Imaging of metabolic bone disease

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Summary. Osteoporosis is the most important metabolic bone disease, with a wide distribution among the elderly. It is characterized by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Identify bone weakening with an appropriate and accurate use of diagnostic imaging is of critical importance in the diagnosis and follow-up of osteoporotic patients. The aim of this review is to evaluate the detection rates of the different imaging modalities in the evaluation of bone strength, in the assessment of fracture risk and in the management of fragility fractures. (www.actabiomedica.it)

Key words: bone densitometry, osteoporosis, aging, high resolution imaging, bone

Introduction

Osteoporosis is recognized as a serious and increasingly public health issue due to its high prevalence in aging people, in which it contribute to reduce physical performance and increase the risk of fall-related injury, disability, and mortality (1-5).

Osteoporosis is the most important metabolic bone disease and is characterized by low bone mass and microarchitecture deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk (6-10).

The most common type of osteoporosis is involutional osteoporosis, which is classified into type I or postmenopausal osteoporosis and type II or senile osteoporosis (11-20). Postmenopausal osteoporosis usually occurs in women between ages 50 and 65 years, affecting those within 15 to 20 years of menopause. The estrogenic deficiency is linked to an accelerated trabecular bone resorption, which may lead to fragility fractures that typically involve spine and wrist. Senile osteoporosis occurs in women or men more than 70 years of age and the main feature is that the bone loss pattern involves the cortex and the trabeculae, leading to fragility fractures usually located at the hip, pelvis, and proximal humerus. Despite the well-recognized role of estrogenic deficiency in type I osteoporosis and the consequent higher prevalence of fragility fractures in 40-50 y.o. women, multiple investigations have confirmed an age-related significant prevalence of senile osteoporosis in men as well (21-25).

Although several studies have already highlighted higher mortality rates in women who experienced a vertebral fracture, the social and economic burden
of osteoporosis still remains partially underestimated (26-30).

Identify bone weakening with an appropriate and accurate use of diagnostic imaging is of critical importance in the diagnosis of osteoporosis at an early and in the management of the complications that often implicate differential diagnosis issues, most of all in a geriatric patient. It also allows to predict fracture risk, to determine the treatment approach and to help monitor disease progression and response to therapy.

Therefore, the aim of this review is to evaluate the detection rates of the different imaging modalities in the evaluation of bone strength, in the fracture risk's assessment and in the fragility fractures management.

**Imaging techniques**

Besides conventional radiography, imaging techniques developed to diagnose the loss of bone mass and the micro architectural deterioration of bone tissue are dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) (31-35). Generations of DXA systems provide not only accurate and reproducible measurements of BMD but also the opportunity to use high-quality DXA scans in place of standard X-rays to identify vertebral fractures. Semiquantitative and fully quantitative methods to determine the presence of vertebral fracture (36), as well as indices related to hip geometry (35, 37-40), can be derived from high-quality DXA images. Bone stiffness assessed by finite element analysis of X-ray images (FEXI), a technique that uses a finite element analysis model applied to 2D gray-level images, can also be extracted from DXA images (41-45).

Finally, the evaluation of bone mineral distribution at the proximal femur in hip DXA scans may be well suited to enhance standard densitometric evaluations as a predictor of hip fracture risk. Taking advantage of high-quality DXA images, and based upon previous studies using 2D X-ray images to estimate bone microarchitecture, the trabecular bone score (TBS) was developed as another approach for assessing skeletal microstructure noninvasively from 2D DXA projection images.

**Dual Energy X-Ray Absorptiometry (DXA)**

Dual energy X-ray Absorptiometry (DXA) is the most widely used quantitative technique for bone mineral density (BMD) assessment in clinical practice and represents the “gold standard” for a non-invasive diagnosis of osteoporosis, according to the World Health Organization (WHO) guidelines (46).

BMD, measured in mg/cm³, is determined by peak bone mass and amount of bone loss, whereas bone quality refers to architecture, turnover, damage accumulation (eg, micro fractures), and mineralization (47).

BMD is defined using the T-score, which is the number of standard deviations (SD) above or below the mean for a healthy 30 y.o. adult of the same ethnicity and sex (which refers to the peak bone mass). The World Health Organization (WHO) has defined T-score threshold levels for BMD assessment: ≥-1.0 is considered as normal, values between ≤-1.0 and ≥-2.5 refer to osteopenia, and a T-score ≤-2.5 is classified as osteoporosis.

Z-score is the number of SD above or below the normal values of a healthy subject of the same age, sex, weight and ethnicity; this parameter is mostly used in the assessment of metabolic bone status of children and people aged over 75, but it should be also considered in women prior to menopause and men younger than 50 y.o. (7). A Z-score of −2.0 or lower is defined as “below the expected range for age” and a Z-score above −2.0 is “within the expected range for age” (1).

This definitions of osteopenia and osteoporosis only refer to DXA measurements at the lumbar spine (from L1 to L4, in antero-posterior projection), the proximal femur (neck and total femur as Region Of Interest -ROI) or the distal radius (1/3 distal radius as ROI).

Lumbar spine is the primary site for BMD measurement. The BMD of proximal femur is the best predictor of hip fracture. ROIs include femoral neck, trochanter, Ward’s area, intertrochanteric region, and total hip.

The forearm is a third site used for BMD measurement. The BMD of proximal femur is the best predictor of hip fracture. ROIs include femoral neck, trochanter, Ward’s area, intertrochanteric region, and total hip.

The advantages of DXA are short scan times, low radiation dose, good reproducibility, low cost, and wide availability.
This technique has some limitations, especially in the elderly, because spinal degeneration (most of all marginal osteophytes), spinal deformity, extreme obesity and abdominal aortic calcification may overestimate BMD and reduce the sensitivity of DXA for assessing osteoporosis. Furthermore DXA, being a two-dimensional measurement, cannot distinguish between cortical and trabecular bone (48).

Schneider et al. recommended the use of DXA of the hip for identification of osteoporosis in women aged 65 years and older who are likely to have spinal osteoarthritis (49) (Figure 1a - 1b).

The recent implementation of software for advanced hip assessment into DXA systems have provided a noninvasive description of the structural geometry of the proximal femur, depicting several parameters such as cortical thickness with bone mapping, areal BMD, hip axis length, cross-sectional area, cross-sectional moment of inertia, and the femoral strength index (32, 50-53).

**Trabecular Bone Score (TBS)**

Although BMD measured by DXA is a major determinant of bone strength and fracture risk, most individuals with a fragility fracture will have BMD values in the osteopenic or even normal range (50). In addition to low bone mass, micro architectural deterioration of bone tissue can lead to increased bone fragility and consequent increased risk of fracture.

The evolution of DXA technology has allowed more advanced tools in the assessment of the bone status with the aim to provide bone quality properties unrelated from BMD (54). The trabecular bone score (TBS) evaluates in DXA images of the lumbar spine (L1-L4) pixel grey-level variations, which have been associated to bone micro-architecture (55). An elevated TBS value correlates with better skeletal microstructure; a low TBS value correlates with weaker skeletal microstructure.

TBS has the potential to discern differences between DXA scans that show similar BMD measure-
ments. Since most individuals with fragility fractures may have BMD values in the range of normality or osteopenia, TBS could be useful to select patients to be screened and managed for osteoporosis (34, 56, 57). Several preliminary studies in patients affected by metabolic bone diseases have suggested that lumbar spine TBS, in addition to BMD and clinical risk factors, could be an important tool in the diagnosis of osteoporosis and especially in fracture risk assessment.

Despite these promising results, opinions in literature are still controversial and further normative data, validation and prospective studies are required (31).

Quantitative Computed Tomography (QCT)

Unlike the DXA, which only measures density/area in g/cm², Quantitative Computed Tomography (QCT) allows true volumetric mineral density measurements in mg/cm³. QCT also provides separate estimation of trabecular and cortical BMD.

The major advantage of QCT over DXA is the selective measure of trabecular tissue, because trabecular bone is the main determinant of compressive strength in the vertebrae and purely trabecular bone measure is more sensitive to monitoring changes with disease and therapy (58, 59).

To perform quantitative CT is used a standard CT scanner and phantom which acts as bone mineral reference standard to calibrate each scan. Density values measured in Hounsfield units are transformed into BMD measured in milligrams hydroxyapatite per cubic centimeter by using a phantom.

Typically QCT is performed at the spinal vertebrae (T12 to L4): ROIs are positioned in the trabecular portion of the vertebral body, compared to the calibration phantom. The obtained vertebral densities are averaged and compared to those of a gender- and race-specific normal population (51, 60). The results are usually expressed in absolute values and as Z-scores and T-scores.

Figure 1b. Example of hip DXA of the same 65 y.o. woman showing osteopenic BMD values in mg/cm³ with the corresponding T-score and Z-score.
Despite QCT has shown an excellent ability to predict vertebral fractures and a good sensitivity for BMD changes during the follow-up (61), it has some limitations that have narrowed its clinical diffusion: marrow change processes can affect trabecular measurements, such as myelofibrosis, and the technique has higher radiation doses and costs compared to DXA.

Currently, to obviate the limitations of DXA and axial QCT, is more frequently used a volumetric QCT (vQCT), which provides separate assessment of cortical and trabecular bone at appendicular sites (62). The evolution of post-processing software allowed further analysis on bone geometrical and torsional stability, which correlates to bone strength and consequent susceptibility to fracture (63, 64).

Recommendations in clinical routine to characterize fracture risk with the absolute measurements of volumetric BMD are: 110-80 mg/cm³ = mild increase in fracture risk; 80-50 mg/cm³ = moderate increase in fracture risk; <50 mg/cm³ = severe increase in fracture risk (65, 66).

High resolution quantitative computed tomography (HR-QCT) has been performed on metabolic bone disease patients with the aim of providing a detailed assessment of both cortical and trabecular architecture (67). With an 80-100 μm resolution, HR-QCT can measure (in addition to the parameters classically measured by QCT) bone volume fraction as well as cortical and trabecular parameters including thickness, separation, and number of trabeculae (68-71). Nevertheless, high costs and the expertise level required to handle these techniques has limited their application to few research centers.

**Vertebral Morphometry**

Vertebral body fractures (VBF) are the most frequent type of osteoporotic fractures, and they occur significantly earlier compared with wrist and hip fractures (72-75). After sustaining an osteoporotic fracture, patients are at a 50–100% greater risk of suffering another osteoporotic fracture. For this reason identify and treat patients with newly developed VBF is essential to prevent further and more severe osteoporotic fractures, such as the hip fractures that leads to persisting disabilities, hospitalization and operation costs (44, 76-78).

Current DXA systems allow to use high quality DXA scans instead of standard X-rays to identify vertebral fractures. Radiographic diagnosis with conventional lateral radiographs of the thoracolumbar spine is considered to be the best way to identify and confirm the presence of osteoporotic vertebral fractures in clinical practice. The two most widely used methods to determine the severity of such fractures in clinical research are the semi quantitative assessment of vertebral deformities, which is based on visual evaluation, and the quantitative approach, which is based on different morphometric criteria (79).

The morphological classification (wedge, biconcave, crush) of VBF results from more than 20% loss in anterior, middle or posterior heights of vertebral bodies. VBFs are also classified as mild (20–25%), moderate (26–40%), and severe (>40%) reductions in any height.

The visual semi-quantitative approach proposed by Genant et al. (79) has been integrated with morphometric methods based on vertebral height measurements. The quantitative vertebral morphometry can be applied on spinal radiographs (MXR: Morphometric X-ray Radiography) or on DXA images (MXA: Morphometric X-ray Absorptiometry).

Several semi-automated software have been introduced with the aim of digitize and automatize MRX, improving its reproducibility (80). The operator has to manually identify the vertebral levels (from T5 to L4) then a semi-automated six-points segmentation of the vertebrae calculates the vertebral heights (posterior - Hp, middle - Hm and anterior Ha) and the ratio between heights (Ha/Hp, Hm/Hp) of each vertebra. The last step of the analysis includes the report of fracture assessment based on normative data and models (81).

The widespread diffusion of DXA and the technical improvements have allowed the application of quantitative morphometry on lateral DXA images of the spine. Thanks to its lower radiation exposure, MXA nowadays represents the most widely adopted solution for quantitative assessment of fracture status and has been fully integrated into DXA-based BMD assessment of osteoporosis in clinical routine (82) (Figure 2).

However, the radiologist’s role still remains critical in order to distinguish osteoporotic vertebral frac-
tures from malignancies and other congenital or acquired deformities.

Quantitative Ultrasound (QUS)

Quantitative Ultrasound (QUS) is a portable, radiation-free and low cost technique performed with dedicated scanners. It provides measurements of quantitative parameters related to bone quality properties through the analysis of interactions between ultrasound and bone. It is usually performed to peripheral sites such as calcaneus (primary site), metaphysis of the phalanx, radius and tibia. Transit time velocity and ultrasound attenuation represent the most widely adopted parameters: velocity decreases in osteoporotic bone, whereas ultrasound attenuation increases in osteoporotic bone. QUS results can be expressed in absolute values or in T-score and Z-score linked to normative reference data (66, 83-86).

Several studies have shown that QUS parameters can differentiate individuals with from those without fragility fractures and are predictive of osteoporotic fractures (87-89). However, despite quantitative US can be useful as screening tool for the estimation of fracture risk, the WHO has stated that it cannot be used as stand-alone tool for the diagnosis of osteoporosis and and to monitor treatment response (90).

RM Imaging

The concept of bone strength as result of bone quantity and bone quality have induced the scientific community to explore other imaging modalities capable of obtaining micro-architectural data of trabecular bone with the aim to understand the relationship between bone turnover, density and architecture (47).

Several studies have explored MR’s ability to correlate trabecular content and architecture with bone

Figure 2. Example of quantitative morphometry on lateral DXA images of the spine, showing several vertebral body fractures (VBF), with the corresponding fracture classification in mild (type1), moderate (type2), and severe (type 3)
turnover (45, 91-94). The technique has been mainly established for peripheral imaging of the distal radius, tibia, and calcaneus.

Specific high resolution sequences and imaging analysis algorithms have been developed to obtain a non-invasive assessment of bone strength and turnover (95).

Bone marrow is critical to the viability and strength of trabecular and cortical bone.

Dynamic contrast-enhanced MR imaging (DCE-MRI) studies across different age groups have revealed that vertebral marrow perfusion is reduced in elderly and in patients with osteoporosis compared to subjects with osteopenia (96, 97).

Subjects with osteoporosis or osteopenia revealed a significantly increased marrow fat content compared with the fat content in subjects with normal bone density. The concomitant observation that both adipocytes and osteoblasts arise from common precursor cells has suggested the hypothesis that preferential differentiation of mesenchymal stem cells towards the adipocyte lineage may negatively influence osteoblast differentiation (98, 99).

Proton RM spectroscopy (MRS) has been proposed as a promising candidate into routine clinical procedures for quantifying marrow adiposity non-invasively. MRS-based studies have revealed an age-dependent linear increase in vertebral marrow fat content at various skeletal sites (100, 101). In contrast to the qualitative evaluation of red marrow versus yellow marrow provided by conventional MR imaging, MR spectroscopy provides quantitative assessment of water and fat content in bone marrow (102).

Conclusions

Osteoporosis is a major worldwide health problem, which contribute to reduce physical performance and increase the risk of fall-related injury, disability, and mortality in aging people (103). Without prevention and screening, osteoporosis may be clinically silent with an increased incidence of osteoporotic fractures and consequently with an exponentially grow of the socio-economic costs associated to osteoporotic fracture-related morbidity and mortality.

Therefore, early diagnosis of osteoporosis and adequate management of its complications are becoming a particularly relevant concern in the context of guarantee a true “healthy aging”.

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