Del Pino Montes J
Profesor Titular de Medicina - Universidad de Salamanca - Servicio de Reumatología - Hospital Universitario de Salamanca

Osteoporosis: Concept and importance. Clinical picture

Correspondence: Javier del Pino Montes - Servicio de Reumatología - Hospital Universitario de Salamanca - Paseo San Vicente, 48-183 - 37007 Salamanca (Spain)
e-mail: jpino@usal.es

Introduction

Osteoporosis is a common disease, responsible in great part for the fractures which occur in people over 50 years of age. Due to diverse pathogenic mechanisms a reduction in bone mass is produced, which is accompanied by an increase in bone fragility. Osteoporotic fractures are a health problem of great magnitude due to their repercussions not only in the health and quality of life of the patient, but also for the economic and social costs which its treatments and their side effects brings.

Definition of osteoporosis

Osteoporosis has probably accompanied humanity since its existence, but the current concept and definition are very recent. The definition was decided in two key meetings of experts, the first in 1993[1] and the more recent one, organised by the NIH in March 2000[2], from which resulted two separate consensus documents. In the first of these, osteoporosis was defined as "a systematic skeletal disorder characterised by the reduction in bone mass and alterations in the microarchitecture of bone tissue, with the consequent increase in the fragility of bone and its susceptibility to fracture"[1]. In the consensus of the year 2000, the definition was simplified to indicate that it consisted of a disease "in which bone resistance is deteriorated, which predisposes it to fracture". In addition, it was specified that " bone resistance is the result of the integration of the density and quality of bone"[2]. Viewed in this way, it is considered that a compromise of biomechanical function (resistance) happens not only due to the loss of quantity, but also due to the deterioration of other elements, such as the microarchitecture, on which the quality of bone depends. No mention was made of aetiopathogenic causes or mechanisms, given that they could influence more than one causal factor, and there are various pathogenic mechanisms from which could result in a reduction in bone resistance. It is very interesting that from the clinical point of view only the fracture is mentioned, which could reflect the poor clinical expression of the disease during its development before the fracture.

Much time has passed in achieving a consensus on this concept since the first observation in 1830, when Jean Lobstein confirmed some larger than usual holes in some human bones, which he described as porous, giving birth to the term osteoporosis. Its recognition as a clinical entity is due to Fullen Allbright, who described postmenopausal osteoporosis in 1940 and related it to a reduction in oestrogen[3]. The concept remained for a long time as the equivalent of loss of bone mass. The continuation of this error has, without a doubt, been contributed to by the definition of densitometric osteoporosis proposed by the working group of the World Health Organisation (WHO) which met in 1992[4].

It is important to distinguish between the two definitions which coexists at the moment. They represent two different approaches to the same problem, the diagnosis and assessment of risk of fracture on the one hand, and the conceptual definition on the other. Densitometric classification is an operational proposal for the assessment of risk of fracture using bone mineral density (BMD) cut-off points to diagnostic ends. It is worth remembering that a densitometric diagnosis of osteoporosis does not mean an absolute indication for treatment. And, on the contrary, some patients with

low bone mass, but not low enough to be diagnosed with osteoporosis, may have fractures. It is already indicated in the WHO technical report cited, that other parameters such as age, speed of bone loss or frequency of falls should be taken in to account[4]. This approach towards the assessment of risk of fracture is preferable. The existence of osteoporosis, or diminished bone mineral density, is one more piece of data to be included in the assessment of the patient. Recently, the WHO study group has proposed a tool for the calculation of risk of fracture called FRAX, which includes a series of clinical parameters in addition to BMD for the evaluation of the risk of fractures[5]. From the practical and therapeutic points of view the approach which centres on the patient according their risk of fracture is more useful, than the more simplistic approach which sees osteoporosis only in densitometric terms.

Some bone parameters

In the definition some concepts are introduced such as the mass, microarchitecture, resistance, density and quality of bone.

Bone mass and bone mineral density are related to the quantity of bone. Bone mass increases during the first decades of life until it reaches its maximum called "peak bone mass", at between 20 and 30 years of age[6]. It is possible to measure bone mass *"in vivo"* by calculating the BMD, which is expressed in g/cm^2. Low bone mass is the consequence of two variables: the peak bone mass achieved in youth and bone loss at later stages. Osteoporosis is usually the consequence of bone loss in adults, however, an individual who does not reach their optimum bone mass during youth may develop osteoporosis without there being great bone loss. So, insufficient bone growth in childhood and adolescence is as important as later bone loss in the development of osteoporosis[2]. The WHO has established an operational definition based on levels or cut-off points of BMD for white postmenopausal women. Thus, normal values of BMD are considered to be those above -1 (SD) in relation the average for young adults (T-score > -1); osteopenia entails values of BMD between -1 and -2.5 SD (T-score between -1 and -2.5); osteoporosis entails BMD values lower than -2.5 DE (T-score lower than -2.5) and established osteoporosis is when along with the above conditions are associated one or more osteoporotic fractures[4]. However, this classification should be used for epidemiological studies, but it should not be used in individuals as the sole criterion for the assessment of the patient. BMD only explains 70% of bone fragility[7]. For this reason, in the consensus of the year 2000, another element of bone resistance was introduced, which is bone quality.

Microarchitecture is one of the components not directly related to bone mass which was already introduced into the definition of osteoporosis in 1993. Loss of bone affects bone mass and its microarchitecture, and is especially important for the resistance of trabecular bone. The increase in the fragility of bone, when the number and thickness of trabeculae are reduced, has been confirmed in numerous biomechanical studies[8]. Techniques currently possible allow knowledge of bone microarchitecture and its resistance *"in vivo"* by means of methods such as the micro-TC, and, although at the moment only used by researchers, may become useful for the clinical evaluation of patients in the not too distant future[9].

Bone quality is one component of resistance, along with bone density[10]. It is a broad term, but integrated into bone quality are considered to be some parameters such as microarchitecture, turnover, damage accumulation and bone mineralisation. In a more generic way one may think of quality all those elements related to bone resistance, as distinct from bone mass.

Risk of fracture

A fracture occurs when a force, such as a trauma, is applied to an osteoporotic bone. In this sense, osteoporosis is a risk factor for fragility fractures. From the data of numerous epidemiological studies diverse risk factors for low bone mass and fractures have been identified. It is useful to distinguish between two types of risk factor, since some are related to the BMD, and therefore with suffering osteoporosis, while the rest are associated with osteoporotic fracture, whose prevention should be the principle objective of therapeutic interventions. Some of the risk factors for low bone mass can be seen in Table 1. Greater consideration should be given to risk factors for fracture, such as low BMD itself, and others, independent of BMD, among which are found previous history of fragility fractures, family history of osteoporotic fractures, thinness, active smoking, consumption of alcohol and an increase in bone turnover[11]. Not all these factors have the same predictive force for fractures and notable for their clinical importance are personal or family history of fractures[12-15].

Some extraskeletal circumstances may influence the mechanism of production of fractures. Hence, it is useful to remember that fractures depend on the concurrence in an individual of a fragile bone and a fall. It is not surprising that the frequency of falls is also associated with a higher risk of fractures[16].

When the development of a cohort is observed it is possible to check how a group with negligible fragility fractures occurs in subjects with BMD above the level of osteoporosis[17]. Therefore, strategies directed at the detection of those individuals with osteoporosis are insufficient to prevent fractures. It would seem to be more profitable to direct that effort to the identification of individuals with a high risk of fractures. Hence, the estimation of absolute risk at 10 years allows the approximation of reality with greater objectivity. The WHO has proposed a software tool FRAX, available online, which allows the evaluation of the absolute risk of fracture at 10 years[5]. The calculation is made using an algorithm which includes BMD and

a series of independent clinical factors which are included in Table 2. The strongest clinical factors, in addition to the BMD, are age, personal history of fracture, family history, consumption of corticoids and the existence of rheumatoid arthritis.

Aetiopathology

In the last decade we have seen a revolution in the understanding of bone biology. Part of the intricate network of cytokines, growth factors and the cell's participation in the regulation of bone metabolism and how to modify these cellular signals in different situations are now understood. Osteoporosis is the consequence of an alteration in bone remodelling which consists of an imbalance which favours resorption over formation. The result is low bone mass, and changes in the microarchitecture[18]. There are various types of osteoporosis which can be classified into two groups, primary and secondary[19].

The most common type of osteoporosis is postmenopausal, which is linked to two conditions, the menopause and aging. In women the ceasing of ovary function, and the consequent reduction in oestrogens, is accompanied by a phase of accelerated bone loss. Treatment by substituting the oestrogens reverses, to a great degree, this situation. The oestrogens reduce osteoclastogenesis by means of a complex, and not yet completely understood, interaction of cellular signals and bone cells[20]. Their deficiency increases resorption and the loss of bone mass and structure, which translates into bone fragility.

Another type of primary osteoporosis is involutive osteoporosis, which affects both men and women, and which is more associated with aging. The existence of a negative calcium balance and a certain degree of secondary hyperparathyroidism have been the pathogenic mechanisms linked to this bone loss. However, recent studies suggest that oestrogen deficiency may play a significant role in later stages of life, regulating the homeostasis of extraskeletal calcium. The oestrogens may modulate the cacium balance, favouring its intestinal absorption and limiting its renal elimination. In addition, an active influence of the oestrogens in the metabolism of vitamin D and its capacity to reduce the secretory reserve of parathormone (PTH), has been described. These circumstances have allowed the development of a unitary model of involutive osteoporosis, in which the deficiency of oestrogens plays a central role[21].

Male osteoporosis is less frequent than postmenopausal osteoporosis. From the point of view of using the BMD, recommended as cut-off points for an indication of postmenopausal osteoporosis are a T-score below -2.5 of the average for the young population[22]. The occurrence of primary osteoporosis in males appears to be lower than that for women. In the first situation the production mechanism is principally of an involutive type.

The causes of secondary osteoporosis are those which are produced as a consequence of a disease, or from taking pharmaceutical drugs. The most common is osteoporosis due to glucocorticoids. The risk of fracture is independent of BMD and is both related to the daily dose and the accumulated dose. Yet, even doses lower than 7.5 mg/day of prednisone, or equivalent, increase the risk of vertebral fracture when the accumulated dose is lower than 1g[23]. When the treatment with glucocorticoids is withdrawn the risk of fracture goes down, but remains higher in relation to patients who have not taken them[24]. In general, we may consider that half those patients treated for 6 months with glucocorticoids will have osteoporosis. The greatest bone loss is produced during the first 3 months of treatment due to its effect in inhibiting the apoptosis of the osteoclasts[25]. This action is by empowered by an increase in the apoptosis of the osteoblasts with a reduction in bone formation. The adverse effects of treatment also reach the muscle, which is atrophied, in turn, losing force and resistance, which presents a risk of falls.

Table 1. Some risk factors for low bone mass

Not modifiable	Modifiable
Age	Little physical exercise (sendentarism)
Sex (female)	Diet poor in calcium
Genetic	Hyperproteic diet
Menopause	Smoking
Hypogonadism	Alcohol abuse
Endocrinal diseases: Cushing, primary hyperparathyroidism, hyperthyroidism	Thinness (BMI < 19 kg/m^2)
Rheumatological diseases: Rheumatoid arthritis	Glucocorticoids
Nutritional diseases: malnutrition anorexia nervosa	Immunosuppressors
Disease of the digestive system: celiac disease, severe hepatopathies	Anticoagulants
Neoplasias: multiple myeloma	Heparin
	Proton pump inhibitors

Importance of osteoporosis

Osteoporosis has a great impact on the general population. Osteoporotic fractures impose a load of great magnitude from a socioeconomic point of

Table 2. Variables included in the FRAX tool

- Age
- Sex
- Weight
- Stature
- Previous fracture
- Parents with hip fracture
- Active smoker
- Taking glucocorticoids
- Rheumatoid arthritis
- Secondary osteoporosis
- Excessive consumption of alcohol
- BMD in femoral neck, which nuances the overall result of the other variables

view. It is a very common disease which affects 150-200 million people in the world. Approximately half of these patients come from the developed countries of North America, Europe and Japan. In general terms, it is estimated that around 33% of women over the age of 50 years will suffer from osteoporosis. Although measures have been proposed to reduce the problem, osteoporosis continues to be under-diagnosed and many patients, even with fractures recognisable as osteoporotic, remain without treatment. The social and political measures are not yet sufficient to address the prevention of this serious socio-health problem.

In addition to the personal repercussions due its high morbi/mortality, osteoporosis generates considerable socioeconomic costs. The analysis of these costs carry a high degree of uncertainty. The calculation is difficult and unreliable, since the available information is incomplete[26].

The costs, as is logical, are not limited to the pharmacological or surgical interventions. They are divided into direct and indirect costs. Among the first are those due to hospitalisation, outpatient care and drugs. These may be related to immediate assistive, social and hospital care, both short and long term, and to drugs. The costs of hospitalisation can be seen to be influenced by its duration. Within the outpatient care are included visits to the traumatologist, visits to other doctors, including the general practitioner, nurse visits, physiotherapy, occupational therapy and telephone assistance. Counted in the direct non-medical costs are social care and informal care. Services to be taken into account within social care, among others, are adaptations to the home, home health care, general home help and transport. Finally, among indirect costs, should be considered as key the loss of production of the patient, or of the family who looks after them[27]. On the other hand, the reduction in quality of life related to health has a significant social and individual cost.

Clinical manifestations

Osteoporosis is an asymptomatic disease. For this reason it has been called the "silent epidemic"[4]. It is a mistake to consider that bone loss is accompanied by musculoskeletal pain, and it is relatively common that patients are referred for this reason with the suspicion of osteoporosis, especially women in the peri- or first years of the menopause.

The principle clinical manifestations are due to its complications, fractures. The most frequent fragility fractures are located in the spinal column, the wrist and the hip. They are usually classified in a more general way as vertebral or non-vertebral. Among the non-vertebral fractures are also included those of the humerus, pelvis, ribs and other less frequent types. Not usually included as osteoporotic fractures are those of the finger, and cranium, but there are some doubts about fracture of the ankle[21].

They are produced by a minor trauma, such as a simple fall from a standing position. For this reason also, they are known as fragility fractures. They appear principally after the age of 50 years, and that differentiates them from the traumatic fractures which predominate in youth. The clinical manifestations of these fractures are the same as other fractures in the same location, and are accompanied with pain, loss of functional power and deformity[29].

The vertebral fracture is the most prevalent. Its typical clinical presentation form is acute pain, although not infrequently it can be asymptomatic. It can be the consequence of a mechanical effort in carrying or lifting weight, but also can have no apparent cause. The most typical manifestation is acute, intense pain located in the spine, which is exacerbated with movement and reduces with rest. This becomes very incapacitating, impeding sleep. The intensity of the pain usually reduces after the first 2-3 weeks, before disappearing after 2-3 months. The pain may radiate towards the ribs or the legs, according to whether it proceeds from the dorsal or lumbar spine. However, almost two thirds of vertebral fractures are asymptomatic and can only be confirmed by means of radiography of the lumbar or dorsal spine. For this reason these are classified as clinical or morphometric fractures, the latter only evident through imaging techniques[30,31]. In some patients, as a consequence of structural changes in the spine there may develop an instability of the spine, with paraspinal muscular contraction, ligamentous tension and incongruity in the articular facets which may be the cause of chronic axial pain[32].

Thoracic vertebral fractures usually have a "cradle" compression from which originates the characteristic kyphosis of these patients ("the

widow's hump"). In lumbar fractures the vertebrae are usually squashed in height the centre (devil's vertebrae). The loss of height of the vertebral bodies reduces the distance between the ribcage and the pelvis, which in some patients even results in the establishment of painful contact between the ribs and pelvis (costo-pelvic syndrome). The accumulation of vertebral crushing is translated into a loss of height. Some authors consider that a reduction of more than 3 cm in two years may be a sign of vertebral fractures. It has been proposed that the span of the higher extremities, a measure equal to the body height in youth, be compared with the height of the patient to detect reductions in height. It is of considerable interest that rarely in osteoporotic vertebral fractures are observed the neurological complications which accompany vertebral fractures of a different origin[33]. The appearance of medullary or radicular neurological manifestations should make us think of a non-osteoporotic origin for a fracture[32]. These modifications in the spine may cause difficulties in thoracic movement and affect breathing. The abdomen loses capacity , and becomes prominent, with consequent modification the intestinal tract. The most serious fracture is that of the hip, generally triggered by a fall. Although there are no data which support it, it has become common belief that in the presence of significant osteoporosis, the patient fractures their hip standing up, after which they fall. The highest rate of mortality associated with osteoporosis is related to hip fracture and represents one of its most significant social costs. The causes of death are diverse and in many cases are not directly related to the fracture[34]. The mortality is 20-30% in the first year, which means that the risk of death increases by 2 to 10 times that expected in a population with similar characteristics[35]. Most cases require surgical intervention. But the repercussions of a hip fracture are not limited to its hospital treatment, but also to the deterioration of the quality of life. The majority of patients have residual disability and a percentage of cases lose the capacity to live an independent life. For example, only a fifth of those patients who walked unaided before the fracture can do so 6 months after it[27].

The Colles fracture has fewer repercussions than the two earlier ones. Some patients can experience persistent local pain, functional incapacity, neuropathy and posttraumatic arthritis; in addition, it is a significant risk factor for future presentation of vertebral or hip fractures[27]. Finally, the psychological and social impact should be taken into account, which may result in osteoporotic fractures. The development of depression is the psychological disorder most frequently cited. The appearance of anxiety, fear of new fractures, and other emotional reactions are also important, and influence the recuperation of those patients[36]. The repercussions on families of patients with hip fracture and often with a great physical and psychological dependency, cannot sensibly be calculated due to their complexity.

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