlled studies. There is also need for clinical trials assessing the efficacy of multistep therapeutic approach, that is, for example, antiresorptive drugs plus testosterone in hypogonadal men, and combination therapy (e.g. antiresorptive plus anabolic drugs). End points of treatments should also be better defined, as it is evident that BMD alone is not sufficient, and probably a more integrated approach should be assessed (e.g. with vertebral morphometry, evaluation of sarcopenia and measures of bone and skeletal muscle strength).

Osteoporosis is managed by different professional figures, including orthopaedics, rheumatologists, physiatrists, general practitioners, oncologists, gynaecologists, and geriatricians, but endocrinologists should have a pivotal role, the bone being an endocrine organ and the pathogenesis of osteoporosis itself frequently endocrine in origin.

Finally, male osteoporosis is not simply a disease related to ageing. Many conditions acting before and during puberty might compromise the bone health for the rest of the life. Nevertheless, the early identification of these conditions (such as, for example, the Klinefelter

syndrome, malabsorption diseases, vitamin D deficiency) might allow for better management of fracture risk.

At the very end, hopefully in a near future, we should fix the expression 'osteoporosis: women prevent it, men fracture', which sometimes we bitterly use.

Declaration of interest

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