Session: Osteoporosis Hybrid Imaging
Title: Clinical Imaging of Osteoporosis

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Highlights
1. Quantitative imaging provides information on bone mineral density (BMD) and is used to diagnose and monitor osteoporosis, the clinically established technologies are dual energy absorptiometry (DXA) and computed tomography (QCT).
2. MRI based quantitative techniques used in patients are research applications and target bone quality, these include assessment of cortical bone water and assessment of bone marrow fat content.
3. Morphological MRI allows to sensitively diagnose insufficiency fractures of bone through visualization of bone marrow signal abnormalities.

Target audience: MDs, PhDs and students with interest in bone research.

Objectives: The learner will understand the role and limitations of diagnostic techniques for osteoporosis imaging. This will include both quantitative techniques and those based on morphological analysis of bone and bone marrow.

Purpose:
1. To show how osteoporosis is diagnosed based on quantitative and morphological techniques.
2. To present how techniques to measure bone mineral density work and what their limitations are.
3. To demonstrate some of the novel MR technologies used for quantitative imaging in patients.
4. To illustrate how morphological MRI helps to sensitively diagnose insufficiency fractures.

Methods and Results
Diagnosis of osteoporosis and therapy recommendations:
Osteoporosis is diagnosed based on bone mineral density (BMD) measurements and/or the presence of low trauma insufficiency fractures most frequently found at the spine, the proximal femur and distal radius.

The standard technique to measure BMD is Dual X-ray Absorptiometry (DXA) (Fig. 1) and according to WHO criteria osteoporosis is diagnosed if the BMD is 2.5 or more standard deviations below that of a young normal reference population (T- score ≤ 2.5) at the proximal femur (femur neck or total femur regions), the lumbar spine or the distal radius (1). This definition, however, should only be used for post-menopausal women and men older than 50 years. In men under 50 years of age, premenopausal women, and children, Z-scores (standard deviation compared to an age-matched reference population) not T-scores, should be used when reporting bone density results (2). If Z-scores are -2.0 or less (using pediatric databases of age-

matched controls), then a characterization such as "low bone density for chronologic age" is appropriate (2).
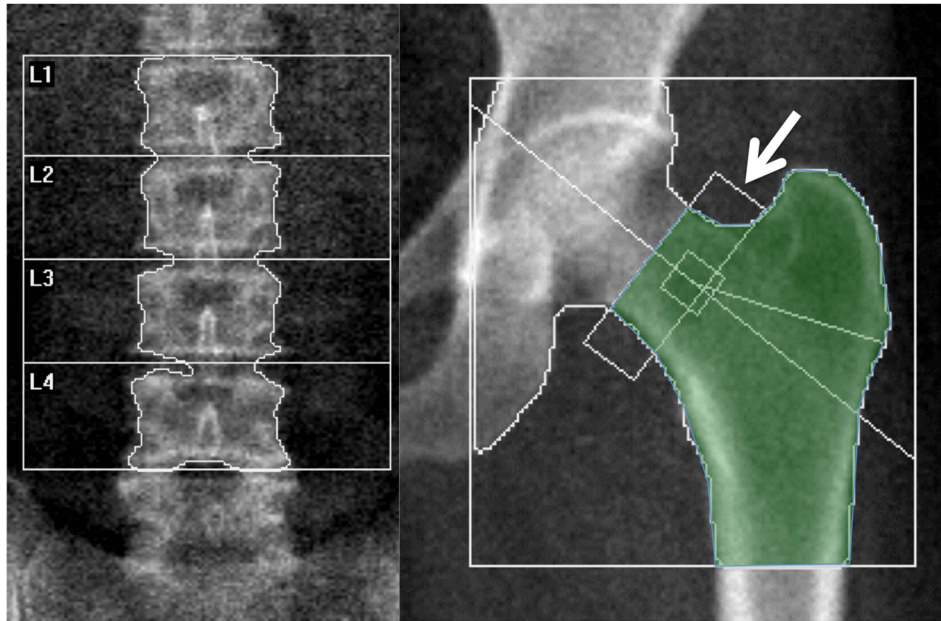
Fig. 1: DXA image of the lumbar spine and proximal femur. Areal BMD is measured in the L1-4 vertebral bodies and the femoral neck (arrow) and total femur region (green).

While WHO criteria do not apply for quantitative computed tomography (QCT) the American College of Radiology has issued practice guidelines for the performance of QCT Bone Densitometry (Fig. 2). Based on this guideline a BMD of <80 mg/cm^3 is defined as osteoporosis, this applies to both single slice and volumetric techniques to measure QCT BMD.
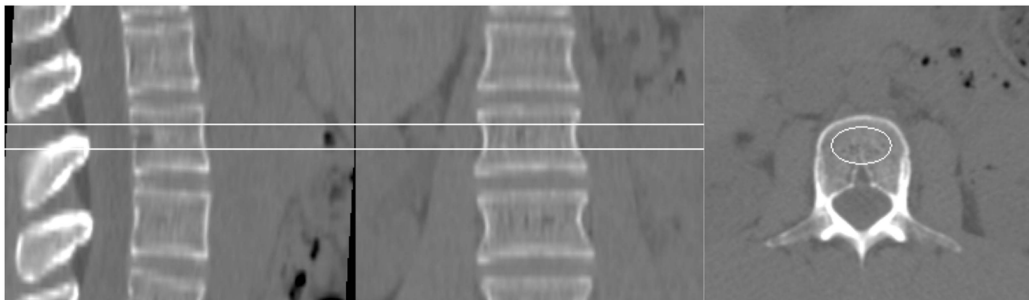
Fig. 2: QCT images of the lumbar spine. Volumetric (3D) QCT is measured in the L2 vertebral body using oval-shaped region of interest.

In addition to BMD measurements the introduction of the WHO FRAX (Fracture risk assessment) algorithm has facilitated the assessment of osteoporotic fracture risk on the basis of fracture probability. FRAX integrates the influence of several well validated risk factors for fracture with or without the use of BMD (3). The FRAX tool is available on the internet (http://www.shef.ac.uk/FRAX/tool.aspx?country=9) and allows to calculate fracture risk for hip or major osteoporotic fractures using a country specific algorithm. It should be noted that in

general FRAX is only used in postmenopausal women and men aged 50 years and older with a T-score between -1.0 and -2.5 at the femoral neck or lumbar spine.

Pharmacologic treatment guidelines were issued by the National Osteoporosis Foundation in 2013 and are applicable to postmenopausal women and men age 50 and older with
1. a hip or vertebral fracture,
2. a T-score ≤ 2.5, and
3. a T-score between -1.0 and -2.5 at the femoral neck or lumbar spine associated with a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US- adapted FRAX WHO algorithm.

Note that a low energy or fragility fracture e.g. at the spine, proximal femur and distal radius is sufficient for the diagnosis of osteoporosis even if T-scores are not in the osteoporotic range. Therefore diagnosis of those fragility fractures will have a significant impact on patient management. Also it has been shown that vertebral fragility fractures are frequently asymptomatic but still require therapy as they are one of the most important indicators for future fractures.

Techniques to measure bone mineral density and their limitations
As previously mentioned the standard technique to measure BMD is DXA. Using two x-ray beams with different kVp (30-50 and >70keV) allows to subtract the soft tissue component and measures areal BMD, typically of the lumbar spine, proximal femur and distal radius. In addition to areal density values in g/cm^2 DXA provides T-scores and Z-scores. DXA is a well standardized and easy to use technique, which has a high precision (maximum acceptable precision error 2-2.5%), low radiation dose (1-50* microSv, *if performed with vertebral fracture assessment) (4). DXA BMD correlates well with the biomechanically determined bone strength explaining approximately 70% of bone strength (5).

Though DXA is the standard technique it has a number of disadvantages which need to be considered (4): (i) it is a 2D measurement, which only measures density/area (in g/cm^2) and not the volumetric density (in mg/cm^3) such as quantitative CT. Areal BMD is susceptible to bone size and will thus over-estimate fracture risk in individuals with small body frame, who will have lower areal BMD than normal-sized individuals. (ii) Spine and hip DXA are also sensitive to degenerative changes and individuals with significant degenerative disease will have increased areal density, which will suggest a lower fracture risk than is actually present. All structures overlying the spine, such as aortic calcifications, or morphological abnormalities, such as status post laminectomy at the spine, will affect BMD measurements.

Though QCT was introduced and studied prior to DXA it never gained the same clinical significance. To perform QCT a standard CT scanner with a calibration phantom underneath the patient is used and density values measured in Hounsfield units are transformed into BMD measured in mg hydroxyapatite/cm^3 using the phantom. Typically the L1-3 vertebral bodies are measured and there are single slice and volumetric techniques to measure the density; in addition volumetric techniques are available to measure proximal femur BMD. One major advantage of QCT is that it allows true volumetric measurements of the lumbar spine and proximal femur, which are independent of the body size. Disadvantages of QCT are a higher radiation dose (0.06-2.9 mSv), a limited number of longitudinal scientific studies assessing how QCT predicts fragility fractures and most of all that T-scores should not be used to define osteoporosis with QCT (4).

What MRI can offer – novel technologies
While BMD measurements are well established they only incompletely capture bone strength. BMD measurements also have shown limitations in monitoring therapy, predicting fracture risk and differentiating individuals with and without fractures. These entities of bone which are not assessed with BMD have been defined as bone quality (6), a term which was initially coined by the NIH Consensus Development Panel on Osteoporosis Prevention in 2000 (5). In the last 20 years multiple MRI based technologies and sequences to characterize bone quality have been developed. Some of the most novel technologies are (a) ultra short TE (echo time) sequences to quantify cortical bone water and (b) spectroscopic techniques to analyze bone marrow composition such as the degree of bone marrow fat (4).

Ultrashort TE
Ultra-short echo time (UTE) imaging techniques allow detection of signal components with T2 relaxation times on the order of only a few hundred microseconds, which are found in highly ordered tissues such as cortical bone and tendons and can not be detected with conventional imaging techniques (7). Techawiboonwong et al (8) validated UTE imaging in bone specimens using an isotope exchange experiment and studied the right tibial midshaft in pre- and post-menopausal females and patients on hemodialysis. The quantitative analysis showed that bone water content was 135% higher in the patients on maintenance dialysis than in the pre-menopausal women and 43% higher than in the post-menopausal women. Interestingly no significant differences were found in tibial volumetric BMD between patients on hemodialysis and pre- and postmenopausal normal controls. This increase in water content was explained by abnormal cortical porosity and microscopic pores being filled with water. More recently investigators have differentiated bound and free water in cortical bone; the bound water concentration has been found to be an indirect measure of organic matrix density while the free water concentration has been shown to be an indirect measure of cortical porosity (9).

Bone Marrow Composition
Bone marrow fat has been identified as an important contributor to osteoporosis and increased fracture risk (10). Proton magnetic resonance spectroscopy (1H-MRS) has been used clinically to quantify marrow adiposity non-invasively. A number of studies have been performed that showed bone marrow fat measured with MRS to be associated with DXA BMD and to be significantly elevated in postmenopausal females and older men (11-13). It has also been shown that MRS can provide information on different compartments of lipids in marrow, such as saturated lipids versus unsaturated lipids (14) (Fig. 3). A more recent study linked altered bone marrow fat composition with fragility fractures and diabetes and suggested that MRS of spinal bone marrow fat may serve as a novel tool for BMD-independent fracture risk assessment (15).
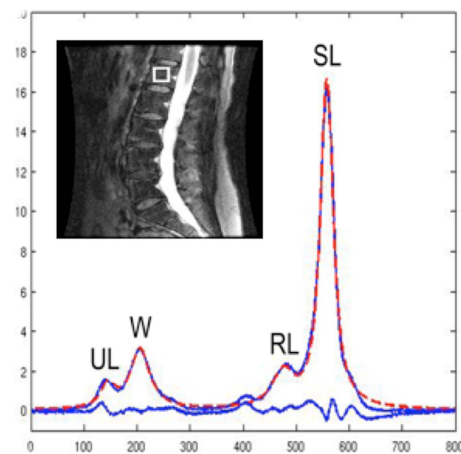
Fig. 3: MR spectroscopy of L1 with saturated lipid (SL), unsaturated lipid (UL) and water (W) peaks.
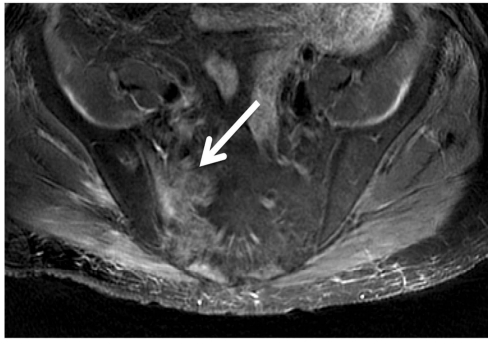
Fig. 4: Axial fluid sensitive MR image of the pelvis showing right sided sacral insufficiency fracture (arrow).

Morphological MRI

MRI is very sensitive to bone marrow abnormalities and shows bone marrow edema pattern and bone remodeling better than any other imaging technology. In the early phase insufficiency fractures or "reactions" may only be characterized by bone marrow signal abnormalities and not by deformity, in particular at the spine and pelvis (16) (Fig. 4). It is critical that these findings are correctly interpreted as they guide patient management. Also during the last decade a number of publications focused on osteoporotic insufficiency fractures and demonstrated that findings previously identified as osteonecrosis are indeed insufficiency fractures (16-21). Both insufficiency fractures at the medial femoral condyle of the knee and femoral head are frequent findings in older individuals and indicate increased fragility of the skeleton.

Conclusion:

In conclusion standard clinical quantitative imaging for osteoporosis heavily relies on DXA and QCT, which have an important role in guiding patient management. A number of new MRI technologies are evolving which may in the future play a role in assessing bone quality and help guide management in patients where BMD measurements are limited. It should also be noted that while quantitative measurements are important, morphological assessment of bone marrow abnormalities using MRI may substantially impact patient management by identifying insufficiency fractures or "reactions".

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