Rev Osteoporos Metab Miner. 2021;13(Supl 1):S4-7

Osteoporosis: definition, physiopathology and clinic

Lladó Ferrer B
Internal Medicine Service. Fragility Fracture Unit. Son Llatzer Hospital. Palma de Mallorca (Spain)

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

Correspondence: Bartolomé LLadó Ferrer (tllado@hsll.es)

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

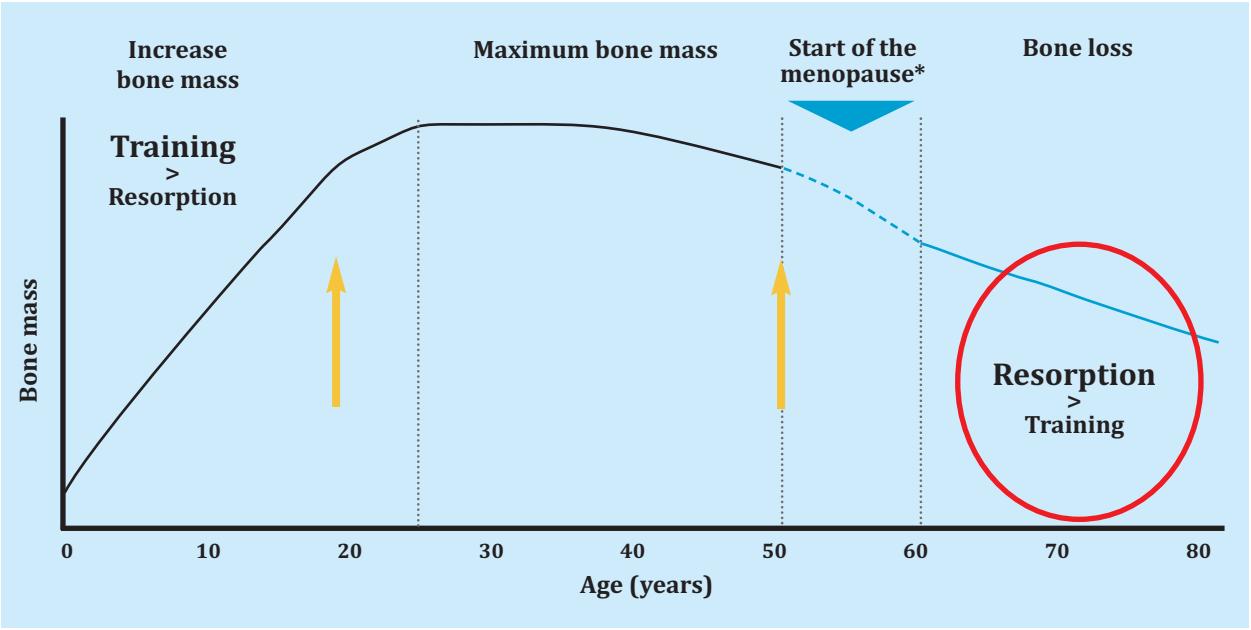

Table 2. Diseases or conditions associated with low BMD, osteoporosis, and increased risk of fragility fractures

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.

Bibliography

1. IOF, International Osteoporosis Foundation.
2. WHO Study Group on assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group.World Health Organ Tech Rep Ser. 1994;843:1-129.
3. Muñoz-Torres M, de la Higuera M, Fernández-García D, Alonso G, Reyes R. Densitometría ósea: indicaciones e interpretación. Endocrinología y Nutrición. 2005;52(5):224-7.
4. National Institutes of Health (USA). Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001.
5. Bringhurst FR. PTH receptors and apoptosis in osteocytes. J Musculoskelet Neuronal Interact. 2002;2:245 51.
6. Sociedad Española de Investigación Ósea y Metabolismo Mineral. Guías de práctica clínica en la osteoporosis postmenopáusica, glucocorticoidea y del varón. Rev Clin Esp. 2008;208 (Supl 1) 1:1-24
7. Lawrence G, Raisz MD, Gideon A, Roldan. Pathogenesis of osteoporosis. Endocrinol Metab Clin N Am. 2003;32: 15-24.
8. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 7ª ed. 2008:206-208.
9. Teitelbaum SL. Bone resorption by osteoclasts. Science. 2000;289:1504-8.
10. Manolagas SC. Pathogenesis of osteoporosis. UpToDate 2014.
11. Rozas Moreno P, Reyes García R, Muñoz-Torres M. Osteoporosis primaria. Capítulo 52. En: Manual de endocrinología y nutrición. Madrid: SEEN; 2015.
12. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest. 2000;106(10);1203-4.
13. Riggs BL, Khosla S, Melton JL. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002;23:279-302.
14. Cosman F, Beur SJ, De Leboff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10)23 59-81.
15. Harper KD, Weber TJ. Secondary osteoporosis: diagnostic considerations. Endocrinol Metab Clin N Am. 1998; 27:325-48.
16. Stein E, Shane E. Secondary osteoporosis. Endocrinol Metab Clin N Am. 2003;32:115-34.
17. Kanis JA, MrCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF). Osteoporosis Int. 2013;24(1):23-57.
18. National Clinical Guideline Centre (UK), ed. Osteoporosis: fragility fracture risk: osteoporosis: assessing the risk of fragility fracture. London: Royal College of Physicians (UK); 2012 Aug. National Institute for Health and Clinical Excellence: Guidance.
19. Cooper C, Campion G, Melton JL III. Hip fractures in the elderly: a world wide projection. Osteoporosis Int. 2001;12:136-9.
20. National Osteoporosis Guideline Group. NOGG. Sheffield: World Health Organization Collaborating Centre for Metabolic Bone Diseases; 2010.