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Osteoporosis. Definition. Importance. Physiopathology and Clinical manifestations

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Introduction. Definition

There is no totally satisfactory definition of osteoporosis. In the 50s Fuller Albright defined it as: "too little bone"¹, a concept which is incomplete, since it only captures the quantitative, and not the qualitative, aspect of the disease. Subsequently, in 1988 the American National Institute of Health (NIH) published its first definition, in which osteoporosis is referred to as "a condition in which the bone mass diminishes, increasing susceptibility of bones to suffer fractures"². Nowadays, we accept as the definition of osteoporosis that published by the NIH in the year 2001, updating the earlier definition of 1988, which considered it to be "a disease of the whole skeleton characterised by a low bone mass and an alteration in the bone microarchitecture which causes fragile bone, the consequence of which is an increased risk of fractures."³.

Although the current definition focuses on what is the fundamental problem in osteoporosis: the existence of greater bone fragility which results in an increase in the risk of suffering fractures, and integrates the loss of quantity (bone mass), with changes in the bone quality, the alterations in microarchitecture, this definition does not have a direct clinical application, because with it we cannot identify patients who suffer from the disease. Thus, in day to day care, the definition of osteoporosis most used is that based the finding of a densitometry with a T-score lower than -2.5, although this definition has the limitation of being based exclusively on quantitative criteria.

Importance of osteoporosis

Osteoporosis is a preventable and treatable disease, but one which lacks alert signs before the appearance of fractures, which results in many patients not being diagnosed in early phases and being treated early and effectively. Thus, some studies have found that 95% of those patients presenting with a fragility fracture did not have a previous diagnosis of osteoporosis⁴.

Osteoporosis is a disease which results for those patients who suffer from it in an increase in morbidity, generating in them a deterioration in their quality of life, as well as increasing mortality, resulting in a significant consumption of social-health resources of all kinds. We discuss each of these independently.

a) Quality of life

Numerous studies have found that those patients who suffer fragility fractures have shown a deterioration in their quality of life in⁵⁻¹². In all of these cases there was a lower score in all the areas evaluated in the quality of life questionnaires.

Although the cause of this deterioration in quality of life is due in the main to the fractures, the feeling of having a chronic disease which requires long term treatment, and which in many cases occasions the development of a real terror of suffering a fracture¹³, means that depression is more common in patients affected by osteoporosis¹⁴⁻¹⁸, which in turn results in a lower score in many of the areas evaluated in the quality of life questionnaire.

Table 1. Mortality associated with the presence of fragility fractures in the Dubbo study, Australia. 1989-2004

Type of fracture	Female	Male
	<i>Odds ratio (IC 95%)</i>	
Proximal extremity of femur	2.18 (2.03-2.32)	3.17 (2.90-3.44)
Vertebral	1.66 (1.51-1.80)	2.38 (2.17-2.59)
Other fractures ("major")	1.92 (1.70-2.14)	2.22 (1.91-2.52)
Other fractures ("minor")	0.75 (0.66-084)	1.45 (1.25-1.65)

b) Increase in morbidity

Osteoporosis in itself does not increase the risk of suffering from other diseases, with the single exception, perhaps, of depressive syndrome, as mentioned above. On the other hand, a large number of diseases, or the medication used to treat them, are capable of producing osteoporosis and increasing the risk of fracture. In these cases the osteoporosis is considered to be secondary.

Fragility fractures increase the risk of suffering other fractures^{19,20}. So, after suffering a vertebral fracture there is an increase by a factor of 7-10 of suffering new vertebral fractures, and the presence of previous vertebral deformity predicts the occurrence of a hip fracture with a risk quotient of 2.8-4.5, increasing with the number of vertebral deformities²¹⁻²³.

In the same line of argument, Lindsay et al, stated that 20% of patients who had a vertebral fracture would suffer a new fracture of this type within a year²⁴.

The coexistence of various types of fragility fractures is not rare in patients with osteoporosis. Thus, for example, in a national cooperative multicentric study carried out in women who had been admitted after presenting with a fracture of the proximal extremity of the femur, it was observed that there was at least one vertebral fracture in 62.6% of cases, with the notable fact that in practically all those cases there had not been, prior to the study, a diagnosis of vertebral fracture²⁵.

The fracture of the distal third of the radius is more frequent in women, with a female-male ratio of 4 to 1. In women these fractures are more common in the perimenopause and their incidence increases rapidly after the menopause to stabilise at 65 years of age. In males the incidence stays practically constant with age. This type of fracture only requires hospitalisation in less than 20% of cases, but increases the risk of hip fracture by 50%^{26,27}.

c) Increase in mortality

Various studies have shown that those patients who suffer fragility fractures had an increase in mortality, both in descriptive studies, in which is

reported the mortality associated with osteoporotic fractures, and in cohort studies, in which it is observed that fractured patients had a higher mortality compared with controls of the same age and sex who did not have fractures. In some studies the description "excess of mortality" was used, since those patients affected by osteoporosis are generally patients of advanced age, especially those with fracture of the proximal extremity of the femur, in whom mortality is naturally high²⁸⁻³⁰.

Thus, various studies carried out in this country on the epidemiology of the fracture of the proximal extremity of the femur^{31,32} have shown that the mortality of the proximal extremity of the femur in its acute phase, considered to be during the first month after fracture, varies between 6% and 10%³³, but if a follow up is made of these patients, the mortality increases up to 30% in the first year after the fracture 31 and reaches 40% at 2 years.

The Dubbo study, Table 1, carried out in Australia between 1989 and 2004 in a population of 2,413 women and 1,898 men of over 60 years of age, also observed that those patients who had suffered an osteoporotic fracture had a higher mortality in comparison with those who did not have fractures. In this cohort the males presented a mortality higher than that of the women in all fractures³³. Similar results were obtained in a metaanalysis carried out in patients of both sexes who had suffered a fracture of the proximal extremity of the femur. It was observed that older people had an increased risk of mortality, from all causes, of between 5 and 8 times, after only 3 months having passed from the moment of the fracture, and that this increased risk was also greater in men than in women²⁹.

Physiopathology³⁴

Bone is a tissue in a state of constant formation and destruction throughout life. This phenomenon is known as bone remodelling and comes about by means of bone remodelling units which consist of a combination of cells charged with destroying small pieces of bone, which are later substituted by new bone. Bone remodelling has two main functions: in the first place, to substitute old bone tissue for new, increasing the resistance of the

skeleton to fractures, and in the second place, to make available minerals such as calcium, phosphorus or magnesium, to be transported from the bone to the extracellular liquid, and vice versa, according to the needs of the organism (Figure 1).

The cells which participate in bone remodelling are of various types, but there are two principal protagonists in the process: the osteoclasts, which are macrophages specialised in destroying bone, a phenomenon called “bone resorption”, and the osteoblasts, cells derived from the connective tissue which are charged with forming bone. There are other cells, such as the osteocytes, lymphocytes, macrophages and endothelial cells which lend their support to the bone remodelling process³⁵.

In osteoporosis there is a dysfunction in the units of bone remodelling which, in turn, is due fundamentally to two types of changes. The first consists in the establishment of a “negative balance”; the second in an increase in the number of units of bone remodelling, which gives rise to what is called “increased bone turnover”.

a) Negative balance

In young adults there is a “zero” bone balance, since the quantity of bone which the osteoblasts form in each unit of bone remodelling is equal to that which has earlier been destroyed by the osteoclasts. However, at around 40 years of age, the quantity of bone formed by the osteoclasts begins to be slightly lower than that destroyed by the osteoclasts. This situation is described as being in “negative balance”, and its consequence, logically, is the reduction in the total quantity of bone. Depending on the initial bone mass, level of negative balance, and the period during which it has been happening (ultimately, the age of the person), this loss may lead to values of bone mass which we would qualify as osteoporotic. Therefore the negative balance is a *sine qua non* for the development of osteoporosis.

The negative balance which develops with age is due fundamentally to a reduction in bone formation, probably related both to a decrease in the number of osteoblasts (due in part to a diminution in their precursors, in part to a reduction in their differentiation, and partly to a reduction in their survival) as well as in their individual activity. This is due, at least partly, to the fact that the concentration of stimulatory factors for these cells also diminishes in the bone’s microenvironment, which in some cases (Wnt proteins) has been attributed to an increase in ROS radicals in aging. On occasion an increase in bone resorption contributes to the negative balance, due to an increase in osteoclastic activity. This increase may translate, also, into a greater range for the osteoclast, up to the point at which the trabecular may become perforated. On the other hand, this increase in the activity of the osteoclasts is accompanied by the birth of a greater number of units of bone remodelling, which leads to the phenomenon we know as “increased turnover”. Against the reduction in the

Figure 1. Physiology of osteoporosis. Heterogeneity of remodelled bone

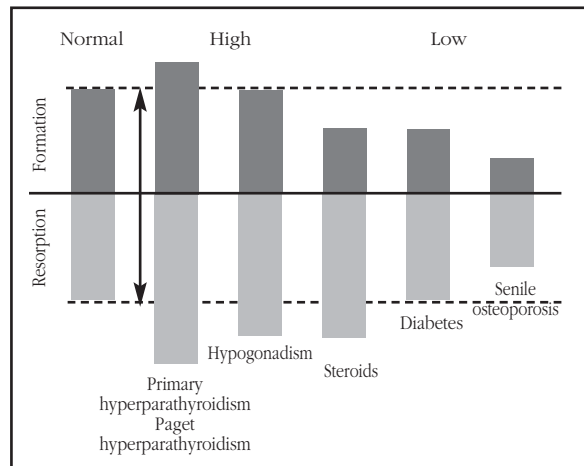


Figure 2. Lateral radiography of the spine showing a vertebral fracture



Figure 3. Measurement of the span



activity of the osteoblasts due to age, the increase in the activity of the osteoclasts bears a relationship with the reduction in estrogens. The lack of this hormone probably also inhibits the formative activity by favouring the apoptosis of the osteoblasts, which intensifies the negative balance.

b) Increase in bone turnover

The increase in the number of units of bone remodelling when they find themselves in negative balance results in an increase in the number of

Table 2. Symptoms and signs which can be observed in patients with diseases capable of producing secondary osteoporosis.

Disease	Symptoms	Signs
Rheumatoid arthritis	Pain Functional impotence Swelling Morning stiffness	Inflammation of the joints Rheumatoid nodules Finger deformities
Cushing disease	Weight gain	“Full moon” face Vinous stretch marks Obesity Arterial hypertension
Anorexia nervosa	Changes in perception of body shape Bulimic behaviour	Thinness Amenorrhea
Chronic alcoholism	Behavioural changes Ethyl fetor	Parotid hypertrophy Gynecomastia Hepatomegalia Spider angiomas* Collateral circulation* Ascitis*

**In the presence of hepatic cirrhosis*

points in the skeleton in which bone mass is lost, and thus an acceleration in this loss. In fact, although the negative balance is an indispensable factor in the development of loss of bone mass, the factor which usually has the responsibility for the greatest quantity of loss of bone mass is the increase in turnover. The forms of osteoporosis in which this factor effectively plays a primordial role are known as “high turnover osteoporosis”. The most characteristic example of increased bone turnover is the menopause, with the depletion of estrogen which it brings. It is this increase in bone turnover to which the acceleration of loss of bone mass which follows is due, and which, ultimately, is the mechanism responsible for “postmenopausal osteoporosis”. In persons of an advanced age, the increase in bone turnover may be due to the development of secondary hyperparathyroidism, which in turn may lead to both a reduction in renal function as well as a reduction in blood levels of vitamin D³⁶.

However, it should be taken into account that the heterogeneity of osteoporosis allows that there are some cases of this disease in which bone turnover is not increased, such as occurs in idiopathic osteoporosis in males, although these clinical circumstances are certainly much less frequent³⁷.

Clinical manifestations

Osteoporosis in itself does not hurt, nor does it produce any kind of symptoms. The clinical manifestations of this disease come as a result of the fractures. It is a general error to attribute to osteoporosis musculo-skeletal pain in any of its manifestations: joint discomfort, arthralgia and myalgia, general pain in the skeleton...etc. There is no clinical relationship between osteoporosis and arth-

rosis or fibromyalgia, and if these processes coincide in a patient, it is by chance.

Fragility fractures constitute the principal, if not the only, clinical complication of osteoporosis³⁸. Although certainly almost any fracture may be observed, with the exception of that of the cranium, the bones most commonly affected are the vertebrae, (Figure 2) the distal extremity of the radius, the proximal extremity of the femur (called, incorrectly, a hip fracture) and fracture of the humerus. From a practical point of view, the fractures are usually classified as vertebral or non-vertebral. We are not, personally, in agreement with this classification, since it considers equally as “non-vertebral fractures” fracture of the rib and fracture of the proximal extremity of the femur.

Vertebral fractures usually cause back pain. In the acute phase this can be accompanied by antalgic muscular contraction. The pain often becomes chronic. In a co-operative multicentric study carried out in Spain in postmenopausal women who attended the internal medicine outpatients clinic due to chronic back pain, it was found that there was at least one vertebral fracture not previously diagnosed in 15.8% of them³⁹. On the other hand, one may also observe loss of height and development of dorsal kyphosis⁴⁰. In the aforementioned study, the women with vertebral fracture had an average of 3 cm less in height than the women in the control group, without fractures.

An approximation can be made of the loss of height which has occurred in a patient by measuring the distance between the two middle fingers, with the patient seated and their arms completely outstretched (Figure 3). In normal conditions, the distance between the ends of the two fingers

corresponds approximately to the height of the patient, a fact which has been known since Renaissance times (remember the Vitruvian Man of Leonardo da Vinci).

Finally, the clinical history and physical examination may show up symptoms and signs of other diseases capable of producing secondary osteoporosis as their complications. A non-exhaustive account of these data is shown in Table 2.

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