



Male osteoporosis: A review

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Abstract

Osteoporosis in men is a heterogeneous disease that has received little attention. However, one third of worldwide hip fractures occur in the male population. This problem is more prevalent in people over 70 years of age. The etiology can be idiopathic or secondary to hypogonadism, vitamin D deficiency and inadequate calcium intake, hormonal treatments for prostate cancer, use of toxic and every disease or drug use that alters bone metabolism. Risk factors such as a previous history of fragility fracture should be assessed for the diagnosis. However, risk factors in men are very heterogeneous. There are significant differences in the pharmacological treatment of osteoporosis between men and women fundamentally due to the level of evidence in published trials supporting each treatment. New treatments will offer new therapeutic prospects. The goal of this work is a revision of the present status knowledge about male osteoporosis.

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Key words: Male osteoporosis; Skeleton involution; Eti-

INTRODUCTION

Osteoporosis has generally been considered a female disease; this may explain why this pathology has focused less attention on men. While osteoporosis has been underestimated and poorly treated in female patients, the situation is even worse in male patients, despite the fact that up to one third of hip fractures are suffered by men^[1]. In Spain, 26% of these osteoporotic hip fractures are diagnosed in male patients^[2]. In addition, the first-year mortality has been reported to be higher among male patients (37.5 %) ^[3]. The risk of suffering a hip fracture among men is linked to age, although 50% of these fractures are experienced by patients under 80 years old^[4]. The incidence of vertebral osteoporotic fractures has been published as being 50% lower in men^[5,6], but many of these fractures are diagnosed in male patients with bone mineral density (BMD) levels above the osteoporotic standard criteria^[7]. The high incidence and mortality rates of hip fractures, together with the incidence of vertebral fractures in men and their impact on quality of life^[8,9], highlight that osteoporosis is also a male disease, and that it must be diagnosed and treated as it is in

female patients^[9].

The association between osteoporosis and aging has been well documented. It seems clear that we face a serious problem due to a marked increase in life expectancy in the United States^[10,11] and the Western world^[12]. In addition, this increase is higher among men^[13]. In Spain, mean life expectancy among men was 76.6 years in 2000^[14], reaching 77 years in 2005^[15]. These data emphasize the relevance of male osteoporosis. Some studies conducted in Sweden^[13], which compared BMD in the femoral neck among men and women based on DXA scan determinations, proved that the higher incidence of male osteoporosis is found in patients aged 70 to 85 years. Up to 34.7% of individuals in that interval fulfilled osteoporosis criteria. Moreover, according to the same authors, about 47% of men older than 50 suffered osteopenia. If the group aged between 50 and 80 years is studied, the prevalence of osteoporosis remains around 21% in the female sex and 6.3% in the whole population.

DEVELOPMENT AND INVOLUTION OF THE SKELETON IN MEN

The appendicular skeleton grows twice that of the axial skeleton during the prepubertal period. In males, puberty starts later than in females, so the male appendicular skeleton is bigger in size and width. However, these differences in the prepubertal period are lesser in the axial skeleton^[16].

The male skeleton shows a progressive increase of BMD during childhood. This increase becomes exponential during adolescence. Although BMD of trabecular bone is similar in both genders, this density is higher in men's cortical bone when compared with that of women, even when adjusted by body mass index^[17]. The human male bone is also bigger in size. These biomechanical advantages provided by the thickness of cortical bone, make the male skeleton more resistant, and thus, less prone to suffer fragility fractures. Androgenic male hormones might explain this advantage^[18]. The bone size enlarges more in males than in females during normal aging. This is due to a greater periosteal apposition in males that increases the previous differences which occurred during adolescence. Volumetric BMD in vertebrae is similar in both genders of the younger population, and the ulterior losses of trabecular bone are also similar. Nevertheless, the male skeleton preserves a higher BMD in the spine during aging due to the greater periosteal apposition. On the contrary, an increased endosteal resorption in men compensates for previous differences in other locations like the hip, where the volumetric BMD is similar in both genders. Cortical porosity is also lower, and the trabecular architecture and connectivity are much more preserved in men than in women^[19]. In a recent study conducted by Patsch *et al.*^[20] analyzing iliac crest biopsies of men with idiopathic osteoporosis concludes that there are an osteoblast dys-

function and a different microstructural pathology than age-related bone loss.

In male idiopathic osteoporosis there is a microstructural alteration in relation to age. In women, bone stock decreases markedly during the sixth decade of life, because of an estrogenic hormone deprivation^[13]. In men this decrease is found in patients beyond the age of 70 years^[21], but the trabecular bone is preserved more years^[22] than in females. There is a relationship between trabecular bone loss in men and the insulin-like growing factor. On the contrary, cortical bone loss is due to a decrease in testosterone and estrogenic hormones^[23,24], that leads to an increased bone turn-over process. These differences between sexes in the bone stock involution make male individuals more resistant to fragility fractures, therefore generally suffering these fractures later in life than women^[25].

ETIOLOGY AND PATHOGENESIS OF MALE OSTEOPOROSIS

Osteoporosis in men has been categorized, classically, into three types: (1) Involutional or senile osteoporosis; (2) Idiopathic in middle aged males; and (3) Secondary osteoporosis^[26]. Up to 50%-65% of the diagnoses in male patients are secondary to metabolic diseases, toxic substances or iatrogenic side effects^[24,27].

In men, testosterone plays a major role in bone metabolism, similar to the role of estrogens in females. Several studies have reported the importance of the estrogen receptor (ER)-alfa^[28] and aromatase inhibitors^[29] on the growth and development of pathological conditions of bone. Other authors^[30] have demonstrated the importance of the androgen receptor (AR) whose function is essential for male-type bone formation and remodeling, because promotes osteoblastic activity. Furthermore they showed that deficiency of AR has a essential effect on the expression of the receptor activator of NF- κ B ligand (RANKL) gene, which encoding an osteoclastogenesis inducer.

Up to 70% of bone turnover and resorption appear to be modulated by estrogens and 30% by testosterone^[31]. Moreover both hormones are substantial in bone formation mechanisms^[26].

Although hormonal changes in men are not so marked as in females, they are also important in the pathogenesis of osteoporosis. Sex-hormone binding globulin (SHBG) levels increase with aging in men^[32]. On the contrary, serum bio-available (or non-SHBG bound) estradiol and testosterone levels decrease with age. BMD is clearly related with steroid levels, especially with bio-available estradiol levels^[26].

The trabecular and endosteal resorption in osteoporosis patients is not compensated by bone formation. The periosteal apposition, capital in the male bone metabolism, is directly related with bio-available levels of testosterone. A deficit in testosterone levels leads to bone loss and increases the risk of fracture^[23,26].

The association between aging and serum SHBG levels remains unclear. Nevertheless, an inverse relation of insulin-like growth factor I (IGF-I) levels and SHBG levels has been widely proven. IGF-I directly inhibits SHBG production by liver cells^[33].

Periosteal apposition, that compensates endosteal resorption, especially in men, is modulated not only by testosterone, but also by growth hormone (GH) and IGF-I levels^[26].

An inadequate peak bone mass is involved in the pathogenesis of osteoporosis in males. Inherited factors such as gene regulation of steroids production, GH or IGF-I, are directly related with the peak bone mass. The lower the peak bone mass, the greater the possibility of developing an age-related osteoporosis.

Idiopathic osteoporosis

Idiopathic osteoporosis can be present in any age group, but it is more prevalent in younger individuals. It is known that low bone mass may be inherited. Genetic factors linked with gene polymorphisms are the supposed etiology for this type of osteoporosis. Polymorphisms have recently been reported in collagen specific proteins (COLIA 1 and COLIA 2), in vitamin D receptors; and in lipoprotein receptor-related protein^[34]. All of these factors might be involved in the development of a low bone mass of uncertain origin^[35]. Up to 40% of the cases affecting male patients are diagnosed as primary or idiopathic osteoporosis^[24].

Secondary osteoporosis

Frequent causes of secondary osteoporosis are:

Hypogonadism: This is one of the most frequent etiologies of secondary osteoporosis in men. Studies carried out in nursing homes showed that, among geriatric individuals who had suffered a hip fracture, up to 66% had hormonal levels lower than the standard^[36].

Other authors^[37] have documented a marked increase in the risk of suffering fragility fractures among patients with low levels of testosterone and estradiol. Moreover, these low levels of sexual hormones lead to muscle atrophy and total muscular mass decrease. Therefore, a hormonal deprivation on muscle function damages the defensive mechanism against falls, thus increasing the incidence of fractures in these individuals.

Nowadays, it is widely accepted that bone metabolism disorders in patients with low levels of estradiol can increase the risk of fractures^[38,39]. This might be caused by a deficit of testosterone transformation into estradiol due to an aromatase enzyme dysfunction. There are several reports along these lines documenting severe male osteoporosis induced by mutations of the estrogen-receptor of the aromatase enzyme^[40,41].

Low serum levels of vitamin D: Vitamin D plays a major role on bone health in all age groups. In younger individuals it contributes to achieving a good peak bone

mass whereas in adults, lower levels of vitamin D lead to substantial losses in bone mass and subsequently to osteoporosis^[42]. Two sources of vitamin D are found in humans: (1) Epidermal synthesis of Vitamin D3 (colecalciferol) under sunlight influence (UV-B radiation); or (2) Absorption in the gastrointestinal tract, from the diet or nutritional supplements [in some countries certain food is supplemented with Vitamin D2 (ergocalciferol)]. Vitamin D is then metabolized in the liver into 25-hydroxyvitamin D (25-(OH) D)^[42].

Vitamin D stimulates intestinal calcium absorption. Few food groups contain high concentrations of vitamin D: fatty fish, fish-liver oils (cod liver oil), and liver. Not all of them are available in all countries or they are not consumed regularly by the adult population. Moreover, certain foods such as milk, margarine, butter, orange juice and cereals are not regularly supplemented with Vitamin D in many countries, such as Spain. Therefore, daily requirements of Vitamin D are frequently insufficient in some regions^[43,44]. Similarly, the substantial epidermal synthesis of Vitamin D in younger populations is reduced in the elderly^[44]. Curiously, in Spain, where the amount of sunlight radiation is high, the older population is usually poorly exposed to this radiation, and the synthesis of Vitamin D is even lower^[45].

The European SENECA Study, carried out in 12 European countries, showed serum levels of 25 hydroxyvitamin D lower than 30 ng/mL in 36% of the elderly population^[46]. In our country, a recent study also showed low levels of 25-hydroxyvitamin-D serum in elderly people, with a 95% sensibility to detect secondary hyperparathyroidism^[47].

The presence of low levels of vitamin D in men over 65 years of age is very common. It has been considered that about 15% of male osteoporosis cases are caused by this deficiency^[48]. Several studies^[49-51] have found a high prevalence of 25-hydroxyvitamin-D serum levels below 25 ng/mL in the population over 65 years of age (standard levels are above 35 ng/mL).

This has a major impact on bone metabolism^[52]. Firstly, a decrease in the intestinal absorption of calcium decreases the serum ionized calcium concentration. This gives way to an increased production of parathyroid hormone (PTH) which stimulates bone osteoclasts, releasing calcium into the bloodstream. PTH also increases renal resorption of calcium and renal excretion of phosphorus.

All these metabolic disorders, triggered by the vitamin D deficiency, lead to a significant increase of bone resorption and, consequently, to a decrease of BMD.

Our experience with 267 patients sustaining a hip fracture, with a mean age of 80.3 years, proved that 67% of them had vitamin D serum levels below 25 ng/mL at the time of admission. These results assert the high frequency of this deficiency in men with osteoporosis.

Poor calcium intake: The correct daily calcium intake is essential for bone metabolism^[44]. An intake below the

recommended 1.200 mgrs per day is quite usual in the population over 65 years of age. This is directly linked with a low mineral bone density. If, as usual, it is also associated with low vitamin D serum levels, the negative consequences for the mineral metabolism and the health of the individuals are even greater^[39].

Influence of tobacco: Among the toxic substances involved in the etiology of osteoporosis, tobacco plays a major role^[53]. Smokers have been found to have lower BMD and consequently a significantly higher risk of fragility fracture. Smoking is endemic within the Spanish population over 65. It should also be noted, that this harmful effect has usually been maintained for many years, in most cases since adolescence.

Alcohol: Alcohol is another toxic substance affecting BMD^[54,55]. It is also quite well rooted in the Spanish population. A significant percentage of people in this country are regular drinkers, particularly men. A recent population study of a large, representative sample of the population aged 55 or more in Zaragoza (Spain) has documented that, among men, the proportion of heavy drinkers (WHO criteria) is 16.7%, in comparison to only 0.7% among women^[56]. Heavy drinking may lead to significant adverse effects, not only in the mineral metabolism, but also in the whole metabolic system. It might also be hypothesized that different rates of osteoporotic fractures in men and women are influenced by differences in alcohol consumption.

Coffee consumption: Contrary to what was classically thought, we now know that there is not enough evidence to link heavy coffee consumption with osteoporosis in men^[57].

Hormonal treatments: Prostate cancer, a prevalent male disease, can be treated in some cases with androgenic suppression, which is a major risk factor for osteoporosis. In a recent study carried out by Adler^[58], 33% of patients with prostate cancer who were treated with androgenic deprivation therapy, showed low BMD, fulfilling osteoporosis criteria in DXA scanning of their hip and spine.

Adler applied the new fracture prediction algorithm tool (FRAX) with corrected femoral neck T-score, reporting that 17% of these patients required treatment. Without any correction this percentage increased to 54% of the patients. In our experience with 87 patients undergoing hormonal treatment for prostate cancer for more than one year, and whose mean age was 78.3 years, 27.58% of them showed a BMD lower than 2.5 standard deviations in the DXA scanning.

Other causes: Other causes involved in the etiology of secondary osteoporosis in men are: (1) Anticonvulsant therapy; (2) Prolonged steroid therapies; (3) Patients with

rheumatoid arthritis or ankylosing spondylitis; (4) Primary hyperparathyroidism; (5) Hepatic or renal disease; (6) Malabsorption syndromes; (7) Transplanted patients or those treated with immunomodulators; (8) Thyrotoxicosis; (9) Diabetes mellitus; (10) Hypercalciuria; and (11) Patients with human immunodeficiency virus (HIV). Overall we can say that there is no specific pathology affecting male bone metabolism, but various conditions or medical treatments can cause secondary osteoporosis. And these conditions may affect similarly individuals of both genders.

DIAGNOSIS

The key question is how to establish the diagnosis in men with no apparent causes of secondary osteoporosis, nor previous history of fragility fractures. An accurate assessment of risk factors should be carried out in patients over 50 years old. Special attention should be paid to patients with a fragility fracture before the age of 50 years, as well as to those patients suffering diseases or treated with drugs that can cause a loss of BMD^[11]. Several clinical guidelines recommend routine DXA scanning after the age of 70 years in the general population^[11]. In a recent study conducted by Schousboe^[59], the cost-effectiveness of a DXA study was assessed. This author studied men aged 65 or older treated with oral bisphosphonates for 5 years and with a history of fragility fractures, in addition to the male population aged from 80 to 85 with or without a history of previous fractures. The author concluded, after studying quite a large sample, that bone densitometry may be cost-effective for patients aged 70 years or older, with the cost of oral treatment using bisphosphonates below 500\$ per year.

It seems evident that an accurate medical history should be completed prior to the densitometric studies in older men. The main risk factor is the presence of a previous fragility fracture, especially if it happened before 50 years of age. We can also say that male population over 70 years old is at risk for osteoporosis. This risk would be even higher in cases with disorders affecting bone metabolism.

In patients with a BMD under 2.5 or more standard deviations, measured by DXA scanning, standardized laboratory tests should be performed^[11,50].

These laboratory tests should include: calcium and creatinine serum levels, biochemical markers of bone remodeling e.g., bone resorption markers: serum C-Telopeptide (CTx) and urinary N-Telopeptide (uNTx); and bone formation markers: serum bone-specific alkaline phosphatase (BSAP) and osteocalcin.

High levels of BSAP in primary hyperparathyroidism and low levels of osteocalcin in endogenous hypercorticism are the most relevant data reported in endocrine diseases associated with osteoporosis, high level of bone turnover markers, may be associated with prevalent vertebral fractures^[60]. Depending on the type of patient, se-

rum proteins, protein electrophoresis, and Bence-Jones protein should be determined, as well as serum levels of testosterone and vitamin D in individualized cases. Finally, in specific cases, anti-HIV antibodies should be investigated.

RISK OF FRACTURE

A quantification of the fracture risk is essential to initiate the treatment of osteoporosis. Several authors have studied the BMD decrease and its predictive value for the estimation of fracture risk^[61-64]. There is no agreement in literature about the hypothetic linear association of BMD declining with fragility fracture risk. Similarly, there is no consensus in the predictive value of BMD depending on the sex of the patient. The EVOS study of vertebral fractures, suggested that the risk of fracture is similar in men and women^[61]. De Laet *et al.*^[65], in the Rotterdam study in 1998, reported a significant predictive value of BMD for fracture risk; and a similar relationship between hip fracture and femoral neck BMD in men and women. Later studies, using the same database, found a higher incidence of vertebral fractures in women^[66]. Although BMD is an important predictor for fracture risk^[67], a tool with which to obtain an accurate determination of fracture risk in men is still necessary^[68]. The importance of age as a fracture predictor was reported by Kanis *et al.*^[13], in addition to the relevance of previous fragility fractures^[69]. In a recent meta-analysis work^[70] to analyze the risk factors in men that provide evidence for association with low bone mass and fractures, showed statistical significance the following: age, low body mass index, history of prior fractures, history of falls, current smoking, excessive alcohol use, chronic corticosteroid therapy, stroke and diabetes. None of these associations were of large magnitude from the statistical point of view. This heterogeneity of factors difficulties the decision to counsel a screening in men to determine bone mass by DXA scan. However, the American Society of Endocrinology in a recent publication^[71] recommended practice of measuring bone mass to all men over age 70 and men aged 50-69 who have risk factors.

A tool integrating predictive clinical factors with or without BMD measurements has been developed by the WHO in collaboration with the group of Sheffield Metabolic Bone Diseases^[72]. The FRAX tool has been reported to be a useful predictor at 10 years follow-up, for fractures in the hip and in other locations^[73]. Nevertheless, it seems that this tool needs to be validated in other countries^[74-76].

Optionally, BMD can be included for fracture risk calculation since bone strength is closely related to BMD. In this regard, both micro and macro-mechanical models have been suggested, with different characteristics and methodologies to correlate bone strength and BMD. These models can be used for prediction of bone strength at different ages, or to prediction of fracture risk^[77-80].

Concerning finite element (FE) simulation, as alternative tool to predict fracture risk, several works can be found in the literature^[77-87]. The development of new techniques for measuring BMD has focused much of the recent research in the clinical setting, but the mechanical aspects have not been adequately studied^[88-91]. Nonetheless, all models assume that BMD is the basic measurement, and it should therefore be used as a benchmark in predicting fracture risk.

From the mechanical point of view, the exposition of the bone to cyclic loads decreasing in strength over the time produces a progressive damage which can lead to a final fracture. It seems apparent that Damage Mechanics and Fracture Mechanics criteria should be incorporated in any model intending to obtain reliable results. Recent works are focused in that direction^[92]. However, till now no model considering the complete correlation between clinical and mechanical magnitudes related to fracture behaviour has been developed.

TREATMENT OF THE OSTEOPOROSIS IN MEN

The indication for treatment of osteoporosis in men with a previous fragility fracture is clear. The key question is whether a DXA screening should be carried out on the rest of the male population, as has been previously recommended by several clinical practice guidelines^[59,93,94]. The use of the FRAX tool could help us make a therapeutic decision for individualized cases. The National Osteoporosis Foundation (NOF) recommends drug therapy in patients over 50 years of age with vertebral fracture; in those with BMD below 2.5 SD; and depending on the risk of fracture estimations at 10 years, in those with BMD figures from -2.5 to -1 SD.

Non-pharmacological treatment

As a general rule, a healthy lifestyle, a proper nutrition and the suppression of toxic substances should be recommended. An adequate daily intake of calcium and Vitamin D should also be encouraged. Low blood calcium levels are often present in men older than 70. The intestinal absorption of calcium is usually diminished in the elderly population^[94]. Oral treatments for chronic comorbidities that interfere with calcium absorption^[40] and the age related decline in glomerular filtration contribute to this situation. In individuals from 50 to 70 years of age with a low calcium intake, oral supplementations of 1000 mg/d of calcium carbonate are usually recommended. In those older than 70, the estimated daily requirements are 1200 mg.

An adequate vitamin D supplementation is also required. We recommend 600 U.I/d in individuals from 50 to 70 years of age and 800 U.I/d in patients older than 70 years^[42,95].

Bone is a living tissue that responds to repetitive loadings with increased biomechanical resistance. Weight

Table 1 Published articles on the pharmacological treatment of male osteoporosis

Ref.	No. cases	Follow-up	Type of trial	BMD increase	Outcome parameter	BTMs
Bisphosphonates treatment						
Orwoll <i>et al</i> ^[108]	241	2 yr	Double-blind	+	Vertebral fracture	NS
Ringe <i>et al</i> ^[110]	316	1 yr	Open label, randomized	+	Vertebral fracture	NS
Ringe <i>et al</i> ^[109]	90	2 yr	Comparative	+	NS	NS
Boonen <i>et al</i> ^[111]	284	2 yr	Double-blind	+	Vertebral fracture	+
Orwoll <i>et al</i> ^[112]	132	1 yr	Placebo-controlled, randomized	+	NS	+
Lyles <i>et al</i> ^[114]	2127	1.9 yr	Double-blind	+	Vertebral fracture	NS
Adachi <i>et al</i> ^[116]	2127	3 yr	Double-blind	NS	HRQoL improve	NS
Sambrook <i>et al</i> ^[115]	265	1 yr	Double-blind	+	NS	NS
Genant <i>et al</i> ^[113]	89	1 yr	Placebo-controlled	+	NS	NS
Anabolic treatment						
Orwoll <i>et al</i> ^[121]	437	11 mo	Randomized	+	NS	NS
Kaufman <i>et al</i> ^[122]	325	42 mo	Placebo-controlled	+	Vertebral fracture	NS
Leder <i>et al</i> ^[124]	17	42 mo	Prospective	+	NS	+
Finkelstein <i>et al</i> ^[123]	42	30 mo	Randomized controlled	+	NS	+
Testosterone treatment						
Finkelstein <i>et al</i> ^[125]	21	31 mo	Prospective	+	NS	NS
Katznelson <i>et al</i> ^[126]	36	18 mo	Controlled	+	NS	+
Amory <i>et al</i> ^[127]	70	36 mo	Randomized	+	NS	NS
Benito <i>et al</i> ^[128]	10	24 mo	Prospective	+	NS	NS
Monoclonal antibody therapy						
Smith <i>et al</i> ^[131]	1468	36 mo	Double-blind	+	NS	NS
Smith <i>et al</i> ^[133]	1468	36 mo	Double-blind	NS	NS	+
Toremifene						
Smith <i>et al</i> ^[134]	847	2 yr	Placebo-controlled	NS	Vertebral fracture	NS

Bone mineral density (BMD) increase mean: Sign +: Increase of BMD. Outcome parameter meaning: (1) Vertebral fracture (decreases); and (2) Health-related quality of life improve the health-related quality of life. BTMs: Improvement of biochemical markers; HRQoL: Health-related quality of life. NS: Not studied.

bearing physical activity has been shown to optimize bone mass^[96]. Recommended exercises are: weight training, jogging, walking, climbing stairs, gardening, dancing and aerobic sports in general^[42]. Strength training machines for resistance exercises can be recommended as well. Significant benefits have been proven with the practice of these activities for just half an hour every day: (1) Increased muscular strength; (2) Preserved or increased bone mass; (3) Improved coordination and (4) Improved general health, self-care and activities of daily living^[42,96].

Daily practice of aerobic activity, such as walking and coordination exercises (tai-chi) should be encouraged in the elderly population^[42]. The practice of regular physical exercise has shown not only to be effective in preventing BMD declining, but also in preventing falls^[97-100]. Falls are a major risk factor in patients with osteoporosis. In relation to this, fall prevention programs have also proved to be very effective^[101-106].

Pharmacological treatment

There are significant differences in the pharmacological treatment of osteoporosis between men and women. The list of pharmacological agents approved by United States FDA for the treatment of female osteoporosis is larger than the one approved for male osteoporosis. The main differences are due to the level of evidence in published trials supporting each treatment. Drugs approved for female osteoporosis have been tested in

large, multinational, randomized control and placebo-controlled trials that included thousands of patients. These drugs have shown efficacy in the prevention of vertebral fractures, and less consistently in the reduction of the incidence of non-vertebral fractures. In contrast, the available articles dealing with the pharmacological treatment of male osteoporosis are mainly based on the increase of BMD. Trials that, either provide evidence on vertebral fracture prevention or the decreased number of new vertebral fractures after suffering a prior fracture, are scarce. Furthermore, the size of samples studied and the follow up periods tested are significantly more reduced in males than in females^[107]. The methodology used is shown in different studies, from which the number of patients treated and the effects demonstrated by the drugs used are detailed in Table 1.

The drugs most widely used are antiresorptive agents, anabolic agents, hormonal therapy and more recently, for secondary osteoporosis, monoclonal antibody therapy.

Treatment with bisphosphonates: The most extended treatment for osteoporosis is oral therapy with bisphosphonates. However there is little evidence in literature of their effectiveness in male patients.

Several studies have demonstrated that alendronate improves BMD after 2 years of treatment in both spine and femoral neck. There is also evidence of a significant decrease in the incidence of vertebral fractures, although this decrease has not been demonstrated for fractures in

other locations^[108]. Another study showed that a combination of weekly alendronate with alfacalcidol, compared to a combination of alendronate, vitamin D and calcium, was more effective in the increase of BMD in the lumbar spine and in the hip at the two year follow-up^[109].

Other studies assessing oral treatment with risendronate have also confirmed an increase in BMD in both spine and hip, and a significant reduction in the incidence of vertebral fractures^[110]. Once-weekly risendronate for 24 mo showed a significant increase of BMD in lumbar spine and hip, but showed no difference in the number of new fractures when compared with the placebo group^[111].

After a monthly dosis of Ibandronate over a 2-year period, it has been demonstrated that it increases BMD in lumbar spine and hip, to decrease the bone resorption marker serum C-terminal telopeptide of type 1 collagen (sCTX) and to increase the bone formation marker BSAP, in people with low BMD^[112]. One year of ibandronate treatment was associated with a significant improvement in some parameters of hip geometry, suggesting that ibandronate may improve strength of the hip^[113].

However, further investigation is needed to confirm the effectiveness of oral bisphosphonates in decreasing the incidence of hip and other non-vertebral fractures.

Intravenous bisphosphonates (zoledronic acid) have been reported to decrease the incidence of fractures, but their use has not shown a significant reduction in the rate of new hip fractures in those patients who suffered a previous fracture^[114]. A study published in 2012 shows that the zoledronic acid clearly increases the BMD^[115].

In a recent study about men and women who had suffered a hip fracture, the effectiveness of zoledronic acid was evaluated by means of the health-related quality of life, demonstrating a significant improvement of their functional scores^[116].

Although there are not as many studies on the use of bisphosphonates in men as there are in women, some authors claim that their effectiveness is similar in both genders^[117].

Finally, in prostate cancer patients treated with androgenic deprivation and presenting a strong BMD decrease, bisphosphonates have been proved as an effective therapy for bone loss^[118,119].

Treatment with anabolic drugs: Anabolic treatment with parathyroid hormone derivatives has been approved by the FDA for the treatment of men at high risk of fragility fracture; and for patients treated with steroids suffering a significant reduction in their BMD.

According to Hodzman, the main indications for treatment with parathyroid hormone in men are severe osteoporosis or an unsatisfactory response to antiresorptive therapy^[120].

Parathyroid hormone has demonstrated to be effective in the treatment of male osteoporosis. A significant

increase in the BMD of patients treated with subcutaneous doses of 20 micrograms of teriparatide per day has been documented. This BMD increase was demonstrated in both femoral neck and spine, as well as in patients with or without hypogonadotropic hypogonadism^[121]. Evidence has shown that teriparatide may decrease the incidence of vertebral fractures, but the reduction of fractures in other anatomical locations has not been proved^[122]. Another recent investigation has demonstrated the efficacy of teriparatide in increasing BMD in eugonadal men and in a group of men and women with BMD below the standard figures corresponding to their age^[123,124].

The controversy of treatment with parathyroid hormone derivatives remains in their possible side effects. These side effects have not been extensively studied so far. Therefore, these anabolic treatments should be kept in use for up to a maximum of two years. A good option, after the anabolic interruption, would be to continue the therapy with bisphosphonates.

Treatment with testosterone: Testosterone treatments for male osteoporosis are not usually recommended in the clinical practice guidelines. This hormonal therapy may produce severe secondary effects which include: polycythemia, sleep apnea, benign prostate hypertrophy, and even prostate cancer. Due to these side effects it has not been used as a standard treatment for osteoporosis.

However, it seems apparent that testosterone, as was demonstrated in 1989^[125], could markedly increase the quality and quantity of bone in young patients with hypogonadism. In 1996 the same group demonstrated the positive effects of testosterone in order to increase the lean muscle mass and trabecular bone density^[126].

Subsequent investigations^[127,128] have found positive effects on BMD and bone quality in osteoporotic elderly patients treated with testosterone. Positive effects have been detected not only on bone but on muscle mass^[129]. However, it still does not represent a treatment of choice in male osteoporosis. The main problem of treatment with testosterone is little published evidence and safety problems with testosterone replacement therapy^[130].

Other treatments: Many recent studies carried out on prostate cancer patients undergoing hormonal treatment, showed good results using a monoclonal antibody (Denosumab)^[131-133]. This antibody, which acts on the RANK-ligand, demonstrated an increase in BMD and a significant decrease in the incidence of vertebral fractures for these patients.

A recent study with a drug in phase III (Toremifene) has proved effective to prevent occurrence of new vertebral fractures in patients treated with androgenic deprivation therapy^[134].

In a near future we might use other drugs, currently in development, which could be effective in the treatment of male osteoporosis.

CONCLUSION

The adequate diagnosis and management of male osteoporosis remain controversial. The origin of idiopathic male osteoporosis should be further investigated. Mechanisms of trabecular bone loss in men are not fully defined. We don't know if the same range of standard deviations applied to women in DXA studies to assess osteoporosis, are applicable to men, especially considering that many fractures occur in men with less than 2.5 SD in densitometric studies. There are no standard criteria for the implementation of diagnostic screening tests in men. There are obvious differences in bone structure and properties between men and women, but further investigations are needed to ascertain the fracture risk assessment in men, prior to its clinical application. A research area in the future could be the use of simulation models using the Finite Element Method, these researches should be focused to establish an appropriate and reliable correlation between clinical and mechanical magnitudes, in order to develop more robust models that can be applied to evaluate the bone strength, and therefore the fracture risk, at different ages and in any conditions of the patient (with-out or under treatment).

Bone loss and fracture risk in men are clearly associated with decreased levels of bio available estrogens. There is little evidence on the effectiveness of bisphosphonates or treatments using anabolic steroids in humans, indicating the need for further studies. Testosterone is indicated just for symptomatic hypogonadism.

Recent research in to new treatment options, like the use of RANK-ligand monoclonal antibody (Denosumab) and other drugs still in phase III (Toremifene) opens new perspectives, although more evidence is still needed.

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