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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].

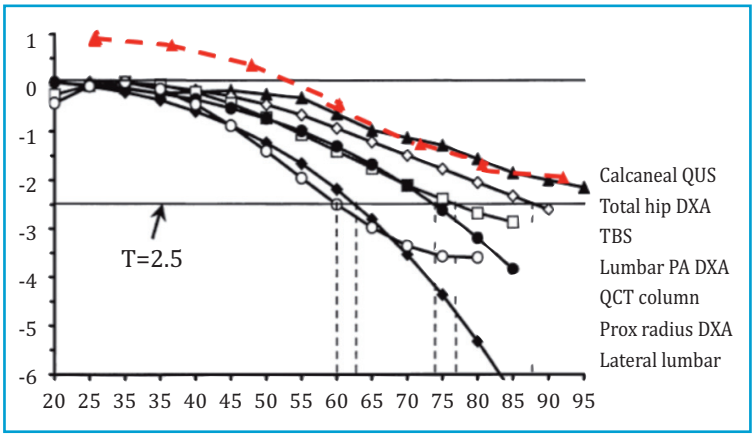
Other societies consider it either as a prior screening or as a third option for, subject to the objective risk, establishing a treatment with cut-off points of 20% for major fractures or 3% for hip fractures, and even variable intervention thresholds depending on the age, being 9-15% between 40-65 years-old, 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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