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Clinical impact of misinterpretation of dual-energy X-ray absorptiometry during the evaluation of osteoporotic patients

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ABSTRACT
Osteoporosis is a highly prevalent systemic skeletal disorder leading to decreased bone strength and increased susceptibility to fragility fracture. The global burden of osteoporosis negatively impacts health systems around the world, and the estimation of millions of individuals at high risk for fracture in 2010 will double by the year 2040. There are many techniques to evaluate bone mineral density, but the preferred method in clinical practice is dual-energy X-ray absorptiometry (DXA). This method, despite offering multiple advantages, can lead us to a wrong diagnosis if we do not take into account certain clinical and technical considerations. The objective of this review is to analyze the different aspects that we must consider when, as clinicians, we have to evaluate a densitometric report. These aspects are presented as technical factors influencing DXA results and patients’ conditions limiting DXA interpretation.

Introduction
Dual-energy X-ray absorptiometry (DXA) is the most commonly used technique for measuring bone mineral density (BMD) and is considered the ‘gold standard’ of BMD testing [1]. Its value is expressed as standard deviations (SDs) from the population mean in young adults (T-score). The reference range recommended by the International Osteoporosis Foundation (IOF), the International Society for Clinical Densitometry (ISCD) [2], the World Health Organization (WHO) [3], the National Osteoporosis Foundation (NOF) [4] and the American Association of Clinical Endocrinologists (AACE) [5] for calculating the T-score in postmenopausal women is the National Health and Nutrition Examination Survey III reference database in Caucasian women aged 20–29 years [6].

The diagnosis of osteoporosis in postmenopausal women and men aged 50 years and older is based on the densitometric result of low BMD, T-scores and the WHO diagnostic criteria [7,8]. The WHO diagnostic criteria may also be applied to women in the menopausal transition [2]. Some modifications to the original WHO diagnostic criteria have been included in recent international guidelines (Table 1) [5].

The Z-score describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex [2]. For BMD reporting in females prior to menopause and in males younger than age 50 years, Z-scores (not T-scores) are indicated. This also applies to children and adolescents. A Z-score \( \leq -2 \) SDs is defined as ‘below the expected range for age’ and a Z-score \( > -2.0 \) SDs is ‘within the expected range for age’. A low Z-score in a postmenopausal woman indicates the need to evaluate for secondary osteoporosis [2,9].

DXA technology offers advantages, such as minimal radiation and high precision and reproducibility. DXA results correlate well with fracture risk, bone mass being one of the best risk factors for fracture [3,4]. Despite these advantages in clinical practice, numerous errors in interpretation of the results often lead the treating physician to make mistakes, with negative consequences for their osteoporotic patients [10,11]. Most of these errors can be avoided with proper training of technical personnel, proper equipment calibration and medical education.

Dual-energy X-ray absorptiometry
DXA is considered the reference standard for BMD measurement, being the most widely used densitometric technique for diagnosing osteoporosis [5] and predicting fracture risk [12]. This technique offers multiple advantages: non-invasive, low cost, widely available and very good reproducibility.
Table 1. WHO and AACE diagnostic criteria for postmenopausal osteoporosis.

<table>
<thead>
<tr>
<th>Category</th>
<th>WHO diagnostic criteria for postmenopausal osteoporosis and osteopenia</th>
<th>AACE diagnostic criteria for osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥ −1 SD</td>
<td>≥ −2.5 SDs in the lumbar spine, femoral neck, total proximal femur and third portion of the distal radius</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>Between −1 and −2.5 SDs</td>
<td>Low spine or hip fracture (regardless of bone mineral density)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ −2.5 SDs</td>
<td>Between −1 and −2.5 SDs and a fragility fracture of the proximal humerus, pelvis or distal forearm</td>
</tr>
<tr>
<td>Severe or established osteoporosis</td>
<td>≤ −2.5 SDs and fragility fracture</td>
<td>Between −1 and −2.5 SDs and high FRAX (or, if available, TBS-adjusted FRAX) fracture probability based on country-specific thresholds</td>
</tr>
</tbody>
</table>

*AAdapted from [3].

**Adapted from [5].

AACE, American Association of Clinical Endocrinologists; FRAX, Fracture Risk Assessment Tool; SD, standard deviation; TBS, trabecular bone score; WHO, World Health Organization.

**Areas of study**

The diagnosis of osteoporosis is established when the physician selects the lowest value from the accepted regions of interest (ROIs). These are the lumbar spine, proximal femur and third portion of the distal radius (defined as 1/3 distal radius).

For spine evaluation, a postero-anterior scan of the L1–L4 vertebral bodies is recommended. Vertebrae with significant lesions should be excluded. To assess the lumbar spine, at least two evaluable vertebrae are required. The reported BMD at the lumbar spine is an average of the BMD from L1 to L4 [13].

The density of the total hip is recommended due to its high precision, reproducibility and correlation with fracture risk. The evaluation of the femur can be performed on the right or left hip, and the lowest value should be considered for treatment decisions. Final reporting of BMD is based on the lowest T/Z-score among these sites [10,13,14].

The forearm may be used when the hip or spine cannot be measured or interpreted, but there can be a significant difference in BMD between the dominant and non-dominant arms. Patients with changes due to hip fracture or prosthetic hip replacement cannot be evaluated and the study of the non-dominant forearm could be measured, as is usually done for patients with morbid obesity and primary hyperparathyroidism [13].

Spinal and total hip BMD should be used for monitoring treatment [13].

**Quality control program at the DXA center**

Each DXA center should follow a program of quality control following manufacturer guidelines, performing periodic phantom scans and follow-up, and complying with government inspections, radiation and regulatory requirements. Cross-calibration should be performed when changing hardware or systems [13].

**Precision errors**

DXA has low values of precision error, expressed as the coefficient of variation [10]. Low precision error is important to detect small longitudinal changes related to disease progression or treatment intervention. For this reason, the ISCD [13] considers the minimum acceptable precision values, for an individual technologist, with their corresponding least significant change (LSC) [13] (Table 2).

Precision errors can be influenced by several factors, which are mainly related to daily quality assurance procedures and the operators’ training.

**Follow-up**

Absolute measurements from different machines differ significantly, so standardized reference ranges should be used. Serial measurements should be performed on the same machine to identify true changes in the patient’s BMD.

Previous or baseline study ROIs should be used for comparison. Significant changes between current and previous studies have to be reported in grams per square centimeter and as a percentage based on the precision error and LSC [13].

**Contraindications**

Some contraindications to DXA include pregnancy, recent (<5–7 days) administration of a contrast agent and a recent (<2 days) isotopic study [15,16].

**Misinterpretation of DXA results during the evaluation of osteoporotic patients**

During the clinical evaluation of a patient with osteoporosis, adequate measurement of the BMD by DXA, integrated with the patient’s risk factors, allows the clinician to make appropriate decisions in terms of follow-up and drug interventions.
It is necessary that the DXA scan has been technically performed properly in order to have reliable results. On the other hand, the clinician must evaluate the clinical conditions of the patient and their specific risk factors and make therapeutic decisions through risk calculation tools for osteoporotic fracture. There are numerous clinical conditions that can alter the measurement of BMD and, on the other hand, there are numerous medical conditions associated with increased fracture risk, independently of BMD.

**Technical factors influencing DXA results**

The DXA scan must be properly performed in order to provide reliable information. Acquisition errors in patient positioning and other physical artifacts can usually be overcome by trained staff, quality control and regular services of the machines.

The most frequent errors are related to incorrect patient positioning, ROI placement, movement and foreign bodies.

**Incorrect patient positioning and ROI placement**

Correct positioning is critical for accurate measurements and should be confirmed by the clinician. Incorrect positioning is one of the main causes of errors in the estimation of BMD. Inadequate placement of the ROIs is another important source of errors [14].

In the postero-anterior study of the lumbar spine, the patient lies supine on the table with their legs flexed over a support pad that reduces the lumbar lordosis and approaches the spine to the table. The ROI is placed on the L1–L4 vertebral bodies. Spine images should be centered, straight and not rotated [10,17] (Figures 1 and 2).

For the study of the hip, the patient lies supine with legs slightly in abduction in order to maintain the femoral axis straight and in internal rotation (15–30°), in such a way that the lesser trochanter is not visible on the image [10,17] (Figures 3 and 4).

**Movement**

Motion artifacts can also interfere with a quality report. Specific indications must be given to the patient by the technician during the study (Figure 5).

**Foreign bodies**

Surgical clips, navel rings, zippers, coins, chains, necklaces and metal structures of underwear interfere with the BMD evaluation (Figure 6).

Radiographic contrasts or orthopedic casts are other interference factors. Radiographic contrast media presumably increase the attenuation of soft tissues to a level greater than that of the bone. DXA measurements can be performed in association with other radiological techniques, with the exception of computed tomography scanning conducted with iodine-based contrast agents during the previous 7 days [15,16] (Table 3).

**Patient factors limiting DXA interpretation**

Factors directly related to the patient can alter the assessment of BMD during the DXA scan. On the other hand, the underlying medical conditions can become a real challenge for the clinician when making therapeutic decisions. For this reason, there are specific clinical guidelines and therapeutic intervention thresholds for specific cases with the aim of guiding the treating physician, beyond the technical aspects of carrying out the DXA scan [18,19].

Although there are numerous medical conditions associated with a high risk of fracture independent of BMD, we have chosen three medical conditions for this presentation (diabetes mellitus and obesity; osteomalacia; and glucocorticoid-induced osteoporosis), not only because of their high prevalence in routine clinical practice but because they allow us to reiterate the importance of a comprehensive approach to the patient in which the combination of the results of BMD from DXA ideally with complementary information – such as vertebral fracture assessment and the trabecular bone score (TBS), bone markers and calculation of the probability of fracture through a validated tool, for example FRAX – allows the physician to estimate the individual degree of fragility and adequate management of the patient.

**False increase of BMD results**

**Vertebral diseases**

Numerous clinical conditions can invalidate the spine BMD assessment: osteoarthritis, spondylosis and osteophytes are
associated with bone proliferation and morphologic changes. Vertebral fracture, sclerotic lesions, bone metastasis, tumors and Paget’s disease are conditions that falsely increase BMD. Patients with scoliosis cannot be positioned with the spine straight on the table, and often those with severe scoliosis have degenerative changes that invalidate the spine measurement (Figures 1 and 2).

**Calcifications**

Vascular calcifications, specifically aortic calcifications, are common causes of misinterpretation of DXA scans.

**Medical conditions with high risk for fracture independent of BMD result**

Despite the multiple advantages of DXA, this technique will not provide an accurate reflection of fracture risk in patients with degenerative changes, those treated with corticosteroids, and obese and diabetic populations, which show higher results and underestimation of risk fracture. Underestimation of risk fracture is also observed in those with small bones or low body weight. Different studies have shown that other techniques such as evaluation of the trabecular bone structure (TBS) can complement BMD evaluated by DXA in predicting fracture risk [20].

Figure 2. Improper positioning: incorrect scan analysis and artifacts. In this case, new degenerative changes appeared and the selected region of interest is not the same. The difference in bone mineral density is not real.
Diabetes mellitus and obesity

Diabetic patients, both type 1 and type 2, of both sexes suffer from osteoporotic fracture at higher BMD than the general population. This condition is known as the diabetic paradox [21,22]. A complex multifactorial pathophysiology is involved in this condition, where chronic hyperglycemia, advanced glycated end product accumulation by direct and indirect mechanisms, chronic inflammation, increased levels of sclerostin and low vitamin D modify the biomechanical bone properties, increase bone porosity, reduce bone density and increase fragility fractures. This condition is aggravated by chronic diabetic complications. Diabetic retinopathy and neuropathy increase the falls and fracture risk [23,24] and the fracture incidence rises progressively with chronic kidney disease (CKD) stage impairment, from 15.0 to 46.3/1000 person-years, and the risk of skeletal fracture is up to five times higher in individuals with an estimated glomerular filtration rate <15 versus >60 ml/min/1.73 m² [25].

The relation between CKD and a high fragility fracture risk is associated with multiple risk factors: advanced age, specific diabetic factors and low BMD. A range of disturbances of bone and mineral metabolism, including secondary hyperparathyroidism, low serum levels of active vitamin D metabolites and metabolic acidosis, are involved. CKD plays a greater role in altering bone architecture and reducing bone strength in younger than in older age groups, when other traditional risk factors for hip fracture become more prevalent. In this population, DXA provides an assessment of BMD, but does not provide information on bone quality and is not a good predictor of risk for hip fracture in patients with CKD [26].

Some diabetic medications have been associated with an increased risk of fracture in this population, such as rosiglitazone and canagliflozin [27,28].

Risk fracture assessment can be improved by the integration of clinical risk factors with or without BMD, and treatment decisions should be based not only on the T-score for BMD, but also on the independent contribution of other validated risk factors [29].

The WHO Collaborating Centre in Sheffield, UK released FRAX, the Fracture Risk Assessment Tool, in 2008. FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of hip and major osteoporotic fractures (clinical spine, distal forearm and proximal humerus fractures) [30].

The selection of FRAX clinical factors was based on the follow-up data from nine prospective population-based cohorts. These comprised age, parental history of hip fracture, exposure to systemic glucocorticoids, prior history of fragility fracture, current smoking, high intake of alcohol (three or more units daily, on average) and the presence of rheumatoid arthritis as an indicator for secondary osteoporosis [31]. FRAX models have to be calibrated to the fracture and death epidemiology in individual countries [29].

FRAX has several limitations that need to be considered when the results are interpreted. FRAX assessment does not take into account dose–responses for several risk factors (glucocorticoid exposure in terms of dose and duration, smoking cigarettes and alcohol intake), and other risk factors like diabetes mellitus, CKD, history of falls and androgen depletion or hormone antagonist therapy. Previous multiple fractures and the importance of time dependence with a previous fracture and the status of imminent risk following the event are also important risk factors proposed for FRAX adjustments [31].

Based on recent clinical trials, correcting factors have been proposed to adjust FRAX probabilities for recent fracture [32], glucocorticoid dose and duration [33], diabetes mellitus [34] and falls history [35].

The risk underestimation using FRAX and DXA delays therapeutic interventions [36]. Adaptations of risk calculator tools and individualized therapeutic intervention schedules, with lower thresholds than usually indicated for the general population, have been proposed in order to attend to this chronic and unrecognized diabetic complication [18].

Adults with obesity have significantly higher BMD than healthy-weight adults [37]. But, as for diabetic patients, an elevated BMD does not give protection against fractures, configuring the obesity and diabetes paradox [23].

The affected bone quality and structure result from a combination, on the one hand, of the release of inflammatory and immunomodulatory cytokines, counterbalanced by the mechanical overload. Complementary techniques such as TBS evaluation could offer more accuracy during the fracture

**Figure 3.** Proximal femur: shaft is straight, leg internally rotated (lesser trochanter small or not seen). Visually verify bone edges and regions of interest.
risk evaluation. The TBS is a textural index obtained from lumbar spine DXA, which provides indirect information on skeletal quality [38,39].

### Osteomalacia

Osteomalacia, a mineralization defect of the bone matrix, leads to low mineral content of the skeleton. Caused by chronic vitamin D deficiency, it represents the most common cause of secondary osteoporosis. BMD may be normal or slightly reduced in patients with osteomalacia and may lead to underestimation of the fracture risk due to decreased bone mineralization. Osteomalacia cannot be distinguished from osteopenia or osteoporosis evaluated by radiographic examination or DXA. Patients and physicians should be alert to the potential presence of osteomalacia, and should correct vitamin D deficiency before starting treatment of osteoporosis [40,41].

### Glucocorticoid treatment

Glucocorticoid-induced osteoporosis is a frequent cause of osteoporotic fractures. The combination of reduced BMD and

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Figure 4. Top: femoral shaft is angled and internal rotation limited due to hip osteoarthritis. Bottom: gluteal implant artifact.

Figure 5. Forearm scan: motion artifacts.
bone quality induces bone fragility in these patients. DXA evaluation and the available fracture risk calculators underestimate the fracture risk in this population. For the 10-year fracture risk calculator, the WHO’s FRAX, many adjustments have been proposed in order to solve this limitation based on the dose, duration of use and mode of delivery of glucocorticoid preparations [42].

The BMD decrease does not correlate with the high risk of fractures observed in glucocorticoid-induced osteoporosis. For this, lower BMD thresholds for therapeutic intervention have been proposed in this population. Other radiological methodologies, with some limitations, such as quantitative computed tomography and the TBS, have been suggested to be a better approach to predict osteoporotic fractures than DXA [43].

**Discussion**

The global burden of osteoporosis negatively impacts health systems around the world and the estimated 158 million individuals at high risk for fracture in 2010 will double by the year 2040 [44]. In 2000, the prevalence of osteoporotic fractures was estimated at 9 million, with the well-known impact that this high number of fractures imposes on our societies due to their high cost of treatment, excess mortality, morbidity and disability [45].

Suboptimal DXA reports are common and may adversely impact clinical patient management. Recently, the ISCD and the IOF invited fracture liaison services to participate in a survey assessing the access to, and quality of, their DXA facilities and DXA reporting worldwide. This survey found...
Table 3. Technical source of errors during dual-energy X-ray absorptiometry (DXA) examination.

<table>
<thead>
<tr>
<th>Technician errors</th>
<th>Vertebral diseases</th>
<th>Calculations</th>
<th>Metals and surgical elements</th>
<th>Contrast media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect patient positioning Movements Region of interest placement</td>
<td>Osteoarthritis Spondylosis Spondyloarthropathy Osteophytes Scoliosis Fractures Sclerotic lesions Bone metastasis Tumors Paget’s disease</td>
<td>Vascular calcifications</td>
<td>Keys Coins Piercings Metallic buttons Bra clips Stents Cava vein filters Surgical clips Vertebroplasty cement Other surgical hardware</td>
<td>Gastrointestinal contrast material Computed tomography scanning conducted with iodine-based contrast agents</td>
</tr>
</tbody>
</table>

considerable variation in the method for assessing significant BMD change over time. Less than 50% of DXA facilities confirmed the use of LSC values for assessing significant change in BMD, which is extremely important in the follow-up of our patients and in the evaluation of treatment efficacy. Around 40% of facilities failed to state the frequency of phantom calibration [46].

The authors, in their experience, have identified the following problems with high frequency in the clinical interpretation of DXA studies:

1. Wrong interpretations when comparing two reports from different DXA machines. The comparison of two densitometries requires the incorporation of a statistical evaluation between the two pieces of DXA equipment.

2. The diagnosis of osteoporosis in premenopausal people. The diagnosis must be very different. This should be reported as BMD below the expected range for age and not osteoporosis. It warrants evaluation but does not necessarily warrant treatment with drugs.

3. In the interpretation of follow-up densitometries, many centers do not publish their own LSC value and use the one reported by the manufacturer.

4. Ideally, there should be good communication between the clinician and the densitometric center. Effective communication between healthcare professionals and the densitometric center is needed to make accurate diagnoses.

5. Finally, we have frequently observed therapeutic implementation and treatment suspension based solely on erroneous interpretations of densitometric studies.

Screening and follow-up BMD evaluation shall take place in certified units, and should instruct the patient to carry out follow-up at the same center, in order to be able to compare results and evolution. The radiologist for the local DXA should be able to provide the LSC.

Some situations should alert us that the results are not real or cannot be interpreted as expected responses to prescribed treatments. For example, a large increase in BMD greater than 10% may result from a technical error, caused by the interference of some metals, vascular calcifications or medical devices, or from a pathologic condition, like a fracture or metastasis. On the contrary, a BMD decrease greater than 5% per year would be an unexpected change for age-related changes in relation to osteoporosis. If measurement errors are excluded, lytic metastasis or secondary causes for osteoporosis should be considered [47].

Other important aspects to evaluate when analyzing the results of densitometry are the underlying pathologies of the patient, such as the presence of diabetes mellitus, obesity or osteomalacia, or the chronic use of glucocorticoids, conditions in which a normal or slightly low BMD could be associated with a high risk of fragility fracture and could require therapeutic interventions earlier than the general population.

Serial DXA BMD testing is useful in monitoring response to therapy. Detection of loss of bone density may indicate therapeutic failure, lack of adherence or coexistence of secondary causes of osteoporosis [13].

The evaluation of BMD by DXA presents some limitations that can be partially overcome with the complementary use of the TBS and vertebral fracture assessment. DXA cannot differentiate trabecular from cortical BMD, which may be important in patients with high cortical porosity, as occurs in glucocorticoid-treated patients. Other newer technologies like high-resolution peripheral quantitative computed tomography, multi-detector computed tomography and magnetic resonance imaging measure bone quality, given valuable complementary information about bone fragility. At the present time, technical limitations limit the use of these techniques in clinical practice and high-resolution peripheral quantitative computed tomography is not approved for clinical use [48].

Conclusion

DXA is commonly used to assess BMD, although several pitfalls can lead to misinterpretation. We have provided a basic approach to reduce errors during the densitometric BMD evaluation and to be able to make appropriate clinical decisions. We emphasize the importance of maintaining technical high-quality standards in order to optimize patient management. Scanners, software, calibrations, patient positioning, selection of ROIs and patient-related artifacts should be evaluated. Results from different scanners are not interchangeable; to compare different studies, it is important to use the same scanner and software program.

DXA studies offer extremely useful information in the evaluation of patients at risk of fragility fractures and continue to be the gold standard in the diagnosis of
osteooporosis. Their interpretation requires rigorous attention, since errors can induce incorrect diagnosis and inappropriate clinical decisions.

Potential conflict of interest The authors report no conflicts of interest.

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