

REVIEW

Bone densitometry: current status and future trends

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Osteoporosis is the most important metabolic bone disease in geriatric patient and is characterized by quantitative bone deficiency with consequent increased bone fragility and susceptibility to fractures.

Diagnostic imaging has a critical role as in the diagnosis and follow-up of osteoporosis.

The aim of this review is to encompass the capabilities of the different imaging modalities for the evaluation of bone strength, the assessment of fracture risk and the management of fragility fractures.

Key words: Bone densitometry, Osteoporosis, Aging, High resolution imaging, Bone

INTRODUCTION

Loss of bone properties in aging people represents an increasingly important public health issue, being associated to other age-related processes (such as muscle strength impairment), which contribute to reduce physical performance and increase the risk of fall-related injury, disability, and mortality ¹.

Osteoporosis is the most important metabolic bone disease in geriatric patient and is characterized by quantitative bone deficiency with consequent increased bone fragility and susceptibility to fractures ². Involutional osteoporosis has been classified into type I or postmenopausal osteoporosis and type II or senile osteoporosis ³. Postmenopausal osteoporosis usually occurs in women between ages 50 and 65 years. The estrogenic deficiency is linked to an accelerated trabecular bone resorption, which may lead to fragility fractures that typically involve spine and wrist. In type II osteoporosis 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 ⁴.

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 ⁵.

Diagnostic imaging has a critical role as in the diagnosis and follow-up of osteoporosis, as in the management of the complications that often implicate differential diagnosis issues, most of all in a geriatric patient. Therefore, the aim of this review is to encompass the capabilities of the different imaging modalities for the evaluation of bone strength, the assessment of fracture risk and the management of fragility fractures.

IMAGING TECHNIQUES

Imaging in osteoporosis aims to identify bone weakening at an early stage, to differentiate patterns of bone alterations, to predict fracture risk, to determine the treatment approach and to help monitor disease progression and response to therapy.

Besides conventional radiography, other imaging techniques such as dual-energy x-ray absorptiometry

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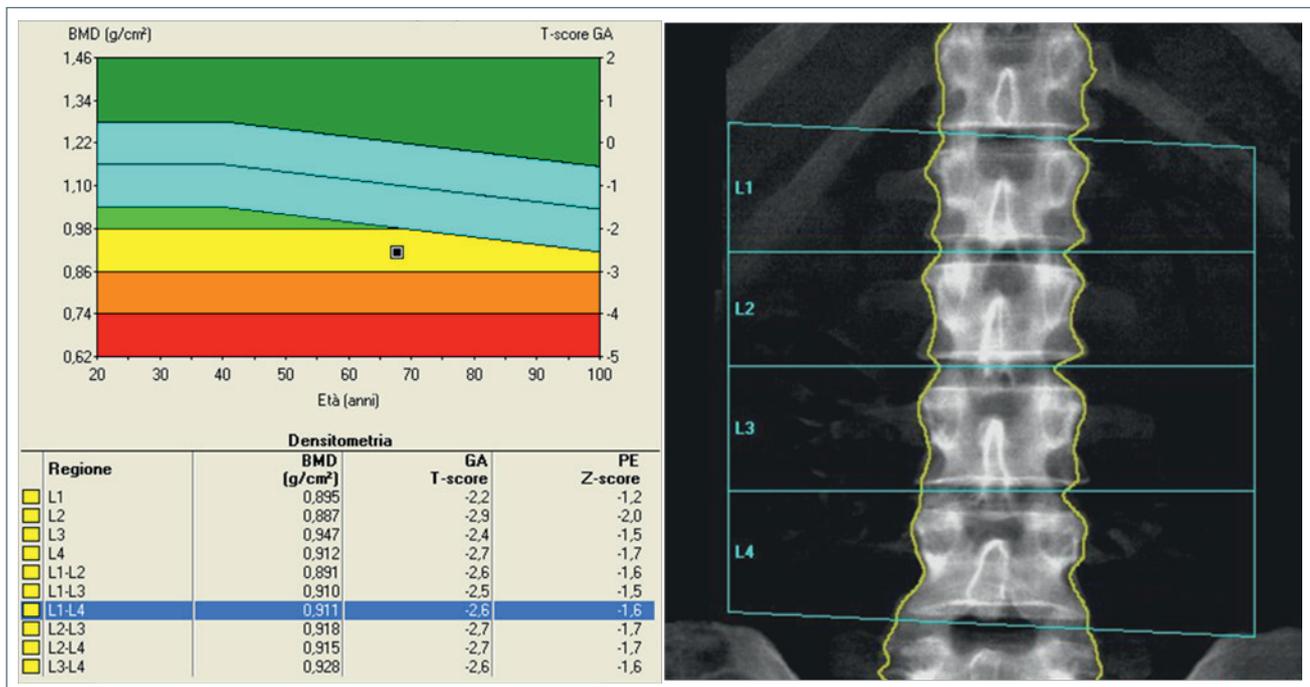


Figure 1. Example of lumbar spine DXA showing BMD values in mg/cm^3 with the corresponding T-score and Z-score.

(DXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) have been developed to quantify BMD and to assess bone loss ⁶.

DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA)

It is well known that bone mineral density (BMD) correlates with bone strength and predicts fracture risk ⁷. As a consequence, highly reproducible and available methods to quantitatively measure BMD are required. Dual energy X-ray Absorptiometry (DXA) is the most widely used quantitative technique for BMD assessment in clinical practice and represents the “gold standard” for a non-invasive diagnosis of osteoporosis ⁸. BMD is measured in mg/cm^3 and comparing these values with a known parameter, 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). 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. 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. 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. According to the WHO, the definitions of osteopenia and osteoporosis only refer to DXA measurements at lumbar spine, hip and forearm, and cannot be applied to other densitometry techniques, neither at other skeletal sites. Lumbar spine is the primary site for BMD measurement: total spine (from L1 to L4) and individual vertebral T-scores are obtained from several Regions of Interest (ROIs) (Fig. 1).

The hip represent the other most common site of measurements, being the BMD of proximal femur 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, useful when spine and hip are not measurable or interpretable due to severe degenerative processes, and implantable devices.

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 ⁹.

Despite short scan times, low radiation dose, good

reproducibility, low cost, and wide availability, DXA has shown some limitations. Most of them rely in its bi-dimensional technology: it cannot distinguish between cortical and trabecular bone, it cannot discriminate changes induced by bone geometry from those only related to bone density. Above all, in clinical practice BMD can be overestimated by marginal osteophytes and vascular calcifications projecting on lumbar spine ¹⁰.

TRABECULAR BONE SCORE (TBS)

Although BMD by DXA is a major determinant of bone strength and fracture risk, most individuals may experience a fragility fracture without significant BMD impairment ¹¹. 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 ¹². 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 ¹³. Several preliminary studies in patients affected by metabolic bone diseases have suggested that TBS, in addition to BMD and clinical risk factors, improves the prediction of fracture risk. 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 ¹⁴⁻¹⁶ (Fig. 2).

Despite these promising results, opinions in literature are still controversial and further normative data, validation and prospective studies are required ¹⁷.

QUANTITATIVE COMPUTED TOMOGRAPHY (QCT)

Quantitative Computed Tomography provides separate estimation of trabecular and cortical BMD as true volumetric mineral density in mg/cm^3 . It can be performed at the spine (axial QCT) and peripheral sites (peripheral QCT-pQCT).

Axial QCT measures trabecular bone in spinal vertebrae (T12 to L4) adopting commercial CT scanners and a phantom which acts as bone mineral reference standard to calibrate each scan. 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 ¹⁸. The results are usually expressed in absolute values and as Z-scores and T-scores. The main advantage of QCT over DXA relies in the selective measure of trabecular tissue, the main determinant of compressive strength in the vertebrae. QCT has shown an excellent ability to predict vertebral fractures and a good sensitivity for BMD changes during the follow-up ¹⁹.

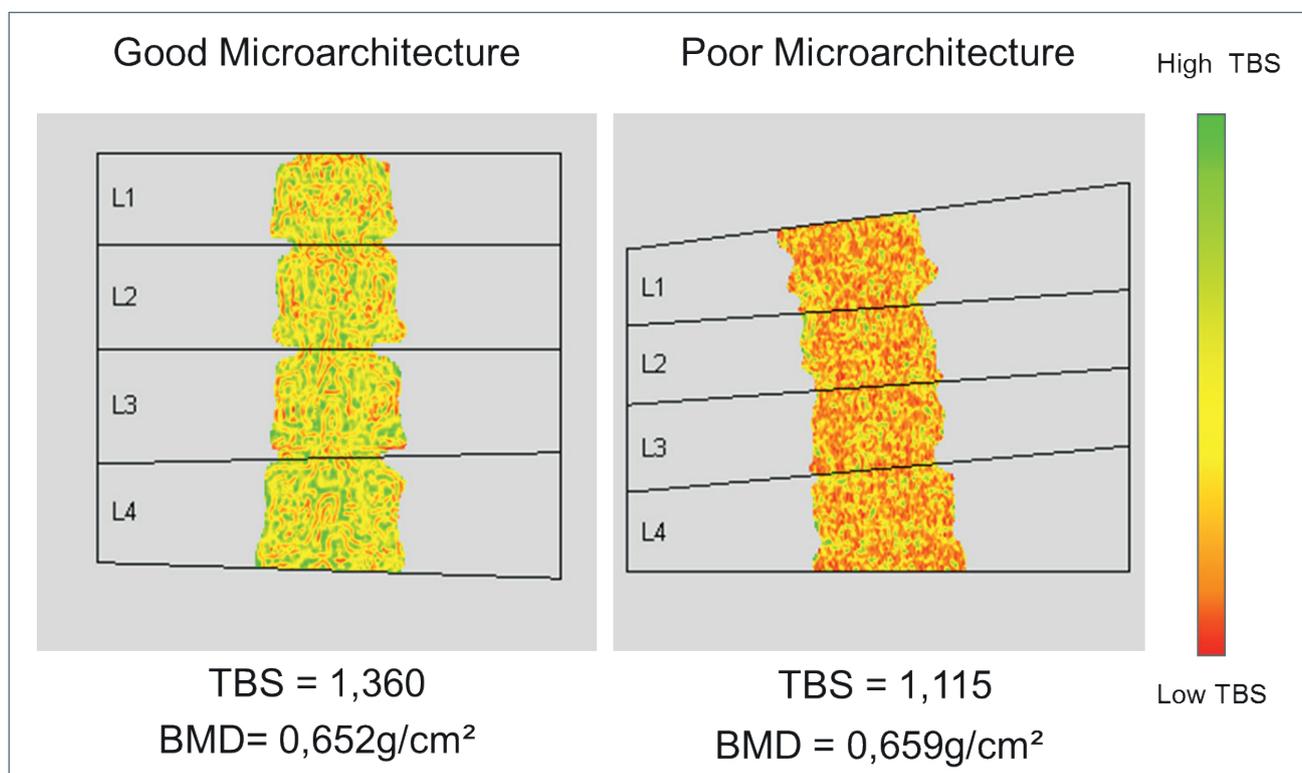


Figure 2. Graphic representation of Trabecular Bone Score (TBS) on DXA images of lumbar spine. These two different patients show equivalent BMD but different TBS values.

Besides these advantages, QCT has some limitations that have narrowed its clinical diffusion: marrow change processes can affect trabecular measurements (myelofibrosis, hematopoietic disorders ecc.), and the technique has higher radiation doses and costs compared to DXA. The introduction of volumetric QCT (vQCT) has improved axial QCT and extended its application to the hip, allowing separate analysis of trabecular and cortical components²⁰.

PERIPHERAL QCT (pQCT)

This technique has been developed to obviate the limitations of DXA and axial QCT, provides separate assessment of cortical and trabecular bone at appendicular sites. 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^{21 22}.

VERTEBRAL MORPHOMETRY

Vertebral fractures are considered the hallmark of osteoporosis and represent a frequently used endpoint in clinical trials and epidemiological studies investigating the effectiveness of different therapeutic regimes on osteoporosis²³.

A vertebral fracture is defined as more than 20% loss in anterior, middle, or posterior vertebral heights within a vertebra or between adjacent vertebrae

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

Most of all in elderly, VF often appear as atraumatic and asymptomatic mild deformities, which can be easily under-reported in radiological routine²⁴.

In the last decades a significant effort has been invested in order to reduce the subjectivity of the visual approach. The visual semi-quantitative approach proposed by Genant et al.²⁵ 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 reproducibility²⁶. 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 models²⁷.

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 routine²⁸ (Fig. 3).

However, the radiologist’s role still remains critical in order to distinguish osteoporotic vertebral fractures



Figure 3. Example of Vertebral Fracture Assessment (VFA) on lateral spine DXA image.

from malignancies and other congenital or acquired deformities.

QUANTITATIVE ULTRASOUND (QUS)

This technique measures quantitative parameters related to bone quality properties. QUS provide portable, radiation-free and low cost measurements of bone density, elasticity and structure through the analysis of interactions between ultrasound and bone. Transit time velocity and ultrasound attenuation represent the most widely adopted parameters measured at peripheral sites such as calcaneus (primary site), metaphysis of the phalanx, radius and tibia. QUS results can be expressed in absolute values or in T-score and Z-score linked to normative reference data²⁹. Several studies have shown that fractured patients have lower calcaneal ultrasound values than normal subjects and that QUS parameters are predictive of osteoporotic fractures³⁰⁻³². However, despite several advantages and promising results, the WHO has stated that QUS cannot be used as stand-alone tool for the diagnosis of osteoporosis and can be useful as screening tool for the estimation of fracture risk³³.

OTHER TECHNIQUES

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 architecture³⁴.

Several studies in the past decade have explored the capabilities of MR in the exploration of physiologic differences in aging bone. As routine MR sequences revealed to be not suitable for cortical and trabecular bone assessment, specific high resolution sequences and imaging analysis algorithms have been developed to reveal bone network³⁵. The most adopted sites of analysis were the calcaneus and the distal radius in order to correlate trabecular content and architecture with bone turnover³⁶.

More recently other MR-based approaches have been explored, all aiming to obtain a non-invasive assessment of bone strength and turnover.

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^{37 38}.

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^{39 40}.

Hydrogen 1 (1H) magnetic resonance spectroscopy (MRS) allows a non-invasive quantification of bone marrow fat and fat/water ratio. MRS-based studies have revealed an age-dependent linear increase in vertebral marrow fat content at various skeletal sites⁴¹⁻⁴³. More recently, Water-Fat-Imaging (WFI) sequences have been introduced for marrow fat assessment revealing good performances in water and fat content differentiation⁴⁴. Besides advanced MR techniques, other research centers have focused their studies on CT-based systems. 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 architecture⁴⁵. 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 trabeculae⁴⁶. Nevertheless, high costs and the expertise level required to handle these techniques has limited their application to few research centers.

CONCLUSIONS

Osteoporosis represents a worldwide health problem with age-related incidence of fragility fractures. With the increase of life expectancy, the socio-economic burden associated to osteoporotic fractures will grow exponentially. Therefore, early diagnosis of osteoporosis and adequate management of its complications are becoming more critical in order to guarantee a true "healthy aging".

References

- 1 Kanis J; On behalf of the World Health Organization Scientific Group. *Assessment of osteoporosis at the primary health-care level: technical report*. World Health Organization Collaborating Centre for metabolic bone diseases. 2008. University of Sheffield, Sheffield.
- 2 Compston J. *Osteoporosis: social and economic impact*. *Radiol Clin North Am* 2010;48:477-82.
- 3 Anil G, Guglielmi G, Peh WC. *Radiology of osteoporosis*. *Radiol Clin North Am* 2010;48:497-518.
- 4 Kenny A, Taxel P. *Osteoporosis in older men*. *Clin Cornerstone* 2000;2:45-51.
- 5 Blüch D, Nguyen ND, Milch VE, et al. *Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women*. *JAMA* 2009;301:513-21.

- ⁶ Guglielmi G, Diano D, Ponti F, et al. *Metabolic*. In: *Geriatric Imaging*. Berlin: Springer 2013;53-81.
- ⁷ Blake GM, Fogelman I. *The role of DXA bone density scans in the diagnosis and treatment of osteoporosis*. *Postgrad Med J* 2007;83:509-17.
- ⁸ Damilakis J, Guglielmi G. *Quality assurance and dosimetry in bone densitometry*. *Radiol Clin North Am* 2010;48:629-40.
- ⁹ Takakuwa M, Iwamoto J, Konishi M, et al. *Risedronate improves proximal femur bone density and geometry in patients with osteoporosis or osteopenia and clinical risk factors of fractures: a practice-based observational study*. *J Bone Miner Metab* 2011;29:88-95.
- ¹⁰ Setiawati R, Di Chio F, Rahardjo P, et al. *Quantitative assessment of abdominal aortic calcifications using lateral lumbar radiograph, dual-energy x-ray absorptiometry, and quantitative computed tomography of the spine*. *J Clin Densitom* 2016;19:242-9.
- ¹¹ Kazakia GJ, Majumdar S. *New imaging technologies in the diagnosis of osteoporosis*. *Rev Endocr Metab Disord* 2006;7:67-74.
- ¹² Silva BC, Bilezikian JP. *Trabecular bone score: perspectives of an imaging technology coming of age*. *Arq Bras Endocrinol Metabol* 2014;58:493-503.
- ¹³ Pothuau L, Carceller P, Hans D. *Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture*. *Bone* 2008;42:775-87.
- ¹⁴ Boutroy S, Hans D, Sornay-Rendu E, et al. *Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study*. *Osteoporos Int* 2013;24:77-85.
- ¹⁵ Krieg MA, Aubry-Rozier B, Hans D, et al.; Manitoba Bone Density Program. *Effects of anti-resorptive agents on trabecular bone score (TBS) in older women*. *Osteoporos Int* 2013;24:1073-8.
- ¹⁶ Bandirali M, Poloni A, Sconfienza LM, et al. *Short-term precision assessment of trabecular bone score and bone mineral density using dual-energy X-ray absorptiometry with different scan modes: an in vivo study*. *Eur Radiol* 2015;25:2194-8.
- ¹⁷ Bazzocchi A, Ponti F, Diano D, et al. *Trabecular bone score in healthy ageing*. *Br J Radiol* 2015; 88:20140865.
- ¹⁸ Guglielmi G, van Kuijk C, Li J, et al. *Influence of anthropometric parameters and bone size on bone mineral density using volumetric quantitative computed tomography and dual X-ray absorptiometry at the hip*. *Acta Radiol* 2006;47:574-80.
- ¹⁹ Engelke K, Adams JE, Armbrecht G, et al. *Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions*. *J Clin Densitom* 2008;11:123e162.
- ²⁰ Griffith JF, Genant HK. *New imaging modalities in bone*. *Curr Rheumatol Rep* 2011;13:241-50.
- ²¹ Mueller TL, Stauber M, Kohler T, et al. *Noninvasive bone competence analysis by high-resolution pQCT: an in vitro reproducibility study on structural and mechanical properties at the human radius*. *Bone* 2009;44:364-71.
- ²² Ashe MC, Khan KM, Kontulainen SA, et al. *Accuracy of pQCT for evaluating the aged human radius: an ashing, histomorphometry and failure load investigation*. *Osteoporos Int* 2006;17:1241-51.
- ²³ Bonura F. *Prevention, screening, and management of osteoporosis: an overview of the current strategies*. *Postgrad Med* 2009;121:5-17.
- ²⁴ McCloskey EV, Spector TD, Eyres KS, et al. *The assessment of vertebral deformity: a method for use in population studies and clinical trials*. *Osteoporos Int* 1993;3:138-47.
- ²⁵ Genant HK, Wu CY, van Kuijk C, et al. *Vertebral fracture assessment using a semiquantitative technique*. *J Bone Miner Res* 1993;8:1137-48.
- ²⁶ Guglielmi G, Haslam J, D'Errico F, et al. *Comprehensive vertebral deformity and vertebral fracture assessment in clinical practice: intra- and inter-reader agreement of a clinical workflow tool*. *Spine (Phila Pa 1976)* 2013;15;38:E1676-83.
- ²⁷ Diacinti D, Guglielmi G. *Vertebral morphometry*. *Radiol Clin North Am* 2010;48:561-75.
- ²⁸ Rea JA, Li J, Blake GM, et al. *Visual assessment of vertebral deformity by X-ray absorptiometry: a highly predictive method to exclude vertebral deformity*. *Osteoporos Int* 2000;11:660-8.
- ²⁹ Guglielmi G, De Terlizzi F, Nasuto M, et al. *Quantitative ultrasound at the phalanges in a cohort of monozygotic twins of different ages*. *Radiol Med* 2015;120:277-82.
- ³⁰ Wüster C, Albanese C, De Aloysio D, et al. *Phalangeal osteosonogrammetry study: age-related changes, diagnostic sensitivity, and discrimination power*. *J Bone Min Res* 2000;15:1603-14.
- ³¹ Hartl F, Tyndall A, Kraenzlin M, et al. *Discriminatory ability of quantitative ultrasound parameters and bone mineral density in a population-based sample of postmenopausal women with vertebral fractures: result of the Basel Osteoporosis Study*. *J Bone Min Res* 2002;17:321-30.
- ³² Baroncelli GI, Federico G, Vignolo M, et al. *The phalangeal quantitative ultrasound group. Cross-sectional reference data for phalangeal quantitative ultrasound from early childhood to young adulthood according to gender, age, skeletal growth, and pubertal development*. *Bone* 2006;39:159-73.
- ³³ Guglielmi G, Nasuto M. *Quantitative ultrasound and fracture risk assessment*. In: Guglielmi G (Ed.). *Osteoporosis and bone densitometry measurements, medical radiology, diagnostic imaging*. Berlin-Heidelberg: Springer-Verlag 2003;133-44.
- ³⁴ Link TM. *Osteoporosis Imaging. State of the art and advanced imaging*. *Radiology* 2012;263:3-17.
- ³⁵ Guglielmi G, Selby K, Blunt BA, et al. *Magnetic resonance imaging of the calcaneus: preliminary assessment of trabecular bone-dependent regional variations in marrow relaxation time compared with dual X-ray absorptiometry*. *Acad Radiol* 1996;3:336-43.
- ³⁶ Link TM, Majumdar S, Augat P, et al. *In vivo high resolution MRI of the calcaneus: differences in trabecular structure in osteoporotic patients*. *J Bone Miner Res* 1998;13:1175-82.
- ³⁷ Chen WT, Shih TT, Chen RC, et al. *Vertebral bone marrow perfusion evaluated with dynamic contrast-enhanced*

- MR imaging: significance of aging and sex.* Radiology 2001;220:213-8.
- ³⁸ Montazel JL, Divine M, Lepage E, et al. *Normal spinal bone marrow in adults: dynamic gadolinium-enhanced MR imaging.* Radiology 2003;229:703-9.
- ³⁹ Nasuto M, Pansini V, Cortet B, et al. *Renal failure: a modern semiology for an old disease.* Semin Musculoskelet Radiol 2016;20:1-16.
- ⁴⁰ Parhami F. *Possible role of oxidized lipids in osteoporosis: could hyperlipidemia be a risk factor?* Prostaglandins Leukot Essent Fatty Acids 2003;68:373-8.
- ⁴¹ Schellinger D, Lin CS, Hatipoglu HG, et al. *Potential value of vertebral proton MR spectroscopy in determining bone weakness.* Am J Neuroradiol 2001;22:1620-7.
- ⁴² Kugel H, Jung C, Schulte O, et al. *Age- and sex-specific differences in the ¹H-spectrum of vertebral bone marrow.* J Magn Reson Imaging 2001;13:263-8.
- ⁴³ Griffith JF, Yeung DK, Antonio GE, et al. *Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy.* Radiology 2005;236:945-51.
- ⁴⁴ Bley TA, Wieben O, François CJ, et al. *Fat and water magnetic resonance imaging.* J Magn Reson Imaging 2010;31:4-18.
- ⁴⁵ Burghardt AJ, Buie HR, Laib A, et al. *Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT.* Bone 2010;47:519-28.
- ⁴⁶ Jamal S, Cheung AM, West SL, et al. *Bone mineral density by DXA and HR-pQCT can discriminate fracture status in men and women with stages 3 to 5 chronic kidney disease.* Osteoporos Int 2012;23:2805-13.