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Osteoporosis in men and steroids

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Osteoporosis in men

Osteoporosis is a bone disease characterized by a decrease in bone mineral density (BMD) and an increased risk of fragility fractures. Osteoporotic fractures, particularly hip fractures, cause significant mortality and morbidity in men and lead to considerable social costs in this population, including direct medical costs and indirect costs resulting from reduced quality of life, disability and death[1].

Of all osteoporotic fractures, it is hip fractures that contribute to the highest morbidity and mortality in men. Each year about 80,000 men will have a hip fracture. Of these, one in three will die during the first year after this hip fracture and another third will fracture again[2]. However, there is a lack of awareness among healthcare professionals about the need to screen men for osteoporosis so that male osteoporosis remains largely underdiagnosed and untreated.

Much progress has been made in identifying men who should benefit from treatment (for example, the FRAX management algorithm is applicable to men). However, controversy persists regarding, for example, the criteria for defining osteoporosis in men on the basis of bone mineral density (BMD).

There are important differences between men and women in terms of bone development and loss. Men generally begin puberty later in life and continue through puberty longer than women, which may cause differences in reaching higher peak bone mass in men. While both men and women lose bone mass during aging, men undergo a more gradual decline in sex steroid levels with aging, which may explain the less severe decline in bone strength[3]. There are also differences in the way bone remodeling occurs in men and women. In men, as the trabecular surface area decreases, bone formation increases. In general, the result is a smaller BMD loss in men than in postmenopausal women[4].

Male osteoporosis is generally classified into two different categories, primary and secondary osteoporosis. Types of primary male osteoporosis include age-related osteoporosis and idiopathic male osteoporosis. Age-related osteoporosis in men, as in women, is more likely to occur as age increases, and is generally seen in men over 70. Idiopathic male osteoporosis, on the other hand, is generally defined as one or more fractures and a low BMD in men before 65-70 years of age[5]. There are multiple theories about the etiology of idiopathic male osteoporosis, such as genetic factors or family history.

Male osteoporosis that can be linked to or explained by causes other than aging is generally classified as secondary male osteoporosis. Chronic diseases associated with secondary osteoporosis are listed in table 1 and include diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, rheumatoid arthritis, osteoarthritis, and multiple sclerosis. Other causes of secondary osteoporosis in men include alcohol abuse, excess glucocorticoids (exogenous or endogenous), and hypogonadism (including that produced by the use of androgen deprivation therapies). If osteoporosis is due to another condition, the underlying cause must be treated. Whenever possible, potential offending agents (e.g. glucocorticoids, alcohol, tobacco, etc.) should be eliminated.

A recently presented sub-analysis of the MrOS cohort evaluated secondary causes of osteoporosis in subjects who had low BMD versus those who did not have low BMD, and most were similar in terms of their risk factors[6]. Therefore, it is not established that secondary osteoporosis is actually more common in men. Men may be less likely to be referred for a bone densitometry assessment in the absence of specific risk factors for osteoporosis. Furthermore, there may be a general tendency for healthcare professionals to search for causes of secondary osteoporosis in men more carefully than in women.

The osteoporosis treatment drugs in men are: bisphosphonates (alendronate, risedronate, zoledronic acid), denosumab and teriparatide. All of these agents inhibit bone resorption, except teriparatide, which promotes bone formation. The antifracture efficacy of these drugs has been studied mainly in postmenopausal women, and there are few clinical trials for the treatment of osteoporosis in men whose primary objective is to reduce fractures. Most of the studies in men have a small sample size and are aimed at changes in BMD or markers of bone remodeling. In them, the incidence of fracture is included as a secondary aim. Therapeutic equivalence is justified on the basis that if BMD changes are similar to those observed in women with the same duration of treatment, it is assumed that the anti-fracture efficacy effects will also be similar[7].

Bisphosphonates are often prescribed as first-line treatment: alendronate[8], risedronate[9], and zoledronic acid[10] have been shown to reduce vertebral fracture risk in men. Risedronate has also shown reductions in non-vertebral and hip fractures in men.

Denosumab increases BMD in the lumbar spine, total hip, femoral neck, trochanter, and radius in men[11]. In men who received androgen deprivation treatment for prostate cancer, denosumab has also shown a decrease in the incidence of new vertebral fractures[12].

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Table 1. Secondary causes of osteoporosis in men

Medicines
Anticonvulsants
Chemotherapy
Glucocorticoids
Thyroid hormone
Chronic diseases
Chronic obstructive pulmonary disease (COPD)
Gastrointestinal disorders: malabsorption syndromes, inflammatory bowel disease, celiac disease, primary biliary cirrhosis, postgastrectomy, etc.
Hypercalciuria
Hyperthyroidism
Hyperparathyroidism
Hypogonadism
Neuromuscular disorders
Systemic diseases: mastocytosis, malignant tumors
Rheumatoid arthritis
Nutritional deficit
Calcium deficiency and/or low serum levels of vitamin D
Alcohol abuse
Post-transplant osteoporosis
Sedentary lifestyle
Tobacco abuse

The parathyroid hormone, teriparatide, is the only anabolic agent approved for treating severe or glucocorticoid-induced osteoporosis in men, as it has been shown to decrease the incidence of vertebral fractures significantly[13,14].

Uncontrolled studies with a small sample size suggest the immediate use of bisphosphonates after finishing treatment with teriparatide in order to maintain or increase the bone mass gains produced by the drug[15].

The few studies available on the effect of androgens in elderly men with idiopathic osteoporosis do not allow recommending their use in the absence of overt hypogonadism. Intramuscular testosterone (but not from transdermal administration) produces an increase in BMD but has not shown a reduction in the occurrence of fractures[16,17]. One area of uncertainty is when men with hypogonadism should be treated with an osteoporosis drug in addition to testosterone. There are no data from clinical trials addressing this issue and, in particular, the effect of testosterone therapy on the risk of fracture has not been assessed. We agree with the Endocrine Society recommendation to add a pharmacological agent with proven antifracture efficacy in hypogonadal men treated with testosterone whose risk of fracture is considered high[18].

The drug choice strategy for men would be similar to that for women:

a) alendronate or risedronate in patients without digestive problems in whom adequate adherence is expected.

b) zoledronate or denosumab in older patients with digestive intolerance and polymedicated with a higher risk of hip fracture.

c) teriparatide in severe osteoporosis with a high risk of fracture.

For the same reasons as in women, the administration of calcium and vitamin D is recommended for all patients. And androgens, as we have already mentioned, are only justified if there is hypogonadism. Even in this case, one of the above drugs should probably be associated if, in addition to hypogonadism, there is osteoporosis.

Steroid osteoporosis

Glucocorticoids (GC) play an important role in the treatment of many inflammatory conditions. An estimated 1% of the US population receives long-term treatment with GC[19]. However, the use of GC causes significant toxicity, including bone loss and fractures. More than 10% of patients receiving long-term GC treatment are diagnosed with a fracture and 30-40% have radiographic evidence of vertebral fractures[20,21].

Vertebral fractures are particularly characteristic of corticosteroid osteoporosis, although the risk of non-vertebral fractures, including hip fracture, is also increased. In subjects who started CG in the last 6 months, the annual incidence of vertebral fracture is 5.1% and non-vertebral fracture is 2.5%[22]. And in patients with rheumatoid arthritis, it has been seen that 60-182 days after suspending the SLN the risk of fracture is 29% lower than in those who continue to receive GC treatment, and at 12 months this risk decreases so that it is already similar to the risk of patients who do not receive GC[23].

The widespread use of corticosteroids today has made glucocorticoid-induced osteoporosis (GIO) the most common cause of drug-associated osteoporosis. Glucocorticoid administration is the most common cause of secondary osteoporosis. Risk factors for fracture in GIO include low bone strength at the beginning of GC treatment and the rate of decrease in bone mass during treatment, which is largely determined by the dose and duration of GC use.

In all available studies, prednisone doses greater than or equal to 7.5 mg/day cause loss of BMD. Subjects who receive these daily doses have an increased risk of loss of BMD (which occurs mainly in the first six months), of vertebral fracture (RR=2.83; 95% CI, 2.35-2.40) and hip fracture (RR=2.21; 95% CI, 1.85-2.64)[24].

The risk of fracture increases especially after the third month of treatment. There is a clear dose-dependent relationship in the risk of fracture and 30-50% of chronically-treated subjects will suffer fractures[25]. Furthermore, these fractures appear with higher BMD values in relation to what usually occurs in postmenopausal osteoporosis.

Advances have been made in understanding the mechanism of production of GIO, as it appears to be different from that of postmenopausal osteoporosis. The most important changes observed in GIO are a decrease in osteoblast activity, which translates into a decrease in the synthesis of the bone matrix, and a decrease in the half-life of the osteoblasts[26]. The loss of bone mass occurs, above all, in the trabecular bone, where it reaches up to 30% in some studies.

Thus, the loss of bone mass associated with corticosteroids should receive optimal treatment, particularly in those patients already with other factors for a high risk

Table 2. Adjustment of the calculation of risk of fracture in the FRAX tool according to the dose of GC

Daily dose of prednisone (mg)	Medium setting for osteoporotic major fracture probability	Medium fit for hip fracture probability
<2.5	-20%	-35%
2.5-7.5	None	None
≥7.5	+15%	+20%

Adapted from Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int. 2011;22:809.

of fracture. For proper management, an assessment of the risk of fractures should then be made, since patients with the highest risk of fracture are those who are most likely to benefit from drug therapy. Therefore, patient selection must be made based on fracture risk, as determined by a combination of BMD and clinical risk factors[27].

Patients with established osteoporosis (history of fragility fracture or T-score on their BMD -2.5) have the highest risk of fracture.

For patients without established osteoporosis, fracture risk can be assessed using a fracture risk calculator, such as the FRAX fracture risk assessment tool. FRAX estimates the 10-year probability of fracture for untreated patients between 40 and 90 years of age, using femoral neck BMD and clinical risk factors, including glucocorticoid exposure. FRAX does not take into account the dose or duration of glucocorticoids, so Kanis et al. have proposed an adjustment of the FRAX risk estimates according to the GC dose[28]. For patients taking prednisone >7.5 mg/day or equivalent, the risk estimate should be increased by 15 percent for major osteoporotic fracture and by 20 percent for hip fracture (Table 2).

Reasonable thresholds corrected for glucocorticoids to indicate high, moderate, and low risk of fracture are as follows:

- High risk: FRAX hip fracture or major combined osteoporotic ≥3% and ≥20%, respectively.
- Moderate risk: FRAX hip fracture or major osteoporotic combined between 1 to 3% and 10 to 19%, respectively.
- Low risk: FRAX hip fracture or combined major osteoporotic <1% and <10%, respectively.

Numerous clinical guidelines and updates on the treatment of OIC have already included this management of the risk of fracture in these patients through the FRAX tool: National Osteoporosis Guideline Group (NOGG)[29,30], American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis[31], Joint IOF-ECTS GIO Guidelines Working Group[32,33], Spanish Society for Research in Bone and Mineral Metabolism[34].

Some patients receiving glucocorticoids are at high risk, even if they do not meet the FRAX criteria for high risk. For example, for patients with clinical risk factors for fracture, low lumbar spine BMD, but normal femoral BMD in the neck, FRAX is likely to underestimate the risk of fracture. This situation is especially likely in patients taking glucocorticoids, who are more likely to cause axial than hip osteoporosis. Therefore, the intervention guidelines with or without the use of FRAX provide only general clinical guidance. Treatment must be individualized through shared decision-making between the patient and the clinician.

General non-pharmacological measures should be taken in all patients who are to receive corticosteroids for ≥3 months and consist of:

- Prescribe corticosteroid treatment at the lowest dose and for the shortest period possible and replace topical corticosteroids (such as inhaled corticosteroids or enemas for asthma or inflammatory bowel disease respectively) whenever possible.
- Promote physical exercise in these patients, as it prevents bone loss and muscle atrophy.
- Patients receiving GC should have a diet rich in calcium and protein.
- Avoid toxins such as tobacco and excess alcohol.
- Fall prevention measures.

Since bone loss and the incidence of fractures increase rapidly after initiation of GC treatment, therapeutic intervention should be started as soon as possible, ideally from the start of steroid therapy if GC treatment is suspected to last more than 3 months.

In 2017, the American College of Rheumatology (ACR) published guidelines to prevent and treat glucocorticoid-induced osteoporosis, with recommendations and algorithms to assess and categorize the risk of fracture, both initially and at follow-up[31]. We currently have a new review in 2020 that summarizes these ACR recommendations, as well as advances in treatment since then[35].

Postmenopausal women and men >50 years: Drug therapy is indicated for postmenopausal women and men >50 years at moderate to high risk of fracture.

- For men in their 50s and postmenopausal women (who are initiating or are chronically treated with any dose of glucocorticoids for any duration) who have osteoporosis (prior fragility fracture and/or a T-score of BMD-2.5) in initial evaluation, we recommend drug therapy.
- For high-risk men in their 50s and postmenopausal women who initiate or are chronically treated with any dose of glucocorticoids for any duration and have T-scores between -1.0 and -2.5, we suggest drug therapy.
- For postmenopausal women and men >50 years with T-scores between -1.0 and -2.5 who have an absolute risk corrected for glucocorticoids, calculated by FRAX below these thresholds, we suggest a pharmacological treatment if they are taking 7.5 mg/day of prednisone or its equivalent for an expected duration of 3 months.

Pre-menopausal women and younger men: In the absence of definitive data, the decision to initiate drug treatment should be individualized in pre-menopausal women and younger men. The FRAX tool was not developed for

use in men <40 years or pre-menopausal women. In pre-menopausal women and younger men enrolled in clinical trials for glucocorticoid-induced osteoporosis, fractures were generally rare in both treated and control groups. The risk of fracture in these patients taking glucocorticoids is not clearly defined and may differ from the risk of fracture reported in other populations treated with glucocorticoids.

Bisphosphonates are the first-line drugs in the treatment of GIO for patients with moderate or high risk of fracture, based on their efficacy, safety and low cost. Zoledronate (intravenous), teriparatide, and denosumab are second-line options for patients at high risk of glucocorticoid fracture who cannot tolerate oral bisphosphonates[36-38]. If the patient has several vertebral fractures, treatment with teriparatide is justified[39,40]. As we have already mentioned, calcium and vitamin D should be administered. The active metabolites of vitamin D by themselves have a certain preventive action on bone loss, but there are no convincing data on their effect in preventing fractures[41]. Treatment should be maintained while the patient receives prednisone at the indicated doses. If this circumstance ceases to occur, but the patient meets the general criteria for receiving antiosteoporotic treatment, this should be maintained. In patients treated with corticosteroids, densitometric monitoring at shorter intervals may be justified than in other patients with osteoporosis.

The use of alendronate 5-10 mg/day for 48 weeks has been shown to increase bone mass. A study by Adachi et al. reported an increase in bone mineral density of the lumbar spine by 2.8% (5 mg/day) and 3.9% (10 mg/day) in patients with prolonged glucocorticoid therapy[42]. Risedronate at a dose of 5 mg/day increases bone mass and also reduces the risk of fracture[43]. Zoledronic acid is approved by the Food and Drug Administration (FDA) for the treatment and prevention of osteoporosis in postmenopausal men and women, as well as glucocorticoid-induced osteoporosis. The adequate dose of zoledronic acid is 5 mg intravenously infused once a year, which has been shown to reduce the risk of spinal, non-vertebral and hip fracture in postmenopausal women with osteoporosis[44].

Denosumab is an antibody against RANKL, also with antiresorptive action on bone remodeling, which is used for the treatment of primary osteoporosis. Because denosumab is not filtered by the kidneys, it may be a therapeutic option for patients with renal dysfunction who cannot tolerate bisphosphonates.

In the study by Dore et al. in patients with rheumatoid arthritis receiving GC treatment, it demonstrated an increase in bone mineral density and a reduction in resorption, compared to placebo[45].

Denosumab has shown a greater increase in BMD in the lumbar spine compared with risedronate at one year in the subpopulation that started glucocorticoid treatment, at one year (3.1% vs. 0.8%; p<0.001) and at 2 years (4.6% vs. 1.5%; p<0.001). In addition, a significantly higher mean percentage increase in BMD from baseline compared to risedronate in the total hip, femoral neck, and trochanter of the hip[46].

The study was not designed to demonstrate a difference in fractures. At one year, the incidence of new vertebral fractures per patient was 2.7% (denosumab) compared with 3.2% (risedronate). The incidence of non-vertebral fractures per patient was 4.3% (denosumab) versus 2.5% (risedronate). At 2 years, the corresponding figures were 4.1% versus 5.8% for new vertebral fractures and 5.3% versus 3.8% for non-vertebral fractures. Most fractures occurred in the subpopulation that continued glucocorticoid therapy.

Teriparatide is a PTH analog obtained by recombinant DNA technique (PTH1-34). This analogous agent increases osteoblastic function and decreases apoptosis of osteocytes. The use of teriparatide at a dose of 20 μg/day subcutaneously should be considered as a treatment for GIO, since it significantly increases bone mineral density in this group of patients, in addition to reducing vertebral fractures[47].

In conclusion, glucocorticoids are the first cause of secondary osteoporosis, this being an independent factor of morbidity and mortality in these patients, since the progressive loss of bone mass and increased risk of fracture begins shortly after the start of treatment with glucocorticoids. It is important to identify, and if possible correct, the risk factors and comorbidities in this group of patients, initiate preventive measures and health promotion advice such as change of habits, and give calcium and vitamin D supplements, in addition to specific treatment.

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