Bone fragility and imaging techniques

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Summary

Bone fragility is a silent condition that increases bone fracture risk, enhanced by low bone mass and microarchitecture deterioration of bone tissue that lead to osteoporosis. Fragility fractures are the major clinical manifestation of osteoporosis. A large body of epidemiological data indicates that the current standard for predicting fragility fracture risk is an areal BMD (aBMD) measurement by DXA. Although mineral density measurements assess the quantity of bone, the quality of the tissue is an important predictor of fragility. Thus, bone strength is explained not only by BMD but also by macrostructural and microstructural characteristics of bone tissue. Imaging diagnostics, through the use of X-rays, DXA, Ultrasonography, CT and MR, provides methods for diagnosis and characterization of fractures, and semi- and quantitative methods for assessment of bone consistency and strength, that become precious for bone fragility clinical management if they are integrated by clinical risk factors. The last employment of sophisticated non-invasively imaging techniques in clinical research as high-resolution CT (hrCT), microCT (μ-CT), high-resolution MR (hrMR) and, microRM (μRM), combined with finite element analysis methods, open to new challenges in a better bone strength assessment to enhance the comprehension of biomechanical parameters and the prediction of fragility fractures.

KEY WORDS: bone fragility, bone architecture, bone assessment, quantitative densitometry, high resolution imaging.

Introduction

Osteoporosis is a serious but undervalued disease that affects more than two hundred millions of people all over the world: up to one in three women and one in five men over the age of fifty will experience an osteoporotic fracture (1).
Osteoporosis has been defined as "a disease characterized by low bone mass and microarchitecture deterioration of bone tissue, leading to enhanced *bone fragility* and a consequent increase in *fracture risk*" (2).
Low bone mass has been shown to be the biggest risk factor for fragility fracture; thus, the World Health Organization (WHO) has defined osteoporosis by Bone Mineral Density (BMD) measurement, based on values derived from Dual-energy X-ray Absorptiometry (DXA) (3).
Besides BMD, that only partly explains bone quality, other abnormalities occur in the skeleton that contribute to fragility, that may be better estimated by a quantitative assessment of macrostructural and microstructural characteristics.
The Imaging Techniques play a central role in the evaluation of bone status by a) fractures diagnosis and characterization, and b) bone quality assessment.
The commonly used imaging modalities to assess bone mass and macrostructure are X-ray, DXA and Quantitative Computed Tomography; an indirect evaluation of the bone mass and microstructure uses Ultrasonography.
As no satisfactory clinical tools are available for bone health assessment, for practical purposes the imaging modalities profit by the integration of clinical risk factors (4).
Nowadays it is necessary to develop non-invasive imaging techniques able to better identify bone microstructure *in vivo* and predict bone strength not only by the analysis of 2-dimensional (2D) measurements, but employing 3-dimensional (3D) imaging modalities, which include CT, MR and finite element analysis using high-resolution CT or MR images.
Non-invasively methods such as microCT and microMR, applied *in vitro* on bone biopsy for the sake of research, are improving the knowledge of bone biology identifying, reporting and evaluating bone fragility.

Bone fragility and bone quality

In the past 15 years a deep interest in the concept of "bone fragility" has induced clinicians, biologists, physicists and engineers to intensify research for identifying and understanding the biological, material and structural features that contribute to "bone quality".
"Bone quality" is now described as "the totality of features and characteristics that influence a bone's ability to resist fracture" (5).
A bone breaks when the load applied generates an internal stress that exceeds the strength of the tissue.
The bone mechanical behavior depends on 1) morphology of the bone, 2) intrinsic properties of bone material itself. Bone biomechanical properties are stiffness or elastic modulus (ability to resist deformation), toughness (ability to absorb energy), fatigue strength (ability to accommodate repetitive loading), fracture toughness (ability to inhibit the progression of a crack) (5).
In particular, resistance to fracture is influenced by a) *overall composition* (proportion of mineral, collagen, water and matrix proteins), b) *physical and mechanical characteristics of these components* (nature of collagen, degree and type of collagen cross-linking, size and structure of hydroxyapatite crystals and

degree of mineralization), c) *morfology and microarchitecture* (bone size, cortical cross-sectional geometry, porosity, osteon size and density and trabecular microarchitecture), d) *amount and nature of preexisting microdamage* (crack length, density and location).
Bone quality, a measure of bone's architecture, geometry and material properties, is evaluated via mechanical, structural and chemical testing. Recent studies have focused on examination of bone on the nanoscale, suggesting the importance of understanding the interactions of mineral crystals and collagen fibrils, and how they can alter bone quality (6).
Is therefore important to understand alterations that occur in bone at the macro-, micro- and nanoscopic levels to determine which parameters contribute to decreased bone quality (7) and to assess the efficacy of emerging treatments (6).

Imaging techniques

The fundamental roles of Imaging Diagnostics in the management of bone fragility are: a) fractures diagnosis and characterization, b) bone mass loss detection and assessment.
For these aims the instrumental diagnostics employ: Conventional X-Rays (X-Rays), Bone Densitometry (DXA), Computed Tomography (CT), Ultrasonography (US) and Magnetic Resonance (MR) (Fig.1).

Fractures diagnosis and characterization

Fragility fractures are one of the most common causes of disability and a major contributor to medical care costs in many regions of the world (8). Early diagnosis of patients at risk of, or with (asymptomatic), fractures is therefore important (9) (Fig.2).

Common osteoporotic fracture sites are: spine, hip, forearm and proximal humerus.
The remaining lifetime fracture risk in percentage in the Caucasian Population at the age of 50 is reported in the Table I below:

Table I - Remaining lifetime fracture risk (%) in the Caucasian Population at the age of 50.

Type of Fracture	Men	Women
Forearm	4.6	20.8
Hip	10.7	22.9
Spine	8.3	15.1
Proximal Humerus	4.1	12.9
Any	22.4	46.4

Kanis et al., Osteoporos Int. 2000;11:669-674.

Conventional X-Rays

The first and most important method to identify fractures is conventional X-rays: while distal radius fractures are almost always identified by standard radiographs, hip and especially spine fractures may have a difficult detection with important significancy in their management, prognosis and therapy, either a conservative or minimally invasive (like vertebroplasty) approach or an invasive treatment (stabilization, osteosintesis or arthroprothesis).
A more accurate evaluation of lateral chest radiographs routinely executed could lead to the detection of a major number of vertebral fractures and earlier diagnosis of osteoporosis (10).

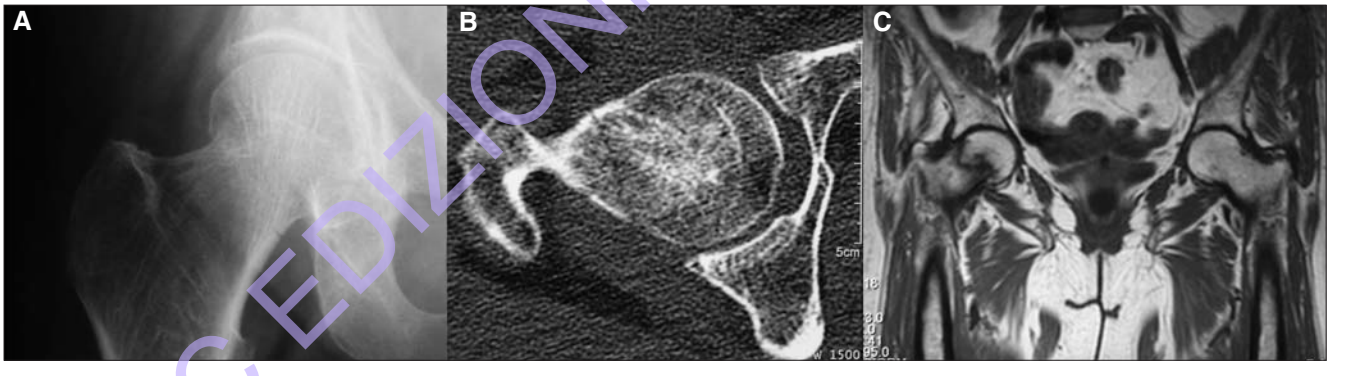


Figure 1 - Femoral neck fracture seen with X-rays (A), more evident in 3D techniques: CT (B) and MR (C).

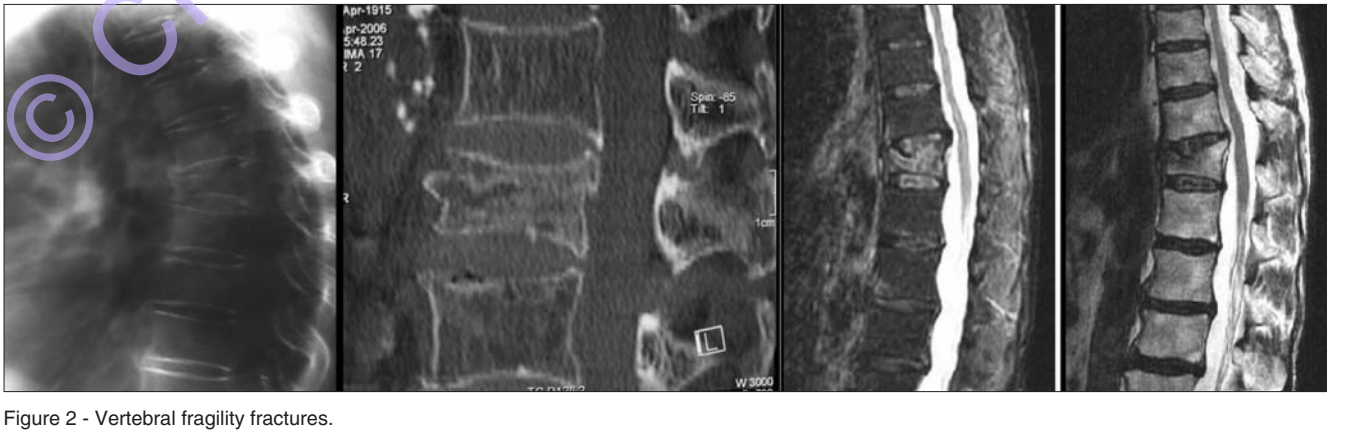


Figure 2 - Vertebral fragility fractures.

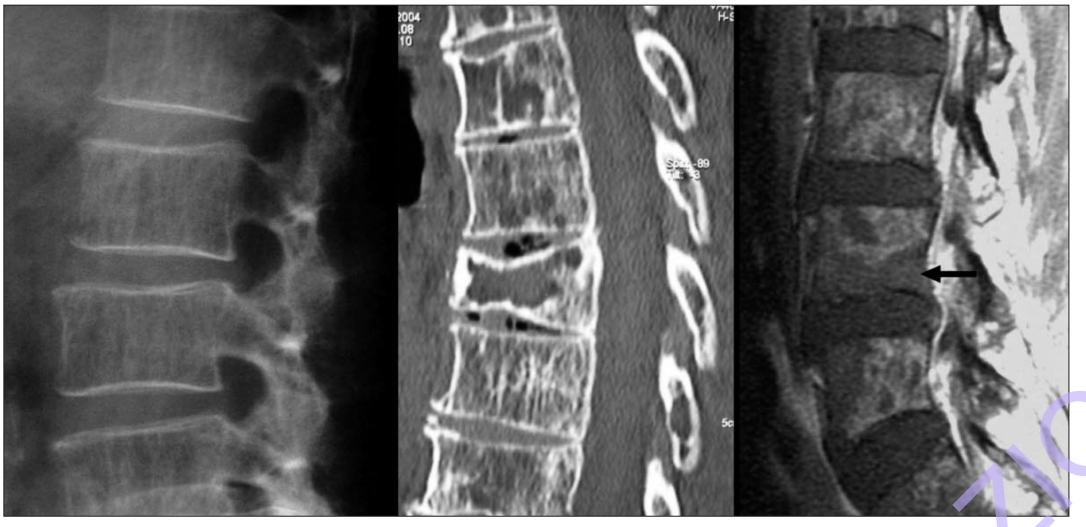


Figure 3 - X-rays, CT and MR of bone rarefactions and vertebral body crash (CT) in Multiple Myeloma.

CT and MR

3-dimensional imaging modalities, which include CT and MR, with their intrinsic panoramic and multiplanar characteristics may solve clinical suspect cases of recent bone fractures with doubt or without radiographic signs; in particular CT shows higher spatial resolution, MR higher contrast resolution.
Not all fractures depend on bone fragility; differential diagnosis between fragility, highly traumatic and pathologic fractures can be often obtained through conventional X-rays, but it receives a determinant contribute from advanced modalities such as CT and MR. Moreover 3D imaging techniques appear precious for the characterization of bone lesions causing fractures (Fig.3).

Vertebral Fracture Assessment (VFA)

Objective quantification of a vertebral fracture can be performed with morphometric evaluation (Fig.4).

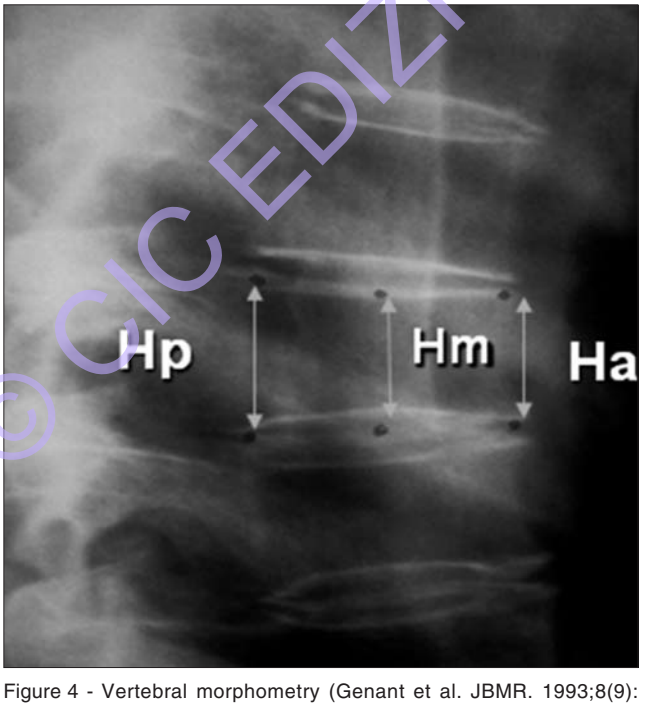


Figure 4 - Vertebral morphometry (Genant et al. JBMR. 1993;8(9): 1137-48).

The grade of vertebral body fracture can be provided in percentage using a ruler and measuring the anterior, middle and posterior heights of vertebral bodies, on a plane X-ray film or digitally on screen (11).
According to ISCD Official Positions: "The Genant visual semiquantitative method is the current clinical technique of choice for diagnosing vertebral fracture with VFA" (12).
Osteoporotic vertebral fractures occur only in dorsal and lumbar spine and their detection is important because over than 50% spinal fractures are asymptomatic and remain unnoticed.
In order to avoid influences of superimposing structures (ribs, pulmon, diaphragm), it is highly recommended to use breathing technique in a recline position (11) (Fig5).

Bone mass loss detection and assessment

Because bone fragility is a silent condition (i.e. it causes no signs or symptoms unless or until there are fractures) and because there are no clinical tools to assess bone quality, at the present measurement of bone mineral density (BMD) is required to identify patients before fractures occur (13).
"The ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke, and significantly better than serum cholesterol to predict myocardial infarction" (14).
However, many fractures may occur in individuals with normal BMD or with BMD values above the osteoporosis threshold. While at the population level, a decrease in BMD is associated with a significant decrease in fracture risk, at the individual level BMD assessment is quite sensitive but not specific for prediction of fractures. BMD, the quantity of bone, reflects only one aspect of bone strength, that is also influenced by macrostructural characteristics such as geometry, and microstructural features like relative trabecular volume, trabecular spacing and connectivity (15).

Clinical setting of bone status

A correct approach to clinical setting of bone consistency and quality contemplates the employment of diagnostic techniques that study: Bone Density and Bone Structure.
Bone Density and Bone Structure assessment at a macroscopic level can be obtained with a) semiquantitative analysis performed by Conventional X-rays, b) quantitative analysis executed by Dual Energy X-rays Absorptiometry DXA and Quantitative Computed Tomography QCT.
Bone mechanical properties, determinated by density, material

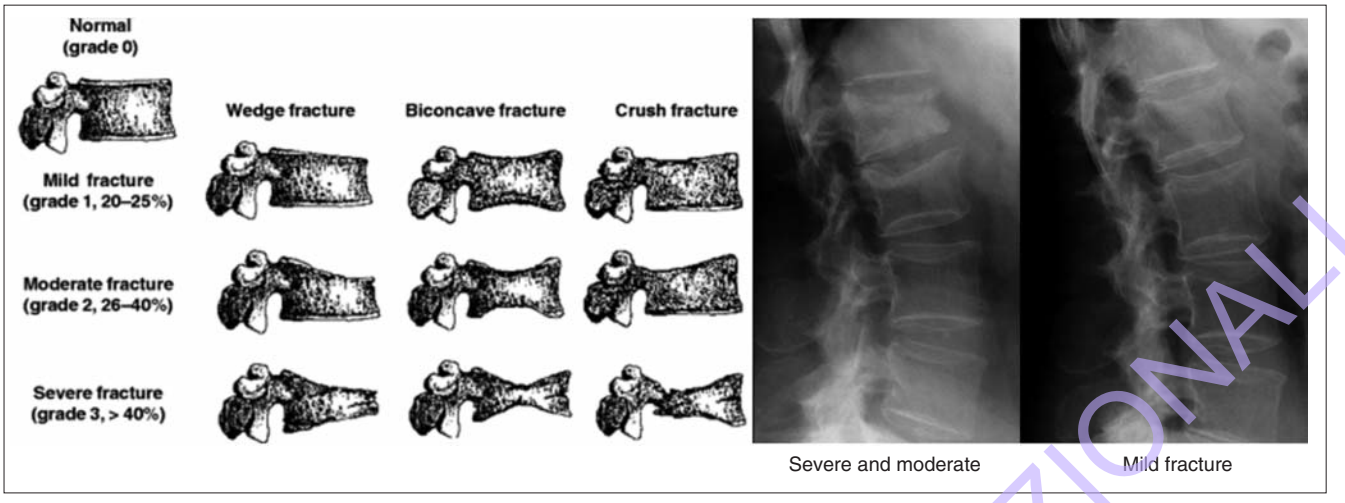


Figure 5 - Genant HK, JBMR 1993.

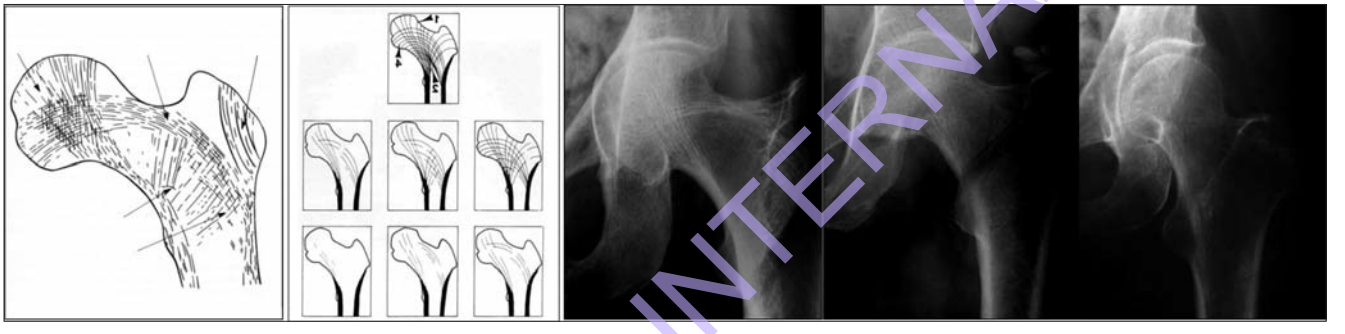


Figure 6 - Singh-index: the progressive disappearance of 5 trabecular bundles at proximal femur means a progressive bone mass loss.

features (i.e. mineralization and elasticity) and structural characteristics (i.e. architecture) influence parameters of Quantitative Ultrasonography (QUS).

Conventional X-Rays

Currently, after the arrival of quantitative modalities, X-Rays are no longer utilized for osteoporosis diagnosis; bone rarefaction is not detected on conventional radiographs until 20 to 40% of bone mass has been lost (16). Anyway, in a radiologic report is possible to indicate signs of supposed osteoporosis based on semiquantitative criteria: increase of bone transparency by reduction of trabecular bundles and cortical thickness. Two radiograph-based techniques that allow estimation of bone density are Singh-index for proximal femur, and cortical-medullary index from standard hand radiographs (17, 18)

(Figs 6-7).

Quantitative densitometry and clinical risk factors

The World Health Organization has defined osteoporosis as a BMD of more than 2.5 standard deviation (T score < -2.5) below the mean value for young adults.
There are several problems with the use of BMD tests alone in the assessment of fracture risk and the principal is that BMD alone has low sensitivity: the majority of osteoporotic fractures occur in individuals with BMD values above the osteoporosis threshold, typically in the osteopenic range (T-score of less than -1 and greater than -2,5 SD) (19).
Therefore, even if bone mass is an important component of the risk of fracture, a variety of non-skeletal factors contribute to fragility (20) (Tab.II). In the past 15 years a great deal of research has

prior fractures, family history of fracture and lifestyle risk factors like physical inactivity and smoking (19).
Risk factors for osteoporosis and for fragility fracture should be both considered when examining a patient (21).
The FRAX® algorithm developed by the WHO from studying

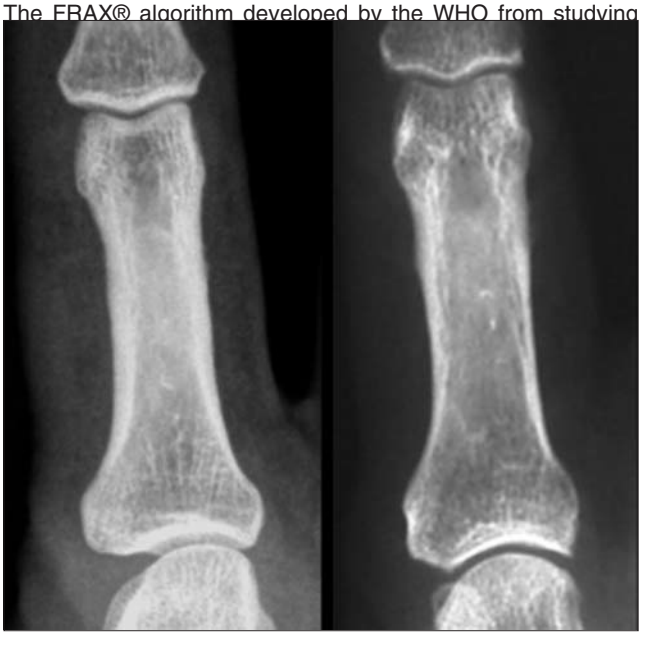


Figure 7 - Hand radiograph: (A) normal finding, (B) reduction of cortical thickness.

Table II - Risk Factors for Osteoporosis and Fragility Fractures.

Osteoporosis Fractures	Fragility Fractures
Female gender	History of falls
Increased age	Poor physical condition
Hypogonadism	Dementia
White race	Impared vision
Low body mass index	Environmental hazards
Family history of osteoporosis	Current use of benzodiazepines or anticonvulsants
Tobacco use	
History of fracture	
Chronic glucocorticoid or anticoagulant use	
Endocrinopathies	
High bone turnover and microarchitectural changes	

population-based cohorts from Europe, North America, Asia and Australia, integrating clinical risk factors, with or without BMD at femoral neck, gives a 10-year probability of hip and major osteoporotic fracture (19).
FRAX ® algorithms, country-specific, are sufficiently flexible to be used in the context of many primary care settings, including those were BMD testing was not readily available (19). They take into account the different contribution of risk factors in the 10-year fracture probabilities (Fig.8).
The commonly used quantitative imaging modalities for densitometry are: DXA, QUS and QCT.
The WHO criteria for assessing bone densitometry are established taking into account the Official Positions of the International Society for Clinical Densitometry (ISCD) that have been developed at a Position Development Conference (PDC) every 2 years since 2001.
An ideal technique for the measurement of bone mass should give a high level of accuracy in order to provide optimal evaluation of fracture risk in a given population.
The precision of devices is represented by the coefficient of variation, which should be considered in order to a) hold BMD changes as due to the therapy or the pathology studied and not to an intrinsic error of the densitometer, b) determine minimal intervals between BMD testing. Typically 1 year after onset of a therapy is appropriate, with longer intervals once therapeutic effect has been established. In conditions associated with rapid bone loss, such as glucocorticoid therapy, testing more frequently is appropriate.
For a clinical practice and research, the choice between different bone imaging modalities must reflect the balance of advantages and disadvantages, including high precision and reproducibility of imaging technologies, accuracy and reliability, the complexity and expense, their availability and accessibility.

Dual-energy X-ray Absorptiometry (DXA)

A large body of epidemiologic data indicates that the current standard for predicting fragility fracture risk is an areal BMD measurement by Dual-energy X-ray Absorptiometry (DXA).
According to "The Official Positions of the ISCD 2007" for DXA (22), schematically resumed:
– the Reference database for T-scores use a uniform Caucasian (non-race-adjusted) female or male normative database for women or men of all ethnic groups and use NHANES III database for T-score derivation at the hip regions.
– the WHO international reference standard for osteoporosis diagnosis is a T-score of -2.5 or less at the femoral neck, and the reference standard from which the T-score is calculated is the female, white, aged 20-29 years (NHANES III database).
– the skeletal sites to measure BMD are both the PA spine (L1-L4) and hip (femoral neck or total proximal femur) in all pa-

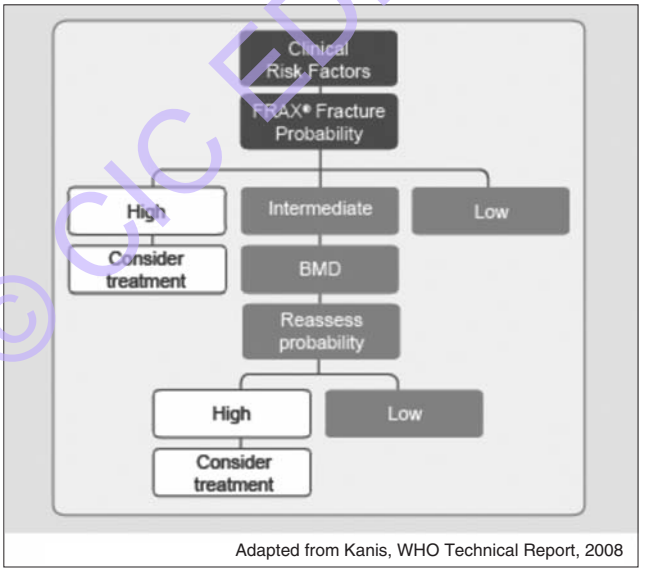


Figure 8 - Algorithm for the assessment of fracture probability.

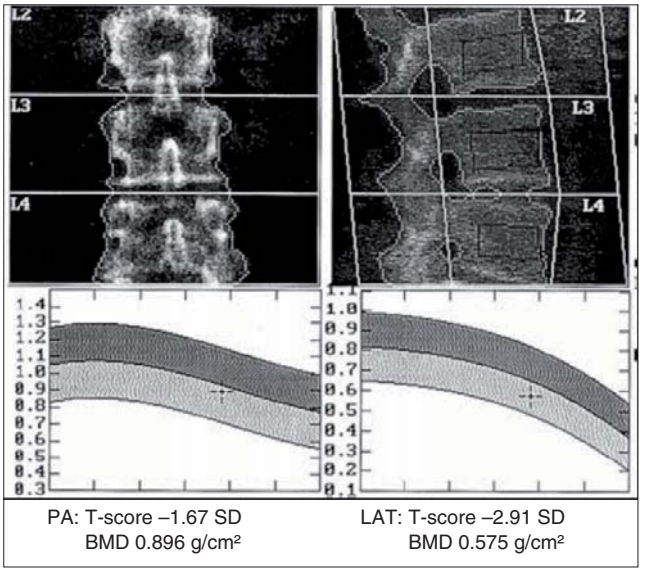


Figure 9 - Despite Postero-Anterior (PA) spine scans, Lateral one is not influenced by overlapping artefacts.

tients. Forearm BMD (33% radius of non-dominant forearm), less accurate at predicting vertebral fractures than hip or spine BMD, should be measured if: a) hip or spine cannot be measured or interpreted, b) Hyperparathyroidism, c) very obese patient (over the weight limit for DXA table).
Conventionally, the hip and lumbar spine are reguarded as the most important measurement site because fractures at these sites have the greatest impact on quality of life, morbidity and mortality of patients (23). However, DXA scanners are relatively expensive and available for a generally restricted number of major hospitals; the introduction of small DXA devices, cheaper, designed to scan only the forearm, referred to as peripheral DXA (pDXA) has extended the diagnostic benefits of bone densitometry (23).

Lumbar scanning

Spine BMD tends to change in response to corticosteroids and treatments more than in other sites, because vertebral bodies are largely made of trabecular bone, that is more sensitive to the effects of hormones and drugs than cortical bone (24).
Falsely elevated BMD values can be obtained by the increased prevalence of degenerative spinal changes or aortic calcifications or other artifacts when Postero-Anterior (PA) spine scans are made. Because of an overlapping of sclerotic-degenerative changes and posterior cortical elements in the PA view, Lateral DXA spine scans may be more reliable and more sensitive, as shown below (25).

Femoral scanning

Hip BMD is a strong predictor of hip fracture, but also of all fractures. This site is unaffected by degenerative arthritis.
The lowest T-score of two sites (total hip and femoral neck) should be considered for the diagnosis of osteoporosis (24).
Ward's area usually shows the earliest bone mass loss or improvement in the hip. It should not be used for diagnostic purpose: because of poor precision and accuracy, it would overestimate the prevalence of osteoporosis (24).

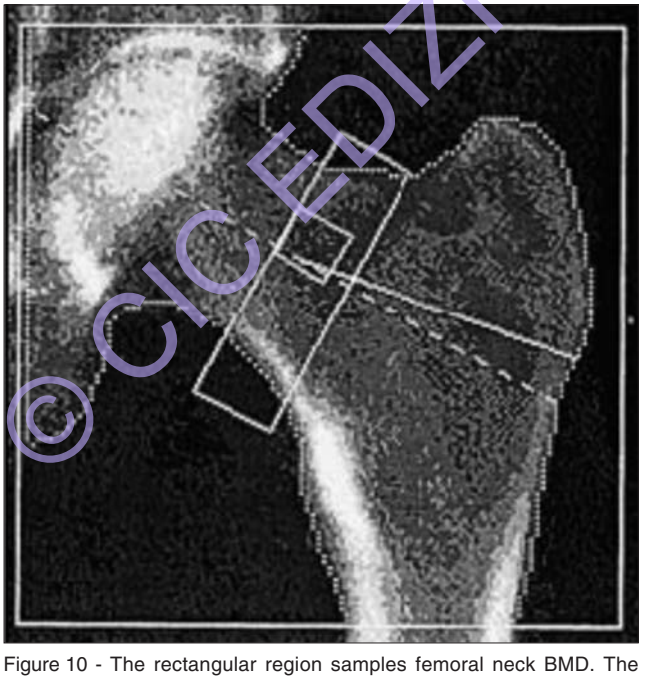


Figure 10 - The rectangular region samples femoral neck BMD. The small square samples "Ward's triangle", which represents the lowest BMD in the hip.

Femural DXA, besides BMD assessment, can be useful to define proximal femur geometry parameters, such as hip axis length (HAL), femoral neck-shaft angle (NSA) and femoral neck diameter (FND), which show a strong relationship with vertebral or femoral fracture (26).
Thus, DXA is the most widely used technique for measuring BMD. The high level of precision of these technique allows not only osteoporosis diagnosis, but also the monitoring of patients' response to therapy.

Peripheral Densitometry

Peripheral densitometry devices –heel and forearm DXA - with advantage of low cost and portability, have similar overall predictive value for estimating fracture risk regardless of the skeletal site measured, although measurement at any particular site best predicts fracture at that location (25). However, the discordance of BMD in the various skeleton sites may lead to misclassification (27). It may therefore be appropriate to measure more than one site in women younger than 65, while in older women discordance seems to be less of a problem.
The case for universal screening for osteoporosis has not been proved, and both peripheral and central bone densitometry are likely to be restricted to those who have risk factors for bone fragility (28).

Advantages of DXA
Measurements obtained from any site in the body (spine, hip, forearm, tibia, heel)
Short examination time
Body composition assessment
Excellent precision and reproducibility
Low radiation dose (1-3 μSv for L-spine, to 4 μSv for total body)
Easily approachable, low cost
Large body of epidemiologic data
Possibility to include spine morphometry

Disadvantages of DXA
No difference between cortical and trabecular bone
Only areal-density assessment, influenced by: bone dimensions, fat tissue distribution, movement artifact
Calcium-density analysis, no bone architecture detection
Sampling errors
Incorrect evaluation in obese patients

Quantitative Ultrasonography (QUS)

A different peripheral technique is quantitative ultrasound (QUS), increasingly used for its low cost, portability and lack of exposure to ionizing radiation. The transmission of ultrasound of frequency range between 200 kHz and 1.5 MHz through bone tissue reflects its density and its structure. In addition to BMD, bone ultrasonography is thought to assess changes in trabecular and cortical architecture and accumulated fatigue. Studies in vitro have clearly underlined that Speed of Sound (SoS), which depends on both the amplitude and the velocity of the signal received, is closely related to bone mineralization, leading to high correlation between SoS and BMD at the same measurement site (29). Broadband Ultrasound Attenuation (BUA), on the contrary, seems to be more influenced by the structural characteristics of trabecular bone (porosity, etc.) (30)
Further reference measurement parameters include the Ultrasound Bone Profile Index (UBPI), a mathematical combination of other signal parameters that describes the probability that the tested subject belongs to the nonfractured group (31), and the Bone Transmission Time (BTT), the interval between the

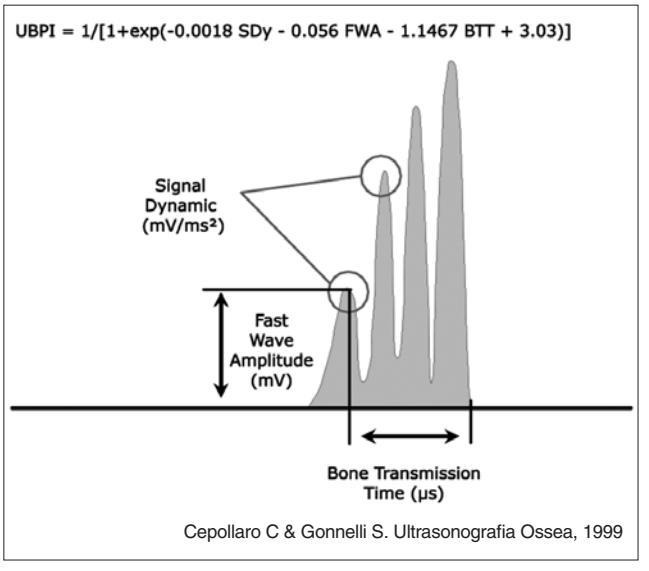


Figure 11 - Physical parameters that are considered for graphic trace analysis.

first received signal and the received signal that is propagated through soft tissue only (32).
The measurement sites analysed by QUS are: phalanges, calcaneus, radius, humerus and tibia.
The only validated skeletal site for the clinical use of QUS in osteoporosis management is the heel (22).
The calcaneus is composed almost entirely by trabecular bone, its external surfaces are flat, homogeneous, parallel and therefore suited to the geometry of propagation of the ultrasound beam. QUS measurements at this site have shown the ability to detect changes associated with age and menopause (33, 34), to differentiate healthy subjects from those with fractures (34, 35), and also identify those who are at an increased risk of fracture (36, 37). Validated heel QUS devices predict fragility fractures in postmenopausal women (hip, vertebral, and global fracture risk) and men over the age of 65 (hip and all non-vertebral fractures) independently of central DXA BMD(37) (38).
Calcaneal QUS measurement is equivalent to DXA in terms of ability to predict fractures, especially hip fractures. However, it can be unreliable in patients with ankle oedema. Variation in temperature (both ambient and of the patient's limb) are also believed to have an adverse effect on measurements (39). An alternative, non-weight-bearing site is phalanges, composed of predominantly cortical bone, easily accessible (23) and actually examinable with devices reporting a good precision (40). There is also evidence suggesting that phalangeal QUS measurements may be more sensitive than calcaneal in identifying trends due to aging and menopause (41).
The reference standard for osteoporosis diagnosis with Ultrasonography is a T-score of -3.2 SD or less.

Advantages
Radiation absence
Easy to execute
Portability and low cost

Disadvantages
Too different advices
Limitations related to measurement sites
Precision and accuracy

Gluer et al., JBMR 2004.

Despite the above-stated correlations between QUS and DXA parameters, ultrasonography, unlike DXA and QCT, currently cannot be used for monitoring skeletal changes over time or evaluating response to therapy.

Quantitative Computed Tomography (QCT and pQCT)

CT image is a two step process of initial scan acquisition and then tomographic image reconstruction by a mathematical process of calculating from acquired raw data. All clinical CT scanners are calibrated to the X-ray attenuation to the water, resulting in CT numbers, measured in Hounsfield Units (HU). To transform HU into bone mineral equivalents (mg/cm³) an appropriate bone mineral phantom is included in the scan field (42).
QCT is the unique modality that measures the real bone density in a determinate volume (mg/cm³) without the overlapping of others tissues, and differently from DXA it allows a selective assessment of both trabecular and cortical bone. Trabecular BMD obtained by QCT shows a more rapid age dependent decrement than that measured by DXA, that provides a com-

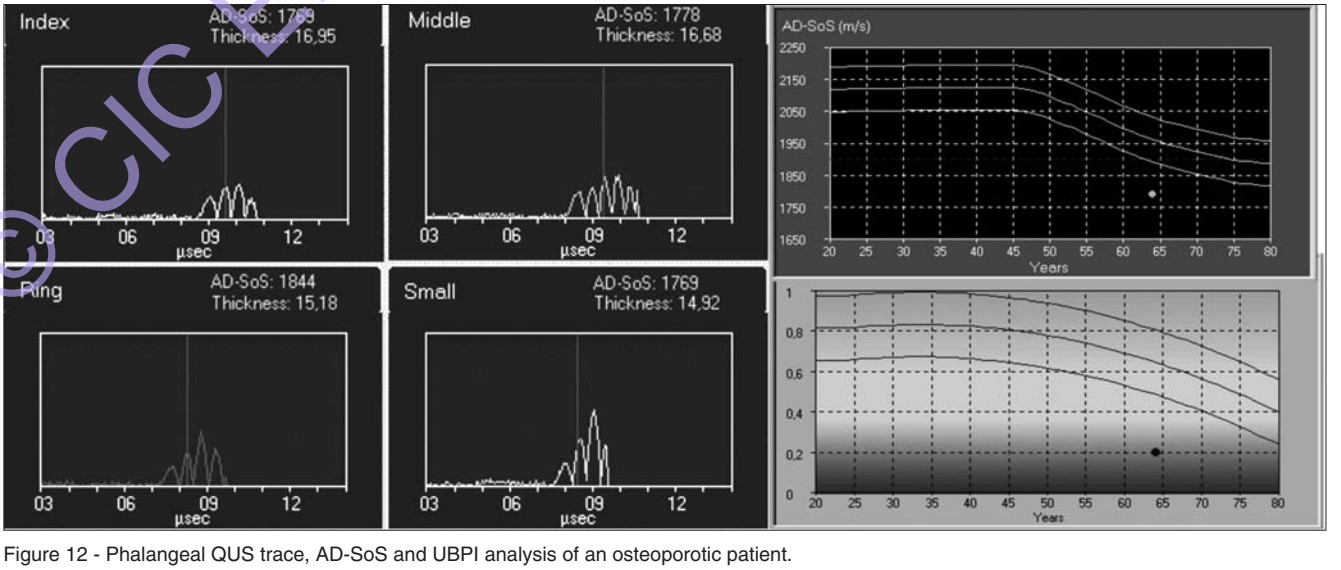


Figure 12 - Phalangeal QUS trace, AD-SoS and UBPI analysis of an osteoporotic patient.

posite measurement of integral trabecular and cortical bone (43). For this reason, T-scores derived from QCT are not equivalent to those derived from DXA T-scores (44). Therefore, to define abnormality in terms of QCT of the spine a measure below Z score –2.0 can be applied, or a BMD spine below 80 mg/cm^3 is indicative of osteoporosis; using average slice BMD from L1–L3 it has been suggested that subjects with a BMD below 80 mg hydroxyapatite/cm3 could be classified as osteoporotic and those with a BMD between 80 and 120 mg/cm^3 as osteopaenic (45).
Single Energy QCT (SEQCT) is normally used for clinical setting, though BMD estimation can be altered by quantity of fat tissue which substitutes the red marrow in elderly people. This effect produces an increasing error of evaluation with the increase of elderly patients. Even if Dual Energy QCT (DEQCT) improves the accuracy of this technique, nevertheless it uses higher radiation dose and longer scanning times without increasing QCT sensibility in discriminating between healthy and osteoporotic subjects (46). In future, it will be interesting to see if the development of dual headed X-ray source CT scanners will have an application to improve QCT in the investigation of the skeleton (42).
Over the last decade, technical developments in CT, including multiple rings of detectors and spiral rotation of X-ray tube (spiral multidetector computed tomography, MDCD) have resulted in images of volumes of tissue being acquired very rapidly, and this has had an impact on QCT in that 3D volume images can be acquired rapidly. Such 3D volumetric QCT enables analysis of the hip, important site of fracture, which was not feasible with 2D single slices (42).
To date only one commercial software package and few advanced university-based research tool are available for detailed analysis of cortical and trabecular volumes of interest in the proximal femour (42, 47).
For clinical applications, QCT of the spine is performed using standard whole body CT scanners, while QCT at the forearm (radius and ulna) and leg (tibia and fibula) are performed using a smaller, dedicated CT device; the latter technique is called peripheral-QCT (pQCT).

Spine QCT scanning

In common CT scanners QCT is applied to the lumbar spine, usually L1-L3, using single two-dimensional (2D) 8-10 mm slices through the middle of each vertebral body, parallel to the end plates. The bone equivalent phantom is placed on the scanner table below the lumbar spine, and a lateral projection radiograph indicates the scanning planes; fractured vertebrae should not be analyzed.
In spine acquisition with 3D QCT (on spiral MDCT), L1-L2 are scanned to limit radiation dose; analysis can be made on 2D slices using the few commercially available packages, and for more complex 3D volume analysis only advanced university based research tools are available (42).

Spinal trabecular BMD as measured by QCT has at least the same ability to predict vertebral fractures (not hip fractures) as PA spinal BMD measured by central DXA in postmenopausal women (44).

Advantages of spine QCT
Volume density can be obtained
Trabecular BMD and Cortical BMD separately obtained
High sensibility of assessing trabecular BMD
Good accurancy and precision

Disadvantages of spine QCT
High radiation dose (spine: 50μSv SEQCT e 100μSv DEQCT)
Hard accessibility, high cost

Peripheral QCT scanning

Dedicated peripheral CT scanners to measure BMD and bone morphology in the radius and tibia are smaller, more mobile and less expensive that whole body CT scanners.
More recently dedicated high resolution pQCT scanners have been developed to image trabecular structure (50).
Volume BMD can be obtained with single-slice or multi-slice mode.
The patient's non-dominant forearm or leg is placed in the pQCT gantry and fixed; a coronal scout scan is performed and a reference line is placed to bisect the medial border of distal radius or the lateral border of distal tibia in adults (in children with non-fused growth plate, the distal metaphysis should be chosen as reference line).
Scanning specific sites are generally 4% and 66% at distal radius, and 4%, 38%, 50%, 66% at tibia.
This technique gives an automatical scan analysis of the trabecular and cortical compartments; it calculates their BMD, the Bone Mineral Content BMC, and bone geometrical parameters. From geometrical parameters, such as marrow and cortical Cross-Sectional Area (CSA), Cortical Thickness (CTh), periosteal and endosteal circumference, biomechanical parameters can be obtained, like Cross-Sectional Moment of Inertia (CSMI), which is a measure of bending strength, polar moment of inertia, indicating bone strength in torsion and Strength Strain Index (SSI).
Also CSA of muscle and fat can be extracted: muscles, which are thought to stimulate growing bones to adapt their geometry and mineral content, are determinant to preserve or increase bone strength; thus, pQCT provides an evaluation of the functional 'muscle-bone unit', defined as BMC/muscle CSA ratio (51-54).
This functional approach to bone densitometry can establish if bone strength is normally adapted to the muscle force, and if muscle force is adequate for body size, providing more detailed insights to devise targeted strategies for the prevention and

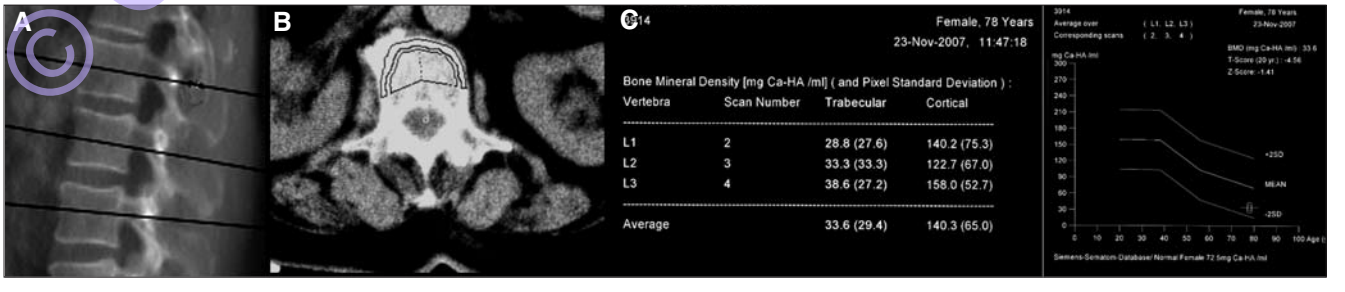


Figure 13 - A) Lateral scan projection radiograph with identification of slices to be performed at L1-L3 ; B) PacMan region of interest selected to encompass trabecular bone area without including the cortical shell or the basi-vertebral vein area (48) (49); C) L1-L3 trabecular and cortical BMD results.

treatment of pediatric bone diseases; the quantified relationship of muscle force to bone stability is a reasonable approach to distinguish between primary and secondary bone diseases (55).

Advantages of pQCT
Measure of bone geometry
Trabecular BMD and Cortical BMD separately obtained
Functional evaluation of pediatric bone diseases
Good accurancy and precision
Low radiation dose (≈3μSv), especially important in children
Easy accessibility, low cost

Disadvantages of pQCT
Evaluation of only appendicular bone with low turnover
Low spatial resolution: partial volume effect in CA and CTh
pQCT and fracture risk: only few transversal data available
Exact repositioning of the extremity required in follow-up

pQCT is increasingly being used to measure BMD in both research and clinical practice to monitor BMD changes to evaluate the fracture susceptibility in old people or the effect following therapeutic intervention (56).
pQCT of the forearm at the ultra-distal radius predicts hip, but not spine, fragility fracture in postmenopausal women.
Repeated measurements in long-term follow-up are an appropriate method to study the pattern of bone loss, and the diagnostic value critically depends upon the precision (reproducibility), in fact positioning is one of the sources of imprecision of this method (57).

Research applications on bone status: advanced imaging modalities

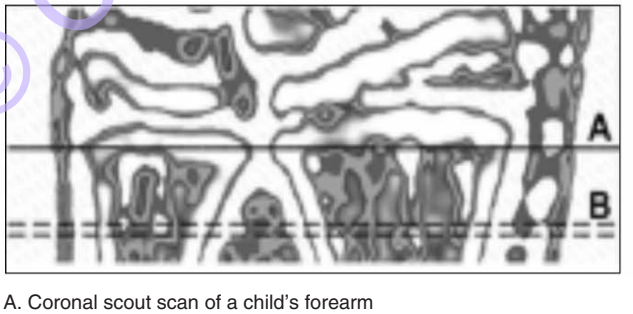
In the last few years, the interest of active research has led to an improvement of sophisticated technologies for the evaluation of Bone Structure assessment at a microscopic level, employing 3-dimensional imaging modalities, such as CT and MR. Methods for quantitatively assessing microstructure of trabecular bone non-invasively, non-destructively are hrCT and hrMR applicable in vivo, microCT and microMR applicable in vitro.

High-resolution CT (hrCT)

Bone is composed by an organic substrate consisting essentially of type I collagen interspersed with mineral crystals composed of non-stoichiometric calcium hydroxyapatite; the remaining volume is occupied by water that is either bound to collagen or resides in the spaces of the lacuno-canalicular system. This combination confers to bone its unique mechanical properties in terms of tensile and compressive strength and is responsible for the material's viscoelastic properties (58). Cortical bone and trabecular micro-architecture, which consists of a complex array of interconnected plates and rods of ~100–150 μm thickness, have different elastic properties.
The CT scanners used in clinical practice have spatial resolution of 400 μm and slice thicknes of 1 mm, inadequate for accurate cortical measurements and for analysis of trabecular morphological parameters, principally because of partial volume effects, comparing with the dimensions of trabeculae (100-400 μm) and trabecular spaces (200-2000 μm). Recently high-resolution imaging wih MDCT scanners has achieved a plane resolution of about 200 μm and slice thickness of 500 μm, and this approach has been helpful in vivo for a better evaluation of bone architecture of lumbar spine (59). The employment of hrCT led to determine a feature called the "trabecular fragmentation index" (length of the trabecular network divided by the number of discontinuities) in an effort to separate osteoporotic subjects from normal subjects (60). Recent assessment of trabecular structure from CT image is obtained through high-resolution spinal CT with postprocessing steps: the structure is segmented by defining the boundary between cortical and trabecular bone, the trabecular network is reduced to a binary image, thinned to produce a representation of the trabecular form (59).
Recent studies have shown that with this technique the trabecular structural analysis from multi-detector row CT images can better discriminate postmenopausal women with vertebral fracture than DXA (61).

Microcomputed Tomography (μCT)

The earlier conventional tool for assessing trabecular bone network architecture was histomorphometry from bone biopsies (62), which produces a two-dimensional representations of tissue structure, while cortical and trabecular bone structure is three-dimensional. Thus, in recent years, it has progressively been imposed the direct 3D analysis of biopsy specimens imaged by micro-computed tomography (micro-CT). The most common application of this technology has been the in vitro quantification of osteoporotic change in trabecular bone architecture.
The resolution of isotropic voxel obtained from micro-CT scanners varies from 15 to 5μm, comparable with resolution of trabecular bone (63). The highest resolution has been provided by the high-intensity, monochromatic beam of Synchrotron Radiation (SR) that shows an extraordinary level of detail: osteocyte lacunae are visible in tomographic images with 1.4 μm spatial resolution (64).
Microarchitectural 3D data elaborated by specific softwares consents to evaluate many structural parameters of bone network such as Tissue Volume (TV,) Bone Volume (BV), Bone Surface (BS), Bone Volume Fraction (BV/TV), Bone Surface to Tissue



A. Coronal scout scan of a child's forearm

B. Coronal scout scan of an adult forearm

Figure 14 - A) If the distal radius growth plate is visible, the references line A) is positioned to bisect the medial border of the end of distal dense metaphysis. B) If the growth plate is fused, the references line (A) is placed to bisect the medial border of the articular surface of the radius.

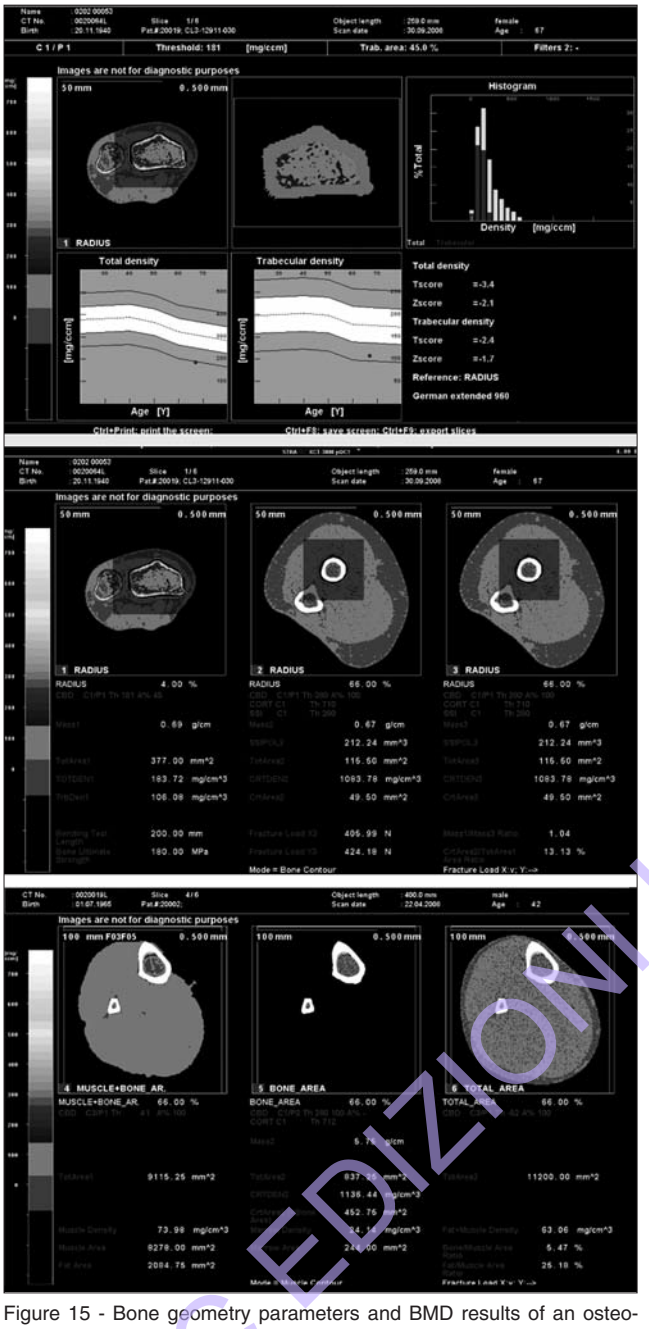


Figure 15 - Bone geometry parameters and BMD results of an osteoporotic patient obtained by a forearm pQCT scan.

Volume (BS/TV), Trabecular Thickness (Tb.Th) Trabecular Separation (Tb.Sp), trabecular bone volume fraction (BV/TV), Degree of anisotropy (DA), Connectivity density (Conn.D).
More recently, additional special purpose ultra-high-resolution micro-CT systems have been developed for imaging bone microstructure at resolutions approaching 10 µm or better; this new systems have found application in preclinical animal studies and clinical research settings.
In a human study the rapid deterioration in trabecular microarchitecture in women in age of menopause was documented by paired iliac crest biopsies before and 5 years after the menopause; prominent thinning of trabeculae and conversion of plate-like to rod-like trabecular structure were observed (65). 3D analyses have also been used to study the longitudinal impact of teriparatide (PTH 1-34) treatment versus placebo on skeleton of post-menopausal women (66).
Micro-Computed Tomography has applied not only to study trabecular bone, but also cortical bone. Structural cortical parameters are Tissue Volume (TV), Cortical thickness (Ct.Th), Canal Surface (Ca.S), Cortical Porosity (Ca.V/TV), Canal Surface to Tissue Volume (Ca.S/TV), Canal Diameter (Ca.Dm), Canal Separation (Ca.Sp). It was found also that age-related change of cortical porosity is more noticeable than that of trabecular parameter. Cortical thickness (Ct.Th) decreased, cortical porosity (Ca.V/TV) almost doubled, and canal diameter (Ca.Dm) increased between the middle-aged and elderly groups for both women and men (67).
The application of flat-panel volumetric CT (fpVCT), which consents larger volumetric coverage, could overcome the intrinsic limit of micro-Computed Tomography that is able to analyze small bones or bone samples with high spatial resolution; flat-panel volumetric CT (fpVCT) could investigate larger samples or animals in studies of bone methabolism (68).
The major drawbacks to further developments with the in vivo µCT technique are the need of specialized equipment and the employment of ionizing radiation, which may limit its use in some patient categories.

Magnetic Resonance Imaging (MRI)

MRI signal of trabecular bone itself is not visualized and trabeculae appear as a signal void, surrounded by high-intensity fatty bone marrow (5).
Two technical approaches, indirect and direct, are employed to obtain high resolution imaging for bone structure assessment.
Indirect detection, the earlier, is based on the property of bone, more diamagnetic than marrow: two coexisting phases induce local inhomogeneous magnetic fields in the proximity of the trabeculae (high-resolution MRI). The most important MRI parameters are T2* (69), (the effective transverse relaxation time) which has been shown to be a function of the density and orientation of the trabeculae (70), and R2* (the rate constant of the free induction signal).
T2* and R2* has been applied to the calcaneus, distal radius (71), spine and proximal femur.
In osteoporotic women bone marrow T2* was found to be significantly prolonged (72), while R2* values resulted lower (73). BMD and T2*measured at the proximal femur have shown to be associated with fracture status (69).
A recent study reported that MRI R2* at the calcaneus discriminated patients with vertebral fracture from control subjects better than BMD (74).
Direct method attempts to visualize trabecular bone and the minimum resolution voxel request for an accurate representation of topology, scale and orientation of trabeculae (micro-MRI). The obtained data must be pre- and post-processed by specific algorithms to yield images in high spatial resolution and finally softwares of binarization and skeletonization converts trabecular rods to curves and plates to surfaces, and each voxel could be characterized as belonging to a surface, curve or junction (75).
Therefore it has been introduced for MR also the concept of "virtual bone biopsy" (VBB), a method combining magnetic resonance microimaging and digital image processing techniques.
Thus micro-MRI can provide structural parameters, such as trabecular bone thickness (TbTh) and mean bone volume fraction (TV/BV), associated with bone biomechanical properties and fracture resistance. Specific algorithms in vivo with resolution of 160 micron were able to detect the structural implications of a 5% loss in bone volume fraction (TV/BV) with high statistical significance.
Micro-RMI examinations at distal tibia and radius metaphysic were performed in early postmenopausal women, divided in groups with and without estrogen, with a commercial 1.5-T

imaging system (performed high-resolution with 3D FLASE sequence) with total scan times of 16 min for tibia and 12 for radius. It represents the first observation in vivo of the short-term temporal changes in trabecular architecture (76). High-resolution MRI presents actually several limits: the presence of haematopoietic bone marrow which, due to its paramagnetic properties, interferes with visualization of single trabeculae: yellow type marrow is prevalent at distal extremities such as the calcaneus, radius or distal tibia. Other limitations are:
– long acquisition time (at least 10–15 minutes) which leads to possible involuntary motion artifacts,
– restriction to evaluation at appendicular sites, reproducibility of bone volume examined in longitudinal studies,
– requirement for specialized coils
– the voxel size achievable for in vivo trabecular bone imaging is strongly conditioned by Signal-to-Noise Ratio (SNR)
– high cost and reduced availability.
SNR can be improved by reducing the size of the receiver Radio Frequences coil (71).

Finite Element Analisys

The mechanical properties of microstructural data of a bone segment can be evaluated using mathematical system of analysis like *finite element analisis* (FEA), a computerized numerical analysis technique for modeling a complex structure under certain conditions of stresses and strains. The object or segment, generally submitted to a hrCT or hrMRI scan is represented by a geometrically similar model consisting of multiple, linked, representations of discrete regions or *finite elements*, triangular, tethraedral, pentahedral or hexahedral shaped, depending the site of force loading. When the mathematical model is subjected to known loads, the displacement of the structure may be determined.
The principal mechanical parameters evaluated are the Young's modulus (E), a measure of the stiffness of an isotropic elastic material, also known as modulus of elasticity or elastic modulus, and the Poisson's ratio (ν) that is the ratio of the contraction or transverse strain (perpendicular to the applied load) to the extension or axial strain (in the direction of the applied load).
HrCT imaging, combined with finite element and applied in fracture's model of distal radius, hip, femur and vertebra are able to predict fracture strength, fracture initiation site, fracture direction, correlation with microarchitectural parameters and structural drug effect (77).
QCT-FE evaluation of biomechanical effects of teriparatide and alendronate on lumbar vertebrae evidenced that both treatments act positively on vertebral strength through their effects on average BMD, but Teriparatide increases vertebral strength by altering the distribution of density within the vertebra and had a 5-fold greater percentage increase in the strength:density ratio (78).
Finally, specific micro-finite element models based on HR-QCT, HR-pQCT and HR-MRI could be applied in biomechanical researches to provide good prediction of fracture risk in population affected by bone diseases.

Conclusion

Bone fragility, composite description of bone's mechanical properties, is directly related to bone's susceptibility to fracture and is inversely related to a bone's fracture resistance.
As fractures compromise life quality and shorten life expectancy, the imaging diagnostic modalities play the first fundamental role in clearly and accurately identifying and reporting the presence and features of fragility fractures (distinguishing these from other nature fractures) by employing first Conventional X-rays, then eventually utilizing more performing techniques such as CT and/or MRI.
In fragility bone assessment, BMD is the main parameter to quantify non-invasively bone properties because of its relationship to bone strength and prediction fracture risk. In the past two decades bone densitometry has been performed with direct methods such as DXA, above all, and QCT (real volumetric BMD), and indirect modalities like QUS, which evaluates also structural bone characteristics. QCT is not only centered on two-dimensional characterization of vertebral trabecular bone, but nowadays it has been developed in three-dimensional reconstructions, and the region of interest is extended to the proximal femur.
Besides BMD, a sensitive improvement of fracture risk prediction is obtained taking into account a clinical assessment of risk factors (WHO FRAX ®); so, for clinical applications, radiologic reports, BMD measurements and clinical risk factors are determinant in the identification of patients with bone fragility.
As bone's susceptibility to fracture depends, beyond bone mass, on macroscopic and microscopic architecture features, in the last decade clinicians and researchers' deeper interest in bone quality has led to develop advanced techniques for bone status assessment. With recent technical advances in CT and MRI including the introduction of high resolution techniques and Micro-CT and Micro-MRI, imaging of true trabecular and cortical bone architecture is becoming more feasible.
Micro-CT is an objective modality, reliable, sensitive and less expensive than histomorphometry, till now almost exclusively employed for clinical research because uses bone biopsies; flat-panel CT can provide higher resolution with analogue radiation dose than MDCT, covering larger areas. MRI, with new developments like the availability of clinical high field scanners, new sequences, may further advance imaging of osteoporotic bone and quantification of fracture risk.
Recent studies have demonstrated the feasibility and potential utility of combining high resolution CT and MRI images with finite element analysis methods to assess the effects of bone structure on mechanical properties.
Further research is required for improvements in reproducibility, standardization and clinical application of these methods remembering that "…the imaging techniques, if taken for diagnostic procedures, must offer high accuracy and reliability, if used for monitoring applications, must have high precision and reproducibility"(Genant) (59).

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