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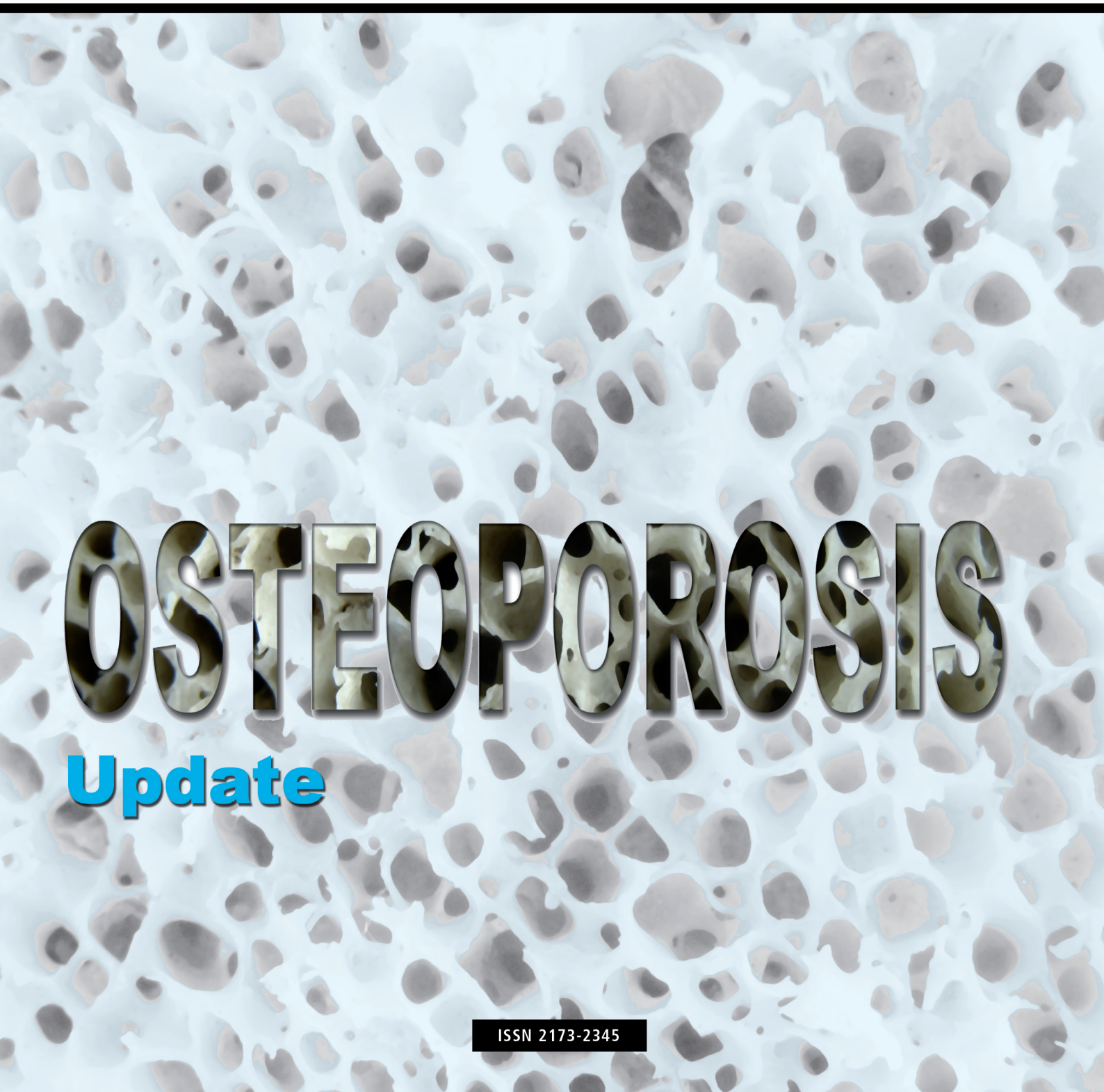

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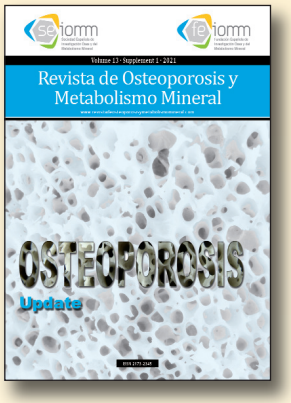

Summary

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Osteoporosis: definition, physiopathology and clinic

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Introduction

Osteoporosis poses a major health problem in modern societies, especially in women. Taking into account the aging of the Spanish population and the fact that osteoporosis and fractures increase with age, with an estimate for 2029 of more than 11 million people over 65 years of age, this problem may become of the first order. Currently it is estimated that there are more than 200 million patients with osteoporosis worldwide, with increasing prevalence[1]. In Spain, the prevalence of osteoporosis in postmenopausal women over 50 years is 26.1% and in men 8.1%.

Therefore, in daily clinical practice, this condition should be diagnosed establishing the previous clinical suspicion and the patients labeled as such in order to avoid its progression and its consequences, which are fragility fractures.

Definition

At the beginning of this 21st century, there is still no conclusive definition of osteoporosis. It began to be defined as a disease in the early 1990s, and coincided with the development, at that time, of new technologies for measuring bone mass, called densitometries. Shortly afterwards, the WHO published a report in which, by "Gaussian" criteria, women were classified as healthy or ill according to their bone mineral density (BMD) value, when compared with the average 30-year-old woman (T-score) and measured with Dual energy X-ray absorptiometry (DEXA), gold standard[2].

But that definition over the years has changed based on our knowledge of bone and so today osteoporosis is defined as "a skeletal disease characterized by decreased bone strength that predisposes a person to an increased risk of fracture". Bone strength is defined as a reflection of the integration of bone density and quality. Bone density is determined by peak bone mass and the amount of bone loss. Bone quality refers to architecture, replacement, accumulation of lesions (microfractures) and mineralization.

The etiology of osteoporosis offers multiple factors, with both genetic and environmental factors contributing to it, with different weight depending on each factor involved. However, none of them is reliable enough to predict the level of bone mineral density (BMD).

The definition provided by the World Health Organization (WHO) in 1994 considers that people suffer from densitometric osteoporosis when the measurement of bone mineral density (BMD) is equal to or below -2.5 standard deviations (T-score ≤-2.5 SD) with respect to the mean BMD during peak bone mass, and that there is established osteoporosis when, in addition to meeting the above criteria, the fragility fracture has already occurred[3]. Osteopenia is referred to when the BMD value is between -1.0 and -2.4 standard deviations. This measurement is established with the determination of bone density after performing a densitometry by dual X-ray absorptiometry (DXA) in the lumbar spine and in the femoral neck, with respect to the standard deviation of those carried out during the maximum peak of BMD[4].

The WHO definition has been exceeded, since it only referred to BMD obtained in a densitometry, a marker of bone quantity, but insufficient to measure bone quality. Currently, osteoporosis cannot be defined only by a BMD value, since very relevant aspects related to trabecular microarchitecture, bone remodeling, genetic, pharmacological and other factors related to the risk of falls would be omitted.

Physiopathology

The skeleton is a metabolically active organ that is continually remodeled throughout life. This remodeling is necessary to, on the one hand, maintain structural integrity, since it avoids the accumulation of fatigue injuries when replacing old bone with new bone and, on the other, to maintain bone resistance to brittle fractures. In addition, it helps the metabolic function of bone as a store of calcium and phosphorus.

The remodeling is carried out in the so-called basic remodeling units, formed by osteoclasts (derived from hematopoietic cells, specifically from the monocyte-macrophage line) and osteoblasts (cells of mesenchymal lineage with bone-forming activity). This process also makes it possible to have an easily mobilizable pool of calcium that helps to maintain homeostasis in the event of disorders that tend to alter calcium levels.

There are an estimated 2 million active remodeling units at any one time. Each of them is made up of a group of osteoclasts that resorb a small volume of bone, about 0.025 mm^3. After this resorption phase, groups of osteoblasts arrive in this area, synthesizing new bone matrix that will then mineralize, thus forming new bone that replaces the old bone destroyed by the osteoclasts.

Interestingly, the cells of the osteoblastic line not only synthesize new bone matrix, but also appear to play a key role in the regulation of osteoclastogenesis and, therefore, in resorption. It is evident that maintaining the skeletal integrity requires an adequate coupling between osteoclasts and osteoblasts, whose action must be coordinated, so that they are activated in the same place and in a correct temporal sequence and, furthermore, that they do so with similar efficiency. In other words, the amount of bone

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Table 1. Dysregulation of the bone remodeling process

Quantitative	Qualitative
	Macroarchitecture
	Microarchitecture
Bone mass	
	Trabecular connectivity
Bone mineral density	
	Osseous remodeling
Bone size	
	Mineralization
	Cross links

destroyed by the osteoclasts is similar to that subsequently formed by the osteoblasts. Otherwise, obviously the bone mass would not remain stable, a situation that occurs in the pathophysiology of osteoporosis.

In osteoporosis, there is a dysregulation of this bone remodeling process, which may be at the expense of quantitative or qualitative aspects (Table 1). It is also worth highlighting the studies carried out in the field of bone biology, of the role of the osteocyte as a fundamental element in the regulation of bone remodeling. These cells are not only simple translators of mechanical stimuli, but also intervene in the regulation of phosphate, bone mineralization and, in addition, they produce certain important cytokines for the regulation of remodeling at both osteoclastic and osteoblastic levels.

This remodeling is regulated both by mechanical factors and by both systemic and local factors. The major systemic factors or modulators are the calciotropic hormones: parathyroid hormone (PTH)[5], vitamin D and, to a lesser extent, calcitonin. Other systemic hormones have important actions on bone tissue, particularly gonadal hormones, growth hormone, glucocorticoids, and thyroid hormones. Due to these mechanisms, hypovitaminosis D with the consequent secondary hyperparathyroidism –a highly springy entity– intervenes in the pathophysiology of osteoporosis, in a considerable way, as well as prolonged treatments with glucocorticoids and their marked and lasting effect on osteoblastogenesis with an inhibitory effect on the herself.

The peak of bone mass in men and women occurs around the age of 30. Blacks have higher bone mass than Whites and Asians, while Latinos have intermediate scores. Men have higher bone mass than women. Once a peak is reached, bone mass remains stable for 10 years, during which time bone formation is similar to bone resorption. Then there begins to be a bone loss of 0.3 to 0.5% per year. Beginning with menopause, this loss accelerates in women at 3 to 5% annually for 5 to 7 years, and then the rate of bone loss slows[6] (Figure 1).

Osteoporotic bone loss affects cortical and trabecular (cancellous, spongy) bone. The cortical thickness and the number and size of the trabeculae decrease, which increases porosity. The trabeculae may be ruptured or absent. Trabecular bone loss is faster than cortical bone loss, because the trabecular bone is more porous and has a greater turnover. However, the loss of both types contributes to skeletal fragility[7].

Therefore, osteoporotic pathogenesis reflects the complex interrelationships that take place between genetics, bone metabolism, other factors that determine bone growth, calcium homeostasis, peak bone mass, and bone loss. All of them at the same time are influenced by age, physical activity or inactivity, certain hormonal deficiencies and nutritional status[8]. Among the risk factors that can trigger or favor the appearance of osteoporosis include:

- Prolonged immobilization or sedentary periods cause bone loss.
- A low body mass index predisposes to loss of bone mass.
- Certain ethnic groups, including whites and Asians, are at increased risk for osteoporosis.
- Insufficient intake of calcium, phosphorus, magnesium, and vitamin D in the diet predisposes to decreased bone mass, as does endogenous acidosis.

Figure 1. Evolution of bone mass

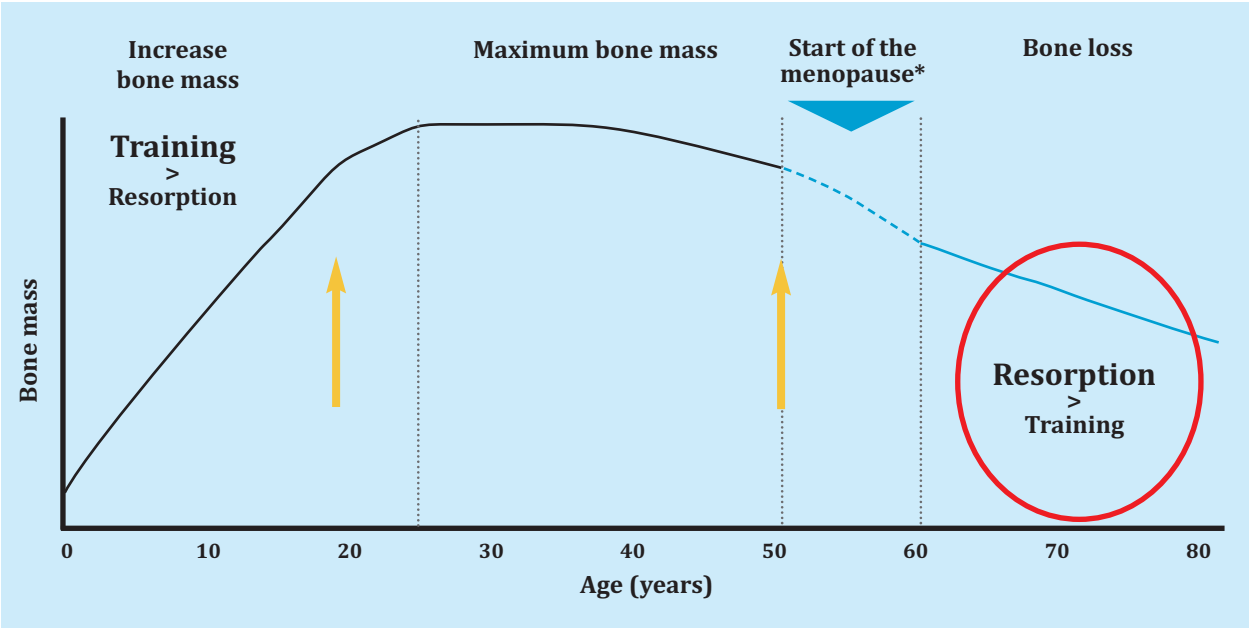

Table 2. Diseases or conditions associated with low BMD, osteoporosis, and increased risk of fragility fractures

Hypogonadal states	Endocrine disorders	Gastrointestinal diseases
- Insensitivity to androgens - Eating disorder - Amenorrhea in athletes - Hyperprolactinemia - Panhypopituitarism - Precocious menopause - Turner and Klinefelter syndrome	- Acromegaly - Suprarrenal insufficiency - Cushing's disease - Type I diabetes mellitus - Hyperparathyroidism - Tumor secretion of PTH - Hyperthyroidism - Nutritional deficiencies of Ca, Mg, vit D	- Celiac disease - Gastrectomy - Malabsorption - Inflammatory bowel disease - Primary biliary cirrhosis - Severe liver disease - Exocrine pancreatic insufficiency
Genetic disorders	**Hematologic disorders**	**Drugs**
- Hemochromatosis - Hypophosphatasia - Imperfect osteogenesis - Ehler-Danlos syndrome - Marfan syndrome	- Multiple myeloma - Leukemias and lymphomas - Systemic mastocytosis - Pernicious anemia	- Anticoagulants: heparins and dicoumarinics - Anticomiciales - Cyclosporine and tacrolimus - Cytotoxic drugs - Glucocorticoids and ACTH - Methotrexate
Rheumatic diseases	**Organ transplant**	
- Rheumatoid arthritis - Ankylosing spondylitis	- Marrow transplant - Kidney, liver, lung transplant or heart	

- Smoking and alcohol also adversely affect bone mass.
- A family history of osteoporosis, especially a hip fracture in a parent, also increases the risk. Patients who have suffered a fragility fracture are at increased risk for other clinical (symptomatic) fractures and asymptomatic vertebral compression fractures.

From the point of view of clinical practice and taking into account the pathophysiological mechanisms that cause osteoporosis, we will classify it as primary and secondary. Within primary osteoporosis in turn we would have; postmenopausal, senile and idiopathic osteoporosis[8,9].

Postmenopausal osteoporosis

The estrogen deficit, consequent to the cessation of ovarian activity, is the cause of an imbalance in bone remodeling with a predominance of resorption over bone formation, which causes a significant loss of bone mass, especially in the first 5- 7 years after menopause[10]. This initial loss of bone mass mainly affects the trabecular bone, which entails a loss of thickness and connectivity of the trabeculae with greater perforation of the same, and more susceptibility to the appearance of vertebral fractures[11]. At the paracrine level, hypoestrogenism is associated with an increase in certain cytokines that leads to an increase in the expression of RANKL. This causes the differentiation, activation and function of osteoclasts on the one hand and, on the other, produces an increase in apoptosis of osteoblasts and osteocytes, with a negative effect on bone formation[12,13].

Senile osteoporosis

Unlike postmenopausal osteoporosis, bone loss occurs after the age of 65, and the cortical bone is mainly affected, with an increase in its porosity. In women, the effect of age is added to that caused by estrogen deficiency. In studies at the cellular level, a decrease in the number of osteocytes with lower bone resistance has been observed, and a greater number of adipocytes in cell cultures that release fatty acids and adipokines, which produce a toxic effect on the osteoblasts fundamentally responsible for the bone formation[14].

Idiopathic osteoporosis

In this type, the appearance of fragility fractures or the presence of low bone mass is detected before menopause in women or in men under 65-70 years of age, without a secondary cause being identified.

Secondary osteoporosis

There are numerous diseases or conditions that are associated with low BMD, osteoporosis and an increased risk of fragility fractures[15,16] (Table 2).

Clinical aspects

The existence of a low bone mass is itself asymptomatic. Patients with osteoporosis are asymptomatic unless a fracture has occurred. Osteoporotic or fragility fractures are those that occur in areas of low bone mass, or that appear after falls from a height. The fractures typically related to osteoporosis are those of the hip, vertebral, distal forearm (Colles fracture) and proximal humerus, although we would also include fractures of the pelvis of the elderly patient as long as the production mechanism is low impact [17].

Non-vertebral fractures are typically symptomatic, but about two-thirds of vertebral compression fractures are asymptomatic. Their prevalence is difficult to determine, given the lack of consensus regarding their radiological definition and because, in many cases, as previously mentioned, they are asymptomatic. Both its prevalence and its incidence increase significantly with age[18].

A symptomatic vertebral compression fracture begins with acute pain that does not radiate and is aggravated in the standing position, may be associated with spinal pain, and usually subsides within a few weeks. However, residual pain may remain for months or be constant. In addition, vertebral fractures cause a reduction in height and an alteration of the static of the spine, with kyphosis, shortening of the trunk and rectification of the lumbar lordosis, depending on the affectation and location of the fractured vertebra.

The most serious osteoporotic fracture is the hip fracture, which is typically caused by a fall from a standing position, although it can also occur spontaneously. It has a high morbidity and mortality, having repercussions that are immediate after the fracture itself, such as surgical intervention. The incidence of hip fracture increases with age, increasing exponentially after age 50, its incidence in people under 35 years of age is 2/100,000 and 3,000/100,000 in people over 85 years[19,20].

Conflict of interests: The author declares no conflict of interest.

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Diagnosing osteoporosis. Bone densitometry. Fracture risk estimate

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Diagnosis of osteoporosis. Conceptual development

The diagnosis of osteoporosis has evolved over the years along the disease's conceptual development. The definition of osteoporosis comes from a description offered by Albright at the outset of the 1940s for postmenopausal and corticoid-induced osteoporosis. This is considered nowadays paradigm of primary and secondary osteoporosis. Its characteristics are reduced bone mass, microarchitectural disorders, unaltered mineralization and presence of fractures[1,2]. It is a histopathological definition with the secondary clinical event. Although osteoporosis is currently the most common metabolic bone disease, rickets and osteomalacia were the main metabolic bone disease from the time of Galen and well into the 20th century[3].

In the 1960s, the basis for peripheral bone mass quantification was established[4]. In the mid-1980s, along with the opportunity of assessing axial bone mass –lumbar spine and hip–, its development with age and the influence of different risk factors to explain its decline, the concept of "fracture threshold" arose, as an initial attempt to classify patients as such before the appearance of fractures, due to minimal trauma[5]. This value, below which 90% of patients with fractures fell, was around -2 standard deviations (SD) below the bone mass peak[6].

At the first Consensus Development Conference held in Copenhagen in 1990, osteoporosis was defined as: "systemic skeletal disease characterized by decreased bone mass and alterations in the microarchitecture of bone tissue leading to bone fragility and consequent increase in fracture susceptibility"[7], without quantitatively defining a cut-off value of bone mass.

In 1994, a technical WHO report[8] based the diagnostic criteria for osteoporosis on bone mass, classifying patients according to their T score or SD divergence in relation to adult women's bone mass peak:

- **Normal:** a T score higher than -1.
- **Osteopenia:** a T score equal to or lower than -1, but higher than -2.5.
- **Osteoporosis:** a T score equal to -2.5 or lower.
- **Severe or settled osteoporosis:** when densitometric osteoporosis is accompanied by at least one fragility fracture.

The document limits this definition to Caucasian women, but leaves the definition open to the different densitometric techniques and measurement areas then in use. In the same document, the difference in the prevalence of osteoporosis using one area of measurement or another is noteworthy.

This classification, although it does not have therapeutic implications at first, has made it possible to universally homogenize the diagnostic criteria, which are essential to compare epidemiological studies and to make the inclusion criteria in prospective clinical trials similar.

Given the controversy arising from the incidence of fragility fractures in patients whose disorder was categorized as "osteopenia" according to the criteria of the WHO (anyway expected since the fracture threshold criterion was established), in the 2001 consensus development conference the notion of bone mass disappears and ultimately defined as a "skeletal disease characterized by decreased bone strength that predisposes a person to an increased risk of fracture"[9]. This definition was clearly ahead of the technical possibilities for measuring bone strength and could even allow other metabolic bone diseases to be categorized as such, some being antagonistic like osteopetrosis[10]. Thus and at a practical level, all the guidelines for diagnosing, preventing and treating osteoporosis have considered the bone mass measurement and/or presence of fragility fractures as basic and fundamental criteria for their definition[11-13].

However, despite acknowledging the relevance of bone mass to predict the increased risk of fracture[13], the relevance of other clinical risk factors unrelated to bone mass was demonstrated almost simultaneously[14-15]. For this reason, different assessment scales have been developed to measure the risk of fracture. The most accepted is the fracture risk assessment tool (FRAX) since its appearance in 2007, although it also includes the concept of bone mass through which the categorization of osteoporosis is established, based on a certain absolute risk of both major fractures and specifically hip fractures[16].

However, and after this historical approach to the diagnosis of osteoporosis, no instrument or parameter negates the required clinical work. Determining bone mass is an objective parameter, with its strengths and weaknesses as we will see later. The presence of fragility fractures must be verified (patients often confuse fractures with dislocations and sprains) as the magnitude of the trauma is very subjective and even the patient may have forgotten notable previous traumas, and not all fragility fractures can be categorized as osteoporotic since there are vertebral deformities that are not fractures, and there are also disease-related fractures[17,18].

Bone densitometry

Historically, the first method of evaluating bone mass and defining osteoporosis was the histological study. Al-

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Table 1. Strengths and weaknesses of axial densitometry via DXA

Strengths
Anatomical sector: lumbar spine and hip
Standardized reference values
Accuracy 1-2%
Evolution with age according to epidemiology
Therapeutic response of all drugs
Reasonable radiological exposure
Prediction of fracture risk
Vertebral fracture assessment ability (IVA)*
Geometric factors assessment ability
Micro-architectural surrogates estimate ability
Trabecular bone score (TBS)
Subregions with cortical/trabecular bone**
Finite element resistance analysis**
Weaknesses
Technology-dependent error factors
Physics and mechanics of the device
Appropriate and up-to-date software
Environmental conditions (temperature, humidity)
• *Daily quality control*
Operator-dependent factors: acquisition systematics
Patient preparation (clothing, foreign elements)
Patient positioning
Analysis systematics (areas of interest)
• *Standardized work procedures*
Patient-dependent factors
Bone structural alterations
Static of the spine
Arthritic changes
Joint (hip) stiffness
Post-surgical changes
Impacted vertebral/neck femur fractures
Adjacent soft tissue alterations
Interposed calcifications
Juxtaposed calcifications
Body fat excess/deficiency
Artifacts
Surgical clips
Prosthetic material
Radiological contrasts
Mediation in digestive tract
• *Careful review of the image obtained*
Conceptual factors
Chosen anatomical sector
Appropriate population reference values
Confusion between risk of fracture/diagnosis of osteoporosis
Minimal significant changes

*: some DXA equipment capable of analyzing the whole body and the lateral projection in supine position; **: software on clinical validation period, but already available; •: minimization of error factors.

though histology/histomorphometry could be considered the gold standard in bone mass assessment, its limitations regarding being a slow, restricted, grueling and expensive method have practically relegated it to research studies[18].

Indirect quantitative evaluation may be carried out using different densitometric techniques based on the alteration produced by mineralized bone tissue on physical agents, such as the Dual X-ray absorptiometry (DXA); Quantitative computed tomography (QCT) with high resolution developments (HrQCT and pQCT), Quantitative magnetic image (qMRI) or Quantitative ultrasound (QUS). All techniques have shown certain capacity to predict the risk of fracture[14,20]. Some techniques (Hr-pQCT) make it possible to discriminate the cortical and trabecular component of the bone and to estimate both the trabecular and cortical volumetric bone mineral density (BMD) and to discern structural characteristics similar to those obtained by biopsy. These, though very important for research, are considered marginal techniques due to their limited diffusion[21].

Despite the predictive capacity of the risk of fracture –it multiplies the risk by 1.5-2 for each declining standard deviation[14], the unimodal distribution of bone mass values between fractured and non-fractured population (due to additional fracture-related factors) makes it scarcely predictive if used as a single and isolated test.

The evaluation of the BMD using axial DXA is the gold standard in the bloodless evaluation of bone mass due to the strengths listed in table 1. Although the discussion of each reaches beyond the limitations of this article, due to their implications in clinical practice, it is worth noting BMD development according to age in relation to other techniques, as shown in figure 1, where it is shown how the BMD by QCT or lateral spine DXA overestimate the diagnosis of osteoporosis, and how calcaneal QUS underestimates diagnosis[22]. If to all this we add the extraordinary distribution of the axial DXA densitometers, the adaptive capacity of the generation of software –some of which are currently under development while others are already in clinical implementation phase–, which allow the evaluation of vertebral fractures (instant vertebral assessment, IVA)[23], geometric factors[24] and surrogates of microarchitecture[25-28] with the same equipment, as well as the evidence that the therapeutic response can be estimated with practically all drugs used in osteoporosis[29], it is the technique recommended by most CPGs[11-13].

The weak points of the axial DXA[30-31], listed in table 1, are mostly avoidable if a correct standardized procedure is followed[32] and we are aware of them at the time of interpretation. The use of adequate population reference values should be highlighted, in the case of the hip, for example, those provided by the Third National Health and Nutrition Examination Survey (NHANES III) which are similar to those of the Spanish population, and in the case of the lumbar spine it is more advisable to use data from the Spanish population, since those provided by commercial companies start from a higher peak bone mass that causes the calculated T-score values to be -0.3-0.4 lower standard deviations[19].

Estimation of the risk of fracture

There are numerous factors related to the risk of bone fractures, both dependent on bone strength and those related to the tendency to fall and their characteristics. Bone factors such as extraosseous factors act in a complex way in each individual. Although BMD, along with the history of fracture and the patient's own age are the clinical objective parameters that explain the higher percentage of risk of fracture, numerous risk assessment scales of other risk factors have been developed so once combined with the aforementioned parameters we could improve the predictive capacity of the risk of fracture in a given patient.

Some of these scales aim to estimate the risk of suffering osteoporosis. The highest regarded questionnaires include the 3-item Osteoporosis Risk Assessment Instrument (ORAI), the 6-item Simple Calculated Osteoporosis Risk Estimation (SCORE), and the ABONE, Oracle and Osiris assessment instruments, of 2 to 4 items. The National Osteopororsis Foundation (NOF) also recommends evaluating patients with any of the major risk factors, with moderate sensitivity but low specificity: age ≥65 years, body mass index (BMI) <22 kg/m^2, and personal or family history of osteoporotic fractures and smoking[33].

In order to assess the risk of fractures directly and in addition to the FRAX[16], used without BMD as some CPGs recommend in order to screen patients in search of those eligible for a DXA[13], other tools have been developed, with the Garvan Medical Research Institute and QFracture Index the most studied[34,35]. Various researchers have carried out comparative studies among them, showing that these three tools have a similar discriminatory capacity with only moderate performance (the area under the curve is between 0.60 and 0.70)[11].

The most widely spread and the only one that has adapted to a large number of countries is FRAX, which provides two fracture risk values: hip fracture and major osteoporotic fracture (clinical vertebral fracture, humerus fracture, distal radius fracture, and hip fracture). Its adaptation to each country has been carried out according to the epidemiological characteristics of their osteoporotic fractures. In Spain as in many other countries, it has been shown that it underestimates major fractures, possibly due to the absence of precise local epidemiological data for this type of fracture, being estimated through data referring to other populations[36]. Various studies carried out in this regard have verified that FRAX's Spanish version offers a much lower risk of major fractures than it should[36,37]. The SEIOMM CPGs do not recommend their use for therapeutic decisions[11], but if used, they advise applying an absolute risk marker adjusted to major fractures in comparison with what can be observed in our population[38].

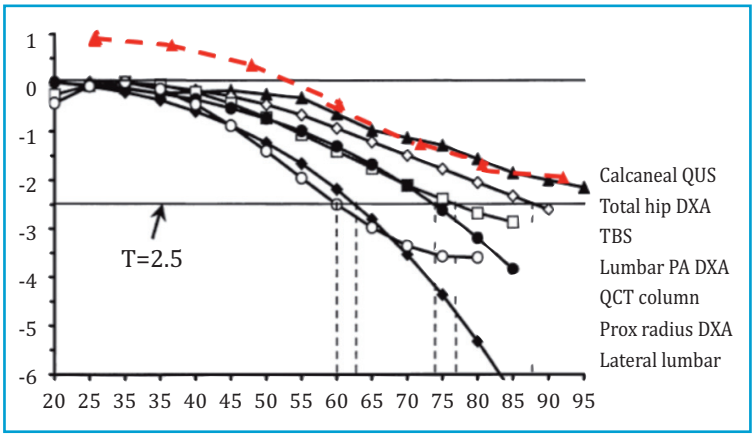
Other societies consider it either as a prior screening or as a third option for, subject to the objective risk, establishing a treatment with cut-off points of 20% for major fractures or 3% for hip fractures, and even variable intervention thresholds depending on the age, being 9-15% between 40-65 years-old, perhaps due to the mismatch between the BMD of the femoral neck (used by the FRAX) and the BMD of the lumbar spine, progressively increasing the intervention threshold from the aforementioned age[13].

With any of the scales or with the simple clinical assessment, it should be taken into account that the history of recent fracture, both vertebral and peripheral, multiplies the risk of fracture by 2-2.5 in the following two years, being considered very high risk or imminent fracture risk[39].

In summary, the diagnosis of osteoporosis requires clinical work, verification of bone mass values by DXA lower than -2.5 T (the lower the value, the greater the risk) and/or the presence of fragility fractures (temporal proximity >2 years significantly increases the risk). The use of tools to predict the risk of fracture, even with their limitations, can be useful for those professionals who are not used to the clinical management of osteoporosis and even to verify the low risk of those patients excessively "worried" about having the disease.

Special attention must be paid to those patients presenting very low bone mass values and recent fragility fractures, who may be considered at very high risk of fracture and require therapeutic initiatives with a faster and more intense effect.

Figure 1. Evolution of population values throughout age in Caucasian women using different densitometric techniques and age at which 50% of the population would reach -2.5 T-score



Modified from Faulkner et al.[22], the TBS data correspond to the Spanish population Cano A et al.[28]

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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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Anti-resorptives in the management of osteoporosis

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Antiresorptive (or antiresorptive) drugs are the cornerstone of osteoporosis treatment. For decades, they have been considered the first step in treating this disease, although more recently some have been discontinued as indication. Others do not always have to be used as the first therapy in the current sequential treatments supported by the main scientific societies. There are five classes of purely antiresorptive drugs: bisphosphonates (BF), estrogen, selective estrogen receptor modulators (SERMs), calcitonin, and monoclonal antibodies against the activating receptor for nuclear factor κB ligand (RANKL) such as denosumab. For its part, a dual-action antiresorptive and osteoforming drug (strontium ranelate) was widely used from 2004 until its marketing cessation in 2017 in Europe for the reasons that will be detailed later. The treatments to be developed here are based on studies in postmenopausal women, although they can be extrapolated to men and to glucocorticoid-induced osteoporosis, although with less evidence[3].

While some of the antiresorptive agents alter bone remodeling markers by acting on the RANK-L pathway (estrogens, SERM, denosumab and tibolone), others have direct effects on osteoclasts as we will now see (calcitonin and bisphosphonates).

Concerns about the safety of antiresorptive drugs have increased in recent years due to the appearance of osteonecrosis of the jaw (ONJ) and atypical fractures of the femur in BF treatments, thromboembolic venous events and fatal strokes in those treated with raloxifene, fractures Multiple vertebral bodies after discontinuing treatment with denosumab and some other adverse events that have led to the suspension of the drug (strontium ranelate and estrogen therapy). Many of these adverse effects depend on the duration of therapy and the presence or absence of adequate sequential therapy.

Here we list and describe the main antiresorptive drugs used in routine clinical practice:

Table 1. Grade of anti-fracture evidence of antiresorptive drugs according to the grades of recommendation of the Oxford Center for Evidence-Based Medicine

Drugs	FV	FNV	FC	Special features
Alendronate	A	A	A	
Risedronate	A	A	A	
Etidronate	A	No	No	No indication
Ibandronate	A	B*	No	In Spain only v.o
Zoledronate	A	A	A	
Denosumab	A	A	A	
Raloxifene	A	No	No	
Bazedoxifene	A	B*	No	
Calcitonin	A	No	No	Retired for OP
Strontium	A	A	A	Retired. Dual action
Estrogens	A	A	A	No indication

A: highest grade of recommendation based on consistent randomized CT; B: second grade of recommendation, based on a cohort or case-control study; *: post hoc studies.
Modified from Sosa et al.[2]

Calcitonin

This is a peptide hormone derived from parafollicular or C cells of the thyroid that inhibits the activity of osteoclasts. It was discovered in 1961 by Copp et al. by considering its hypocalcemic effect in cattle. Synthetic or recombinant human or other animal species (eel, pig or salmon) have been used, of which salmon is the most powerful and therefore most used. The mechanism of action is through the inhibition of osteoclastic resorption and the homeostasis of Ca^{2+}, a powerful hypocalcemic agent. Although at present there is no indication for the use of this hormone in treating osteoporosis in its intranasal presentation (it only slightly increases the number of tumors when used over a long time period), preparations for subcutaneous administration can continue to be used in patients to prevent bone loss associated with prolonged immobilization. For this reason, it has a place in this section. Other uses of the subcutaneous form include treatment of Paget's disease of the bone and hypercalcemia of tumor origin. The recommendations are that the time of use be limited to the shortest possible period.

Tibolone

It is a synthetic hormone that can act as estrogen, progestin and testosterone in different body tissues[5]. It is not more effective than hormone replacement therapy in terms of bone effects or climacteric symptoms and prevents bone loss while maintaining skeletal integrity in postmenopausal women. Its safety is questioned because it increases the risk of breast cancer in women who have already suffered from this. It increases the risk of stroke in women over 60 years of age.

Estrogens *(Hormone replacement therapy)*

Estrogen deficiency (ES) is a key factor in the pathoge-

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nesis of postmenopausal osteoporosis (PMO). ES play an important role in the functioning and maintenance of the skeleton, acting on the induction of osteoblastic cells and inhibiting the production of pro-resorptive cytokines such as IL-1 and IL-6, the activating receptor for nuclear factor kappa-b (RANK) and osteoprotegerin (OPG) by osteoblast cells. They reduce the number of osteoclasts in vivo, suppressing their precursors.

They were used for many years as a treatment for estrogen deprivation symptoms in menopause. In Spain they are indicated in the prevention of PMO with a high risk of fracture in women in whom other types of therapies are contraindicated.

HRT has been a first-line treatment due to its efficacy in preventing VF and CF. However, the WHI (Women's Health Initiative) clinical trial conducted in the United States to verify the risks and confirm the benefits of hormone replacement therapy, was interrupted after 5 years (it was designed for 8.5 years), since in women treated with a certain type of combined hormonal therapy (equine estrogens and medroxyprogesterone), provided evidence that the benefits (decrease in colorectal cancer and hip fractures) did not outweigh the risks (increased risk of invasive breast cancer, cerebrovascular accidents, coronary heart disease and thromboembolic disease[13]).

They have shown potential in VF, FNV and hip. As side effects, cardiovascular complications, thromboembolic phenomena and an increased risk of breast cancer stand out, which has led to discourage its use in both prevention and treatment.

Bisphosphonates

Bisphosphonates (BF) have been known for many years. At first, its use was limited to avoiding the deposit of calcareous salts in the pipes. Many years passed until they were used in humans. They all have in common the chemical structure of pyrophosphate (carbon atom sandwiched between two phosphorus atoms). The first to be used, almost 40 years ago, were the first generation bisphosphonates (etidronate, pamidronate and clodronate), their common characteristic is that they do not have any nitrogen atom, which is why they are also called non-amino BF. Most of them are no longer in use today.

Subsequently, BF with an incorporated nitrogen atom (amino-BF) were developed with a potency 100-100,000 times higher than etidronate. Alendronate, risedronate, ibandronate and zoledronate belong to this group.

The mechanism of action of all of them is by reducing bone resorption by inhibition of osteoclasts (Oc) and increasing intestinal calcium reabsorption. On the Oc they produce an inhibition of their differentiation and an increase in their apoptosis. Likewise, they inhibit the integrins that are responsible for sealing the wavy edge of the Oc on the bone surface, thus producing an equalization of the pH and blocking its destructive action on the bone. In particular, amino-BFs activate an enzymatic system derived from proteases (caspase) that induces an early apoptosis of Oc. It also has a cross effect with statins by interfering with the metabolic chain of mevalonic acid, a precursor of cholesterol.

Regarding their pharmacokinetic properties, BFs are absorbed in a very small proportion (around 1%) of the administered oral dose, therefore they should not be administered with any type of food or drink that interferes with their, already erratic, absorption. Recently, a gastro-resistant formulation of risedronate has been marketed that does not need to be administered on an empty stomach. The plasma half-life is short (approximately 1 hour) and 20% of the drug is incorporated into bone tissue and the rest is eliminated in the urine. The incorporation into the bone is very strong, calculating about 10 years of apposition to the bone tissue, which may condition some of its secondary effects due to increased secondary mineralization to the detriment of the primary one.

They also have effects on the osteocytes responsible for the response to mechanical stimuli and the early detection of microfractures, preventing apoptosis induced by glucocorticoids, which is the action that contributes most significantly to the fragility and fractures of patients under steroid treatment.

BPs are the most widely used therapeutic group in the treatment of osteoporosis and can be administered orally or intravenously. They have a powerful antiresorptive effect that generates a positive balance that stops the process of bone loss. The effect of bone mineral density is most powerful in the first months of treatment. In those of oral administration they should be taken on an empty stomach accompanied by non-mineral water and should remain fasting between 30-60 minutes after taking it depending on the BF used. More recently the galenic of some of them has been modified, making fasting administration unnecessary. Even all their absorption is erratic, reaching a poor 1% under ideal conditions. The intravenous presentations do not have the gastrointestinal limitations of the previous ones, although all of them have been associated with important (although infrequent) side effects in the form of osteonecrosis of the jaw (ONJ) and atypical fractures of the femur. Always in relation to the duration of the treatments. In general, they should be avoided with glomerular filtrations below 35 ml/min[1].

The main action of the BF is on the osteoclasts that internalize the BF by endocytosis and depending on the type of BF the action is different. Non-amines are metabolized and induce apoptosis of osteoclasts. While amino BFs are not metabolized and act by enzymatic inhibition, reducing the concentration of isoprenoids and the subsequent alteration of the osteoclast brush border, preventing their tight union to the bone with equalization of the pH and alteration of their action.

In 2005, a series of patients with VNF considered "atypical" were described for the first time in patients treated for a long time with alendronate (>7 years). These are fractures of the femur after a minimal impact in the diaphyseal or subtrochanteric location and of oblique or transverse distribution. As a background, some patients developed pain in the area. The etiopathogenesis, although not clear yet, could be related to the sustained suppression of bone turnover.

Regarding ONJ, it is a complication of treatment with BP that was initially described in cancer patients receiving treatment with ev BP (zoledronate or pamidronate) but which, subsequently, has also been described in patients with OP treated with oral BP (although much less prevalent). It is a rare but potentially serious complication defined as exposed necrotic bone in the mandible, maxilla, or both for more than 8 weeks in the absence of metastasis or radiation to the area. Its incidence in cancer patients varies according to the series of 1-11% depending on the dose, duration of treatment and previous

dental status. In non-cancer patients the incidence drops to 1 case in every 10,000 patients treated. The etiopathogenesis is not entirely clear, it is postulated that it could be due to the direct effect of the BF on the tooth or to an excessive suppression of the turnover that would prevent the repair of the lesions produced by invasive dental procedures (implants, extractions, etc.). Spanish authors have described a polymorphism of the gene related to cytochrome P450-2C8 that is associated with an increased risk for ONJ in patients with multiple myeloma treated with ev BF[12].

In recent years, a trend of opinion has developed according to which, in patients with a certain number of years in treatment with BP, the suspension of these should be considered in order to avoid the two complications described above. There are several scientific societies that support this measure, based on the study of the clinical factors associated with the appearance of these complications and reaching the conclusion that the use of BP for more than 5 years could be one of those causes[2].

Several studies have shown that adherence to the different treatments for osteoporosis is low, with a 30-50% dropout in the first year. As it is an asymptomatic disease, the patient does not have a feeling of improvement and is more prone to abandoning it. The periodicity of the intake also influences compliance, it seems that those that are taken more widely are those with the best compliance rates. Thus, in the PERSIST study, adherence was compared for 6 months in women who took monthly ibandronate versus weekly alendronate, observing better compliance in those who took it monthly (56.6% versus 38.6%). Other drugs such as denosumab and zoledronate administered biannually and annually, respectively, have changed both non-compliance and patient preferences.

The half-life of circulating BFs is quite short, ranging from 30 minutes to 2 hours; however, once they have been incorporated into bone tissue, they can persist for more than 10 years. The absorption of oral BP is 1% if the patient has eaten or drunk anything other than plain water for up to two hours after treatment. They should not be used by patients with a history of gastrointestinal and esophageal diseases, inability to stand between 30-60 minutes after taking it, hypocalcaemia and patients with kidney disease (they should be used with caution in GFR <30 ml/min for risedronate and ibandronate and <35 ml/min for zoledronate and alendronate). Intravenous BP can produce acute febrile-type reactions and muscle aches, therefore, in the case of zoledronate, the patient must be abundantly hydrated before and after the infusion and paracetamol can be used for general symptoms.

Other reported side effects of BPs are; atrial fibrillation, conjunctivitis and uveitis, hypocalcemia, gastroesophageal disease, acute phase response, mesenteric panniculitis[14].

Ibandronate
It was the first BP for monthly oral use, although there is also a quarterly intravenous preparation for hospital use. It is approved for vertebral fractures, although a post-hoc study provided the reduction of non-vertebral fractures in a subgroup of patients with a T-score <-3. Compared with weekly alendronate, monthly ibandronate was equipotent in increasing bone mineral density and without differences in safety profiles[4]. The available studies limit the use of ibandronate to 3 years, and there are no efficacy or safety data after 3 years. Likewise, the effects observed in the bone when the drug is discontinued have not been published.

Zoledronate
Approved for postmenopausal, steroid, and male osteoporosis. A dose of 5 mg is administered annually in a 15-minute infusion. Reduces the risk of vertebral, non-vertebral and hip fractures. It is a safe drug, in the first infusion there may be general symptoms of malaise, myalgia and fever in up to 30% of cases, which is significantly reduced in the following infusions. There are published studies on its safety and efficacy up to 6 years[6]. It has also been shown in a study that it reduces the possibility of suffering a second hip fracture in patients who have already developed a previous one[7]. There have only been cases of osteonecrosis of the jaw in cancer patients in whom the doses used are much higher. There are published studies of up to 6 years with VF-lowering effects compared to those women who had discontinued the drug before.

Etidronate
It was the first BF to demonstrate anti-fracture efficacy in patients with osteoporosis. They produce an increase in bone mass with a reduction in the number of vertebral fractures without proven efficacy in reducing non-vertebral fractures (including the hip). It was also the first to be used in combination with hormone replacement therapy, inducing increases in bone mineral density greater than those of each drug alone, with a certain tendency to a possible greater decrease in the incidence of vertebral fractures[8]. Its uncomfortable regimen of administration in cycles (400 mg daily for 2 weeks followed by 74 days of rest and repeat) together with its lack of effect on non-vertebral fractures, led to its abandonment in clinical practice, although it still retains its indication.

Alendronate
It was the first amino-BF recorded for the treatment of postmenopausal OP. The FIT clinical trial demonstrated a significant reduction in VFs and currently has an indication in VF and FNV. The recommended dose is 70 mg per week[9]. The FACT study compared the improvement in BMD and the decrease in bone remodeling markers in two randomized groups of alendronate and risedronate, the results being favorable to the alendronate group, although without mentioning the reduction of fractures. Regarding the duration of treatment with alendronate, there are studies that show the advantages of continuous use for 10 years compared to 5 years. Although the concept of "therapeutic holidays" (from English drug holiday) has been intrinsically related to BP in general, there is no clear consensus regarding its usefulness and experts recommend evaluating each patient with BMD and with markers of remodeling and acting based on the changes of those surrogate markers. It has an indication in postmenopausal osteoporosis, male and glucocorticoid-induced (not in Spain) although there are studies that confirm its efficacy. The authors of a meta-analysis of 11 clinical trials that included 12,068 women demonstrated that oral alendronate (10 mg daily) reduced the RR of VF by 45%, HR by 40%, and FNV by 16% versus placebo[10].

Alendronate is a safe drug, the most frequent side effects are gastrointestinal (retrosternal burning or burning, discomfort and abdominal pain) in more serious but rare cases, GI bleeding has been described. It has a 10-year safety study and when it is suspended it has a certain residual effect that allows a "therapeutic vacation" for a period of 1-2 years after having been 4-5 years of continuous treatment.

The NNT (necessary number of cases to treat to prevent a fracture) of alendronate is 24.

Risedronate

It was the second BF recorded, it differs chemically from alendronate by the existence of a nitrogen atom that is incorporated into the pyridinoine ring. In the clinical trial (VERT) the dose used was 5 mg per day. It has an indication in VF, FNV, CF, OP of the male and induced by GC. There is a monthly dosage of 150 mg that favors therapeutic compliance. In a systematic review of 7 clinical trials that included 14,049 women, risedronate at a dose of 5 mg per day was associated with a 39% reduction in VF, 26% in PK, and 20% in FNV[11].

In turn, it has a study specifically designed for hip fracture that yielded 30% protection data for HR (RR 0.7; 95% CI 0.6-0.9). This protective effect became evident 18 months after initiation of therapy. There are 7-year safety studies. After 3 years of treatment, a reduction in the risk of fracture persists that lasts 1 year, so a therapeutic vacation could be applied for that period of time.

The NNT for risedronate is 29, somewhat higher than that for alendronate.

Ibandronate

Approved in Spain for the treatment of postmenopausal OP at a dose of 150 mg in monthly tablets. It was the first BP available for intravenous infusion on a quarterly basis (3 mg). It reduces the risk of VF without prospective studies showing reduction of VF or HR. The side effects are similar to those of the other groups of BP (except in its intravenous dosage where the GI have not been described). The studies are limited to 3 years of use, so that would be the maximum duration of treatment because there is no data beyond that, nor of the effects observed in the bone when suspending it.

Selective estrogen receptor modulators (SERMs)

SERMs are non-steroidal molecules that compete for estrogen receptors (ERs) which are nuclear hormone receptors that function as ligand-dependent nuclear transcription factors. There are two types of RE, alpha and beta. Alpha is almost always activating, and beta can inhibit the action of alpha by forming a heterodimer with it. Tamoxifen and raloxifene are antagonists of beta ERs, and may act as partial agonists of alpha ERs. But ERs can act in the absence of estrogens, responding to growth factors (epidermal growth factor) at their extracellular membrane receptors. This alternative mechanism is of utmost importance in resistance to tamoxifen treatment in breast cancer. Receptors for epidermal growth factor HER2 are the target of trastuzumab treatment of this breast cancer.

The mechanisms by which SERMs exert antiresorptive effects on bone are unknown. Although it is known that this mechanism of action is mediated by binding to estrogenic alpha and beta receptors in which they compete with estradiol with an agonist or antagonist effect, depending on the type of tissue. Although there are 1st and 2nd generation SERMs (tamoxifen, raloxifene), it is the 3rd generation SERMs (bazedoxifene) that have sufficient endometrial safety to recommend their use in PM women.

Tamoxifen is indicated as an adjunct to early breast cancer surgery in women with ER + with a duration of 5 years after it. It has positive effects on the bone (in postmenopausal women, BMD increases in the lumbar spine and hip, contrary to what occurs in premenopausal women) but it lacks an indication for the treatment and prevention of osteoporosis. Among the main side effects are endometrial cancer and thromboembolic problems.

Raloxifene has an indication for the prevention and treatment of OPM, as well as for the prevention of invasive breast cancer in women at high risk of suffering it. In the MORE study observed a 30% reduction in the risk of VF. The NNT was 16. The duration was 4 years. The dose of raloxifene is 60 mg per day to reduce VF as well as FNV in a subgroup of women with previous high risk of fracture. Side effects include cramps in the LES, increased risk of VTE and climacteric symptoms.

There is a presentation in Spain combining bazedoxifene with conjugated equine estrogens, indicated for the treatment of estrogen deficiency in postmenopausal women and with a uterus in whom a progestogen cannot be used, but without an indication for osteoporosis so it has no more place in this revision.

Efficacy is maintained up to 5 years according to studies and safety up to 7 years.

Denosumab

First 100% human monoclonal antibody approved for the treatment of OPM with high risk of fracture. It is directed against RANK-L (RANK ligand) which produces a reduction in the differentiation, survival and action of osteoclasts. It also has an indication in the treatment of bone loss associated with hormonal suppression in men with prostate cancer at high risk of fractures, for steroid osteoporosis and for men. In patients with bone metastases, factors released by tumor cells result in dysregulation of the RANK-RANK-L signaling pathway, leading to bone destruction. Denosumab-mediated RANK-I inhibition suppresses osteoclast development which, in turn, reduces cancer bone destruction and slows bone tumor growth. Denosumab non-reversibly inactivates osteoclasts, deactivation that lasts throughout their life. The effect of the drug lasts for 2-5 months after administration (which is semi-annual) with a half-life of 25 days.

It is used in doses of 60 mg subcutaneously every 6 months. Reduces the risk of VF, FNV and hip with studies up to 10 years. Rare side effects include cataracts, severe infections (including skin infections), eczema, dermatitis, and rashes. Cases of jaw necrosis have been described. Recently a side effect has been observed when suspending or discontinuing the drug, it is a sudden increase in bone remodeling markers, which would lead to a rapid loss of bone mass and an increased risk of fractures, especially vertebral fractures, although have been described in other locations, being able to produce multiple VFs. This effect on markers of bone remodeling was already included in the Freedom study, where the possibility of this "rebound effect" was alerted.

Strontium ranelate
It is a divalent cation made up of an organic skeleton, ranelic acid, attached to two strontium atoms. But we leave this family for last because it is not currently marketed in Spain. Its properties have been known since the 1980s when strontium chloride caused a slight increase in osteoformation and a decrease in resorption in animal models. It was a dual-action drug, with an antiresorptive and bone-forming effect, used in women with severe PMO and in men with no indication for steroids. It was effective in reducing the risk of VF and FNV in 5-year studies. And in post hoc studies it showed a reduction in HR and up to 8 years. But after an alert from the AEMPS that declared an imbalance between its risk and benefit and stopped being marketed. It increased the risk of cardiovascular and thromboembolic disease. Cases of DRESS syndrome (drug rash systemic eosinolphilia symptoms), some of which were fatal, have also been reported.

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Anabolic treatment of osteoporosis

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Summary
The anabolic or osteogenic treatment constitutes one of the pillars in the treatment of osteoporosis as it makes it possible to build new bone and improve the bone microstructure. Over the years, several drugs classified as osteogenic agents have emerged, but some of them have not been effective while the use of others has been discontinued. Nowadays we only have one anabolic drug, the teriparatide, which, despite the time that passed since its approval, has established itself as the anabolic drug of reference.
There are many studies about the usefulness of teriparatide when administered alone, or in combination with antiresorptive drugs, or sequentially, where the order for the drugs administration appears to be important.
We analyze all these sections and make some final recommendations about its use in accordance with the currently available clinical practice guidelines.

Key words: teriparatide, osteogenic, anabolic.

Anabolic discontinued or not available

Sodium fluoride

Sodium fluoride (FNa) was used in the past as a bone-forming drug. Administering fluoride causes the number of osteoblasts to increase as the proliferation of osteoblastic precursors is stimulated, which leads to increased activity. In addition, it has antiresorptive capacity. The combination of osteogenic effect and inhibition of bone resorption leads to an increase in bone mineral density (BMD)[1].

Although the number of randomized clinical trials conducted with FNa is relatively limited, the salt types and dosages used in them, as well as their combination with calcium and vitamin D, make every trial very different from each other and therefore the global assessment of the results turns very difficult.

There are some studies that have shown an increase in BMD and a reduction in the risk of vertebral fractures, but in general the published results have been disappointing. Despite almost uniformly observing a statistically significant increase of BMD, these studies do not record a reduction in the risk of fractures[2]. Moreover, sometimes they instead record an even higher risk of suffering fractures during treatment or when suspending it, especially of non-vertebral nature[3].

One of these studies was the study by Riggs et al.[4], published in the prestigious New England Journal of Medicine. The study showed very poor results, causing the FNa not to be approved by the Food and Drug Administration (FDA). This well-designed, double-blind study included 202 postmenopausal women at an average age of 68 years. All patients received a calcium supplement (1,500 mg/day), while the experimental group also received 75 mg/day of FlNa. The patients' BMD in the experimental group significantly increased by 35% in the lumbar spine and 12% in the head of the femur if compared to the control group patients' BMD, while a significant decrease of 4% was also noticed in the radius. Although the number of vertebral fractures was similar in the 2 groups during the next 4-year follow-up, the number of non-vertebral fractures was higher in the experimental group.

Subsequently, a Cochrane review, including 11 studies with a total of 1,429 patients, concluded that although FNa can increase the BMD of the lumbar spine, no reduction in vertebral fractures is observed. By increasing the fluoride dosage, the risk of non-vertebral fractures and gastrointestinal side effects increase, not showing any beneficial effect on the rate of vertebral fractures[5].

For these reasons, FNa was never approved by health authorities around the world and no results from new trials have been published in the past 20 years. So, its use for treating osteoporosis has been discontinued.

Intact parathyroid hormone (PTH 1-84)

The intact parathyroid hormone molecule (PTH 1-84) was been used in the treatment of osteoporosis in the past decade.

An initial study, published in 2003, showed an increase in BMD in the experimental group treated with PTH 1-84[6] and became a reference in reducing the risk of fractures and thus demonstrating its usefulness for the treatment of postmenopausal osteoporosis, was publis-

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hed by Greenspan et al. in 2007[7]. The randomized, double-blind, placebo-control study was conducted on 2,532 postmenopausal women and showed that patients who received PTH 1-84 had a significant increase in BMD in the lumbar spine and in the proximal femur (femoral neck, total hip and trochanter) and a decrease in the BMD of the distal radius. A statistically significant reduction in the risk of suffering new fragility fractures was observed, but only regarding vertebral fractures, but not so regarding non-vertebral fractures. The dropout rate was significant and up to 95% of the patients suffered some type of side effects. Although several studies on PTH 1-84 have been published[8-12], some on the combination with other antiresorptive drugs, none of them showed a reduction in the risk of non-vertebral or hip fractures. Perhaps, the drug was never approved by the FDA to be used in the US for this very reason, and although it was approved in Europe, the manufacturing lab suddenly suspended its supply shortly after and to this day, not even with a prescription it can be obtained. Lately it has returned to the news for its possible usefulness in the treatment of hypoparathyroidism.

Abaloparatide

Abaloparatide is a synthetic peptide analogue to the PTH-like protein (PTH-RP 1-34) that selectively binds to the cellular receptors for PTH/PTH-RP[13], increasing BMD at both vertebral and cortical bone levels[14]. A study carried out including approximately 2,400 women who were administered abaloparatide to compare it to teriparatide, showed a relative risk reduction in the appearance of new morphometric vertebral fractures, with no statistically significant differences between both drugs[15.] Abaloparatide also reduced the risk of non-vertebral fractures by 43%, but the study did not show significant differences between that and the reduction provoked by teriparatide. In all cases both, teriparatide and abaloparatide, showed differences in the reduction of the risk of statistically significant fractures compared to the placebo group[14-16].

Abaloparatide was approved for commercialization by the FDA, but the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) did not, due to an increased cardiovascular risk seen in postmenopausal women, and also owing to not reducing the risk of non-vertebral fractures in non-menopausal women.

Teriparatide

Teriparatide is a PTH analogue that contains only the first 34 amino acids, the ones promoting its biological activity. More than 15 years after its approval, it is currently the only drug approved in our country for the treatment of osteoporosis, whose mechanism of action produces the stimulation and formation of new bone[16].

Mechanism of action

Osteoblasts (the cells responsible for bone formation) have PTH receptors and its anabolic responses occur as a consequence of the hormone-receptor bindings[17]. Besides osteoblasts, osteocytes and renal tubular cells also have receptors for PTH[16]. The pharmacological efficacy of PTH requires its administration to be intermittent as bone formation is preferentially stimulated this way since prolonged or continuous administration of the hormone seems to promote bone resorption[17,18].

When sequentially administered, and as a consequence of the increase in osteoblastic activity, there is an increase in trabecular bone and an improvement in bone microarchitecture[17,19,20], showing a concomitant increase in bone cortical porosity, as well as in cortical thickness and in bone size[19,20].

Reduced risk of fracture

On the one hand, the clinical trials carried out showed an increase in BMD[21,22] as well as a reduction in the risk of vertebral and non-vertebral fractures[23-27]. The baseline study by Neer et al. was published in the New England Journal of Medicine[27]. It included 1,637 postmenopausal women with low BMD, presenting at least one prevalent fracture and who did not receive hormone replacement therapy or any other antiresorptive treatment. They were randomly grouped into 3 groups that received 20 or 40 µg/day of teriparatide or placebo. Patients who received teriparatide presented an increase in BMD of the lumbar spine of 9% with 20 µg/day, and of 13% with 40 µg/day, as well as an increase in the femoral neck of 3% with 20 µg/day, and of 6% with 40 µg/day. The BMD of the radius decreased in the 3 study groups (two groups under the effects of teriparatide and one control group), but the decrease was statistically significant in the group that received 40 µg/day in comparison with the placebo group. Compared with the placebo group, the risk of developing a new vertebral fracture decreased by 65% in the group receiving 20 µg/day and by 69% in the group receiving 40 µg/day. The risk of non-vertebral fractures decreased by 53% in the group receiving 20 µg/day and by 54% in the group receiving 40 µg/day, also compared to the placebo group[23,27]. Different studies carried out in other types of patients have obtained similar results[28-30].

In this study, no reduction in the risk of hip fracture was observed, but subsequent systematic reviews and meta-analyses have confirmed that teriparatide also reduces the risk of hip fracture[31,32].

On the other hand, several studies have shown that postmenopausal women treated with teriparatide present a decrease in ,both moderate and severe, back pain associated with vertebral fractures[28,33-35] which conditioned an improvement in their quality of life[36].

The beneficial effect of teriparatide is not affected by the age of the patients. In a study carried out in elderly women of over 75 years of age, a reduction in the risk of fracture, both vertebral and non-vertebral, was found, including those in the subgroup formed by patients older than 80 years of age[26].

Osteoporosis in men and steroid-induced osteoporosis

In addition to the initial study by Slovik et al.[37], which we could consider almost anecdotal due to the small sample size, other more methodologically complete studies have been published, allowing us to establish the usefulness of teriparatide in the treatment of osteoporosis in men.

The first study of these characteristics was the one carried out by Kurland et al. which included 23 men who received 400 units of teriparatide or placebo per day (equivalent to 25 µg/day) for 18 months. Patients who received the drug showed a 13.5% increase in BMD of the lumbar spine. The BMD of the hip also increased, but in a minor degree (2.9%) and more slowly, while the BMD in the radius did not change significantly.

In another study, conducted on 437 patients with idiopathic or hypogonadic osteoporosis, Orwoll et al. administered 20 or 40 µg/day of teriparatide to the experimental group, and calcium and vitamin D to the placebo group, obtaining an increase of 5.9% in the lumbar spine and 1.5% in the femoral neck in those treated with the drug.

Since then, several studies about men and patients receiving oral glucocorticoids have been published. On the one hand, these studies have confirmed the efficacy of teriparatide in reducing the risk of fragility fracture[37-40] and, on the other, they have confirmed the superiority of teriparatide for this task, in combination both with alendronate and risedronate[41-43]. For this reason, teriparatide is accepted for the treatment of osteoporosis in men and steroid-induced osteoporosis, in addition to postmenopausal osteoporosis.

Security. Side effects. Osteosarcoma risk

Teriparatide is well tolerated. The side effects collected from the original series of 1,943 patients by Neer et al. include nausea, headaches, and dizziness that occurred in patients who received the highest doses of the drug. Mild hypercalcaemia, defined as a serum calcium concentration greater than 10.6 mg/dl, was also observed in 2% of the women who received placebo, in 11% of the women who received 20 mg teriparatide and in 28% among those in the group that received 40 µg/day. In all cases, hypercalcemia was transient and calcium monitoring is not required in treatment with teriparatide.

When teriparatide was approved in the US for the treatment of postmenopausal osteoporosis in 2003, its use was limited to 2 years, given that a strain of rats received teriparatide at a dose proportionally higher than that subsequently used in humans developed osteosarcoma[44]. That same year, the Osteosarcoma Surveillance Study was founded in that country in order to monitor the possible appearance of osteosarcoma in patients treated with teriparatide.

During the period between January 2003 and December 2016, 3 cases of osteosarcoma were observed in patients who had received teriparatide. Based on the known incidence of osteosarcoma, the expected number of cases was 4.1 and with the 3 collected, a standardized incidence ratio of 0.72 was obtained (95% CI 0.20 to 1.86). This confirmed that the incidence of osteosarcoma associated with the use of teriparatide was not different from that observed in the general population[45].

On the other hand, no cases of osteonecrosis of the jaws have been described after using teriparatide. On the contrary, some studies have published teriparatide could have a certain beneficial effect in these patients[46-48].

What to do after 24 months of treatment with teriparatide?

Treatment with teriparatide is limited to 24 months as indicated above. Once completed, it must be suspended.

Some studies have shown that after stopping teriparatide a certain residual effect is observed[49-51]. This effect has lasted up to 24 months after stopping the drug[51] and the dreaded rebound effect has not been observed, unlike in the case of other drugs such as denosumab[52-54]. However, once the treatment with teriparatide is completed, it is advisable to continue the treatment with a bisphosphonate[55] agent and in all cases with non-pharmacological measures: exercise, a balanced diet, and a supplement of calcium and vitamin D[56-59].

Romozosumab

Romozosumab is a monoclonal antibody that has a dual effect on bone remodelling, since it inhibits sclerostin and secondarily RANKL, producing a rapid increase in bone formation that is associated with a decrease in resorption. As a consequence, it increases the trabecular and cortical bone, which translates into a significant increase in BMD and a decrease in the risk of fracture. It is indicated for the treatment of severe osteoporosis only in postmenopausal women with a high risk of fracture[60-64].

Romozosumab is given as two subcutaneous injections of 105 mg each, once a month for up to one year. The second injection should be given immediately after the first but at a different injection site. It is advisable to assess the cardiovascular risk in the patients for whom it is to be prescribed, before and during its use[65].

When to start an anabolic treatment?

Teriparatide is the only anabolic drug that currently available for treating osteoporosis in Spain. In addition to postmenopausal osteoporosis, teriparatide is approved for use in male osteoporosis and steroid-induced osteoporosis.

In our opinion, PTH is the strongest biological treatment available for osteoporosis. Both teriparatide and PTH (1-84) have been approved in our country for the treatment of postmenopausal osteoporosis. However, to correctly place it within the therapeutic arsenal, the cost of teriparatide must be taken into account, as it is currently higher than any other approved treatment for osteoporosis. Therefore, its use should be restricted to specific cases, with severe osteoporosis, such as in patients with vertebral fractures or multiple osteoporotic fractures, or with a very low BMD (T-score less than -3.5), or in those cases in which patients cannot tolerate other treatments and have a high risk of fracture[66-72]. Finally, we could also consider those cases in which there is a poor therapeutic response to other drugs, this manifesting as the appearance of recurrent fractures or a significant, documented and sustained decrease in BMD despite antiresorptive treatment. In this regard, the guidelines of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) recommend the anabolic treatment with teriparatide precisely in these patients[55].

Sequential treatment

The treatment of osteoporosis is limited in time for several reasons. In the first place, there are drugs that have a limited administration time, such as teriparatide at two years or romozosumab at one year. Secondly, side effects or a lack of therapeutic response may appear making it necessary to change to another drug. Finally, after the time the safety of the administered drug has been established, it may be advisable to change it for a different one.

If we consider all the available drugs individually, the possible combinations are many. But by grouping them into anabolic and antiresorptive agents, we could in general lines indicate that when establishing a sequential treatment, it is advisable to start with an anabolic treatment and then continue with an antiresorptive one.

Thus, the sequential teriparatide-raloxifene treatment managed to maintain or even increase the BMD gain achieved with the previous treatment with teriparatide[73]. The same has been observed when the treatment with teriparatide is administered together with a

bisphosphonate, even producing a subsequent increase in BMD and maintaining the reduction in the risk of fracture[50]. In the case of the abaloparatide and alendronate sequence it was found that when administering this antiresorptive after the osteogenic agent, an increase in the previously achieved BMD was produced and thus preserving the anti-fracture activity[74].

On the contrary, previous treatment with a strong antiresorptive, such as alendronate or zoledronate followed by an osteogenic agent, such as teriparatide, produces a decrease in BMD in the first months after the start of the treatment[75], although the reduced risk of fracture remains[76].

If the risk of fracture in patients has been found to be high, it is advisable to start an osteogenic treatment, with a drug such as teriparatide, and then continue with a strong bisphosphonate, such as alendronate or zoledronate.

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