Mini-review

# Peripheral CT in the diagnosis of osteoporosis

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**Summary**

**This review shows that, compared to both DXA and axial QCT, pQCT is a more versatile technique, allowing for selective assessment of trabecular and cortical bone components, accurate assessment of bone geometry, assessment of muscle mass and muscle/bone relationships. Although pQCT has not been evaluated as thoroughly as DXA in clinical research, recent studies on representative populations in the USA and Italy have yielded normative data on trabecular and cortical bone volumetric BMD, and geometry parameters obtained by pQCT at multiple skeletal sites. These data can be used as reference values by physicians to detect patients with osteopenia, assess their bone strength, and to plan appropriate, patho-physiologically based treatment.**

*KEY WORDS: peripheral CT, osteoporosis.*

## Introduction

Osteoporosis is defined as a condition characterized by reduced bone strength and high propensity to fractures. Therefore, diagnosing osteoporosis implies the capacity to detect reduced bone strength (fragility). Age-associated decline in bone mass is usually considered responsible for the development of bone fragility and the consequent high rate of bone fractures experienced by older persons. Accordingly, current guidelines suggest that in clinical practice, the risk of fractures should be estimated by measuring bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Therefore, DXA has been increasingly used by clinicians to diagnose osteoporosis and estimate the risk of future fragility fractures, using an algorithm based on T-scores, developed by the WHO study group in 1997 (1). Recommendations to use DXA as the standard method to diagnose osteoporosis and estimate fracture risk are based on the assumption that BMD is a good measure of bone mass and strength.
However, this assumption has proven incorrect. In fact, a number of recent reports have argued that DXA is insensitive to changes in the quantitative and geometrical distribution of trabecular and cortical bone tissues which are important factors affecting bone strength in both the appendicular and axial skeleton. Moreover, DXA measurements are affected by several sources of inaccuracy that limit the interpretability of its results (2-8). For these reasons, alternative methods to DXA have been developed, including axial and peripheral QCT.

## Determinants of bone strength: basic concepts

In general, the strength of a given structure is determined by the following: properties, amount and distribution of the constituent material. In fact, the strength of the bone constituent material (material strength) closely interacts with the architecture of the whole bone, which is determined by the size of the bone and the distribution of bone material. Only the evaluation of both the material properties and the architecture, and not either of the two alone, allows to predict if a bone subjected to a certain load will break. The mechanical testing of a structure is performed by the incremental application of force (compressive, tensile, or bending force) and recording its deformation on a load-deformation curve (9, 10). The force at which the structure breaks is called the *breaking strength* or the *ultimate strength* of the structure. The area under the curve describes the capacity of the structure to absorb energy and is called the *work at failure*. In order to obtain information on material strength, both the force and the deformation are divided by the cross-sectional area of the structure; a stress-strain curve is so obtained, where stress (whose unit is the Pascal) is force (in Newton) per unit area (in square meter) and strain is the ratio of the deformation by the initial length. The slope of the linear part of the stress-strain curve represents the *modulus* of elasticity (E) of the material (also called the *material stiffness*), the stress at fracture is called the *ultimate stress* or breaking strength of the material, and the area under the curve describes the *toughness* of the material or the capacity of the material to absorb energy before breaking. The described mechanical testing can be performed in humans only on excised bones and constitutes the benchmark against which the methods for non-invasive estimation of bone strength are validated. Material stiffness (or modulus of elasticity) and material toughness are the main properties describing the strength of bone material. The modulus of elasticity is influenced by the porosity and the degree of mineralization of the bone tissue. On the other hand, toughness (the opposite of tough is brittle) is probably also substantially influenced by bone matrix and collagen structure (11).
Structural strength, as described by the load-deformation curve, will be determined by the material strength and by the architecture (or geometry) of the examined structure. However, the resistance against different types of loads is determined by different geometric characteristics and must be evaluated separately (10). The determinants of compressive strength are the modulus of elasticity and the cross-sectional area (the relative formula is: E*A, where E is the stiffness, and A is the cross-sectional area). Thus, bone size is a simple geometric factor influencing compressive strength; a bigger bone is stronger than a smaller bone in compression. Resistance against bending and torsional loads, on the other hand, is determined more by the distribution of the material than by size itself. The most important geometric component of the resistance against bending

(and torsion) is the moment of inertia, critically determined by the distance of the material from the plane of bending. The relevant formula for the determination of bending and torsional strength is therefore: E*I, where I is the moment of inertia. This concept is important for the estimation of appendicular bone strength, including hip; in fact, the age-related bone loss, leading to thinning of the cortex of long bones, and potentially to a dramatic decrease in strength, is compensated for by the increase in periosteal diameter. With this putative adaptative mechanism bone material is displaced away from the central axis and as a consequence the decrease in the moment of inertia with its attendant loss in bending and torsional strength is prevented (12, 13). There is some evidence of a sexual dimorphism in this mechanism which may, at least in part, account for the greater propensity of older women to undergo fragility fractures (14).
The role of microarchitecture in determining the compressive strength of the trabecular bone has been emphasized in recent years, although controversies on the importance of this factor still exist.

**Limitations of DXA**

As mentioned in the introduction, DXA has inherent limitations that preclude accurate assessments of bone strength. The following is a brief overview of the most critical points which raise serious concerns about the use of the so-called areal BMD as a measure of bone strength.
1. The most obvious source of inaccuracy is inherent in the calculation of areal BMD as BMC/bone area. Bone area, and hence size, is a positive determinant of bone strength, both in compression and in bending or torsion. Therefore, persons with higher bone area have higher bone strength, compared with persons with the same BMC and smaller bones, but DXA would assign them a lower BMD value. This limitation applies to comparisons between individuals of different stature and bone size, because of different race, gender, age, or exposition to anabolic agents (such as teriparatide). As pointed out in a recent editorial, BMC, not BMD should be used in these circumstances as a proxy measure of bone strength (Heaney OI, 2005). However, data from a large survey in healthy women indicate a 1.12 difference in spine BMC Z-score between individuals belonging to the extreme quintiles for stature (8).
2. A second reason why BMD and BMC are inaccurate in assessing bone strength is the influence on measurement by the composition of the soft tissue surrounding the bone. In fact, a large number of *ex vivo* and *in vitro* experiments show that DXA is inherently inaccurate because it operates with two x-ray energies while the human body is composed of three main types of tissues: bone, muscle, and fat. This so called *two-component limitation* can lead to an underestimate of bone density as high as 60%, particularly in frail older women with low bone mass, a low percentage of body fat, and fatty bone marrow. It should be noted that the above-mentioned source of inaccuracy is inherent to the DXA technology; therefore, it does not pertain to incorrect use of instrumentation, incorrect positioning, or conditions related to the examined subject (obesity, extra-skeletal calcifications) which would further increase the probability of measurement errors (2-7). As a consequence of the above, longitudinal assessments of BMC/BMD are also flawed if body composition changes in a given individual, for example because of body weight loss following diet, exercise, or disease.
3. Even assuming that BMC accurately assesses bone mass, it should be noted that bone mass is not itself a satisfactory predictor of bone compressive strength, In fact, compressive strength depends not only on bone mass but also on bone size. This concept is easier to understand if we compare two bones with the same bone mass; one has a very high apparent density and is small, while the other has a wider section and a lower apparent density. The latter bone can resist better compressive loads although the BMC reading of the device will be the same.
4. If BMC and BMD have limitations in predicting compressive strength, they give no information on bending or torsional strength or, worse, they provide misleading results. In fact, bending and torsional strength are related to bone size and distribution of bone material within the bone (bone geometry), structural characteristics that are best described by moments of inertia (or by section moduli in non-cylindrical bones), rather than bone mass. As mentioned above, DXA measures bone mass but not moments of inertia or section moduli, that is bone geometry. Several lines of research suggest that, over the aging process, the bone tissue goes through a remodelling process mostly involving an enlargement of the cortical bone "ring". Although this remodelling process increases the bone mechanical resistance to fractures (8), it is detected by DXA simply as a reduction in BMD. Indeed, since most epidemiological studies on the aging bone were based on DXA measures, very little is known about the dynamics of cortical bone mass in growth and aging.

**The contribution of axial Quantitative Computed Tomography (QCT) to osteoporosis diagnosis and clinical research**

Currently, the standard diagnosis of osteoporosis is based on the assessment of bone mineral density performed with DXA. Although this method is widely used in both clinical and research settings, it has some important limitations, as outlined above. In order to circumvent these problems, alternative methods for assessing bone strength have been proposed, including Quantitative Computed Tomography (QCT) of the axial and peripheral skeleton. QCT allows for separate assessments of cortical and trabecular bone and provides direct information on bone geometry.
Axial QCT has been used most commonly at the spine level for assessment of apparent volumetric density of trabecular bone. The main theoretical advantage of QCT over DXA is the exclusion from the measurement of structures that do not contribute to spine mechanical resistance, yet contribute to DXA BMD values, and the possibility to selectively measure trabecular tissue, considered to be the main determinant of compressive strength in the vertebrae. Indeed, QCT measurements of spinal trabecular volumetric BMD (vBMD) are strongly associated with vertebral fractures; in this respect, its discriminatory capability between fractured and non-fractured subjects is greater than either antero-posterior and lateral DXA (15, 16). Spinal QCT has, however, several disadvantages which have limited its widespread application. First, the relatively high radiation dose to patients limits its use for repeated measurements, especially in children. Second, the cortical shell in the vertebrae is too thin to be accurately assessed by QCT, however a few reports have stressed the importance of cortical bone in the vertebrae: trabecular bone loss is a universal phenomenon, but vertebral fractures occur only when cortical bone is also compromised (17). Third, in spite of a good accuracy in the diagnosis of osteoporosis and in the prediction of fracture risk, spine QCT has a poor precision that limits its applicability to longitudinal assessments. Fourth, the use of CT scanners for densitometry purposes is hindered by several factors, including the high cost, a high degree of operator dependence, space requirement, and limited access to the scanners. Axial QCT has been used only for the assessment of spine vBMD because the complexity of the hip architecture has precluded the development of reliable methods for densitometric

assessment in this clinically important region.
In spite of all these limitations, spine and hip QCT have contributed important information regarding the role of trabecular bone loss and differences in bone size in predicting fracture risk during the aging process and in specific diseases (18).
In conclusion, axial QCT has provided interesting contributions to osteoporosis research but it has gained limited acceptance in clinical applications because of convenience problems such as costs, availability, and irradiation risks, as well as technical limitations, including poor precision, limitation in the assessment of cortical bone, and difficulty to assess bone geometry because of anatomical constraints.

## Peripheral QCT (pQCT) as a mean to diagnose osteoporosis and obtain a reliable assessment of bone strength and fracture risk

In order to obviate the limitations of DXA and axial QCT, a peripheral quantitative computed tomography (pQCT) device has been developed, which allows for separate assessments of cortical and trabecular bone and provides direct information on bone geometry at several appendicular bone sites. From the analysis of cross-sectional images provided by pQCT, information on mass and distribution of bone material can be integrated into indexes of bone stability in response to bending and torsional loads, which are the two most important biomechanical measures of susceptibly to fracture and may improve our accuracy in the prediction of fractures (10).

## Development and technical characteristics of pQCT

pQCT was developed as a result of the concomitant pioneering efforts in the early 1980s by Schneider and coworkers in Wurzburg, Germany, and Ruegsegger and coworkers in Switzerland. Early pQCT devices were designed by the Stratec Company in Germany with the cooperation of the University of Wurzburg, and by the Swiss Company Scanco Medical. While both companies developed and commercialized newer generation, reliable pQCT devices, only the devices produced by Stratec achieved a wide diffusion due to lower cost (19). The Stratec devices XCT 900 and XCT 960 for clinical use, and XCT 960 A for research purpose in small animals utilized an X-ray tube with appropriate filtering and collimating systems, which resulted in higher image resolution and shorter scanning times. The only difference between XCT 900 and XCT 960 is a different calibration. The basic technical characteristics of Stratec pQCT devices include the translate-rotate technique and a multidetector system for different acquisition angles. Moreover, energy dispersion due to the “beam hardening effect”, that is the energy absorption by soft tissues surrounding bones, is successfully corrected by a pre-processing system, based on aluminum step phantoms. For image reconstruction, the Shepp and Logan backprojection algorithm is used. The pQCT devices deliver a radiation exposure to the patients < 0.1 μSv. The reported precision of XCT 900 and XCT 960 *in vivo* for trabecular density is 1-2% (19).
In the late 1990s Stratec released a new generation device, XCT 2000 (and XCT 3000, having a wider gantry), which is now widely diffused in North America, Asia, and in Europe. XCT 2000 provides a better image resolution than the 900 series, ranging from 0.02 to 0.5 mm, using variable matrix sizes of up to 400 x 400, and shorter scan times. The main technical characteristics of the XCT 2000 are shown in Table I (22). *In vivo* precision figures for the XCT 2000 are greatly improved over the 900 series ranging from about 0.8% for trabecular density, to less than 0.5% for bone cross-sectional areas. On the other hand, the calculation of more complex parameters, such as moments of inertia, imply a lower precision (CV about 1-3%) (20, 21). The XCT 2000 is designed to perform multislice measurements at the forearm and the lower leg and, with appropriate softwares, can assess muscle cross-sectional area at both measurement sites (22).

## Research and clinical applications of pQCT

The first applications of pQCT devices in both experimental animals and humans was to obtain a selective measure of volumetric density of trabecular tissue at radial metaphysis. Later, the use of pQCT was extended to include the assessment of cortical bone volumetric density, cortical bone cross-sectional area, and whole bone stability parameters such as moments of inertia and section moduli. Following is a brief overview of the biomechanical meaning and the potential clinical usefulness of these parameters, as well as the problems associated with their interpretation in both the research and the clinical setting.

### *Introduction to QCT procedures*

For the reader not accustomed to QCT measurements, I would like to briefly introduce the basic procedures leading from the reconstructed CT image to the calculation of bone parameters. The first step is to establish, empirically, a threshold density value that provides the best discrimination between tissues. For instance, the external bone contour is sometimes obtained introducing a threshold value of 240 mg/cm$^3$; the contour of the bone is obtained by excluding (using an appropriate algorithm) from the image all the voxels having a density lower than 240 mg/cm$^3$, and presumed to belong to soft tissue surrounding bone. In the case of very osteoporotic bones, however, a lower threshold (180 mg/cm$^3$) will exclude equally well all soft tissues, and will include more reliably the whole bone boundary. Using similar procedures at the metaphysis, a threshold of 430 mg/cm$^3$ can be applied to the interface between cortical and trabecular bone, in order to separate the two tissues; alternatively, or as an adjunctive conservative measure, the operator may decide to accept as “pure” trabecular bone only the inner

Table I - Technical characteristics of the pQCT device XCT 2000 (22).

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| Slice thickness (mm) | 2.3 | High voltage (KV) | 56-60 |
| Voxel size (mm) | 0.2-0.8 | Anode Current (μA) | < 300 |
| Gantry opening (mm) | 140 | Radiation dose CT scan (mSv) | 0.03 |
| Weight (kg) | 45 | Scan time (radius) (sec) | 90 |
| Dimensions (cm) | 55*93*62 | Max movement in Z (mm) | 230 |

45% of the cross-sectional area (CSA) of bone. At the radial or tibial diaphysis, where trabecular bone is not represented, a threshold of 710 mg/cm$^3$ is ideal to separate medullary area from the cortical tissue. Once the tissues are separated as described, an algorythm "counts" the voxels belonging to the tissue of interest and provides the CSA for that specific tissue or, if vBMD is the parameter of interest, provides the average density value of those voxels. These procedures have been consistently shown to be reliable and accurate (23).

*Assessment of trabecular bone*

This was an obvious extension of the axial QCT. The practical advantage of pQCT over axial QCT was to make volumetric bone density (vBMD), a measure independent from body size, widely available to researchers and clinicians. It should be noted that QCT-measured volumetric density is a tissue density, therefore an apparent density, not a material density. This means that bone marrow is included in the measurement and that the measure is actually the average of the density of voxels containing bone marrow and those containing trabeculae, and as such it is similar to the histomorphometry parameter BV/TV. This said, trabecular vBMD is usually assessed at the distal metaphysis of radius and tibia (other potential measurement sites are proximal tibia, proximal radius, distal femur) where trabecular tissue is abundant and shows the typical rapid changes following menopause, aging, endocrino-metabolic diseases, or terapeutical intervention with antiresorptive agents.
Many studies in animals have exploited these features, particularly the rapidity of response, which allowed shorter duration of experiments and greater sensitivity compared to DXA (24). For instance, trabecular vBMD decline is significant within 1-2 weeks after ovariectomy in rats, compared with a lag of several weeks if DXA areal BMD is used (24). Studies in humans have demonstrated that age-related bone loss is similar for the trabecular tissue of axial and appendicular skeleton (25). These studies have also shown that in women, trabecular bone loss begins well before menopause and continues throughout life; a similar life-long decline in trabecular bone density has been reported in men, albeit with a smaller slope (14). These studies, as well as other studies focused on cortical bone, have substantially contributed to dispelling the notion of the existence of a prolonged period of bone stability after the achievement of peak bone mass. Rather, we now know that "aging" of the bone begins as soon as growth ceases.
A European multicenter study with a cross-sectional design (the BME-COMAC study) has compared the sensitivity of trabecular vBMD at spine and distal radius, and areal BMD at the spine to predict vertebral and hip fractures. ROC curves showed that radial pQCT performed as well as spinal QCT and DXA (areas 0.85 *vs* 0.84) for vertebral fractures and also predicted hip fractures. The authors of the study conclude that pQCT should be the method of choice when evaluating generalized bone loss (26). In another study with cross-sectional design, spinal X-ray was obtained in 621 postmenopausal women to verify if a low trabecular vBMD of the radius could predict vertebral fractures. Using a cut-off threshold of 105 mg/cm$^3$, the odds ratio for the association with vertebral fracture was 2.17 (95% CI: 1.69-2.77) in a receiver operating characteristic analysis, and the area under the curve was 0.699 ± 0.023, similar to that obtained using spinal DXA (27). In a comparison between different techniques, spine QCT showed the highest OR for spine fractures (5.3; CI:3.6-8.3), followed by a radial pQCT geometry parameter (5.2; CI:2.8-12.4), spinal DXA (4.8; CI:3.7-6.1), radial trabecular vBMD by pQCT (3.2; CI:2.7-3.8), and ultradistal radial DXA (2.1; CI:1.7-2.4) (28).
Taken together, these studies suggest that trabecular vBMD at radius is as effective as axial DXA to detect generalized osteoporosis and predict fracture risk.
At radial and tibial metaphyses pQCT also measures total bone apparent vBMD, that includes trabecular and cortical bone and can be considered a good measure of compressive strength, similar to the areal BMD obtained by DXA.
*Rationale for cortical bone assessment, and related technical limitations of QCT*

Early research in the osteoporosis field focused on trabecular bone because of its sensitivity to endocrino-metabolic and therapeutic influences; accordingly it was felt that densitometry should capture trabecular bone characteristics in order to be useful in the diagnosis and follow-up of menopause-, disease-, and interventions-related bone changes. Consistently, spine and hip, both containing substantial amounts of trabecular bone, became the preferred measurement sites for DXA.
The important contribution of cortical bone to bone mechanical resistance is increasingly recognized. However, as also noted for spine QCT, cortical bone cannot be assessed accurately at the radial metaphysis, since in this site the cortical shell is so thin that the partial volume effect inflates the magnitude of random error in the measure. This partial volume error occurs whenever a voxel is comprised of both cortical bone and surrounding tissues having lower densities; in this case the algorithm assignes that voxel a value that is intermediate between the two tissues, thus yielding an underestimate of the true value. Since these "border voxels" are located along the external and internal cortical boundaries, the thinner the cortical ring, the greater the proportion of "border voxels" to "full voxels", resulting in a higher degree of confounding by the partial volume effect. I would like to point out that partial volume errror is considered to be troublesome only if cortical thickness is less than 3 times the voxel size (29). Therefore, using a voxel size of 0.5 mm a cortical thickness greater than 1.5 mm allows for accurate assessment of cortical bone density and CSA. In fact, cortical bone should be evaluated at radial diaphysis, where the cortical thickness is greater than 1.9 mm or, better, at the tibial diaphysis where the cortical bone was found to be thicker than 3.0 mm in more than 90% of a representative Italian population in which very old persons were oversampled (13, 14).
Indeed, in previous studies, information on cortical bone obtained by pQCT at a correct anatomic site was a strong predictor of bone mechanical resistance and fracture risk (see above) (26, 30). Moreover, in some instances, a specific assessment of cortical bone is critical for a correct evaluation of bone status. For example, in hyperparathyroidism, in which the cortical bone is specifically compromised, and in the follow-up of some treatments specifically influencing cortical bone density and thickness (e.g. teriparatide, anabolic agents), the assessment either of trabecular bone parameters by pQCT or of the total bone mass by DXA may be misleading (31).

**From cortical bone vBMD and mass to whole bone geometry assessment**

*Cortical bone vBMD:* declines with age with a greater slope in women than men, likely reflecting increasing porosity. Vitamin D deficiency, with its attendant hyperparathyroidism, typically reduces cortical vBMD with two mechanisms: reduced mineralization of bone matrix, and increased intracortical porosity through stimulation of bone remodeling. Reduced cortical vBMD is also found in other conditions characterized by increased remodeling and rapid bone loss, such as hyperthyroidism. Therefore, a low value of this parameter may give an important clinical clue to the presence of elevated bone remodeling and high circulating PTH or thyroid hormones levels.
*Cortical bone CSA* and the composite parameter *cortical BMC*

(Cortical CSA*cortical vBMD*slice thickness) are parameters related to bone mass, which are strictly related to compressive strength of the examined bone, exhibit a fast decline in older women (after 60 years of age), and are greatly reduced in osteoporosis. Interestingly, in men cortical CSA and BMC are stable until old age at population level (13).

*Cortical thickness:* paralleling changes in cortical CSA and BMC, cortical thickness declines in older women, not older men. Age-associated changes in the parameters of bone bending and torsional stability (maximum, minimum, and polar moments of inertia) are strictly related to cortical thickness.

*Total bone CSA:* represents bone size and is a simple, yet very important parameter related to both compressive and bending strength. In fact, changes in total bone CSA, whether age-associated or following anabolic interventions, translate into substantial differences in compressive and bending strength.

*Moments of inertia and the related parameters section moduli:* describe the resistance of a structure to bending loads (maximum and minimum moment of inertia) and torsional loads (polar moment of inertia) and represent the most qualifying contribution of pQCT toward comprehension of determinants of bone strength. The (density-weighted) moment of inertia (also called "Bone strength index") is calculated by summing up the distance of all the voxels containing bone from the center of mass (to the fourth power) multiplied by the density each voxel. Therefore, in this calculation the distribution of bone material is much more important than its amount. Section modulus derives from moment of inertia multiplied by the maximum distance of the voxels from the center of mass and, therefore, it is only relevant in non-cylindrical structures. It should be noted that calculation of moments of inertia and section moduli are not specific to the assessment of bone strength but, rather, are the common modality employed by engineers to estimate resistance of structures to bending and torsion (columns, buildings, etc.). Moments of inertia, paralleling the other cortical bone parameters, decline in old age in women only (13, 14). Unraveling the determinants of the observed sex-difference in age-associated changes in the above described cortical and whole bone parameters is the key to understanding why older women have a higher fracture risk than elderly men.

## Assessment of muscle CSA and muscle-bone relationship by pQCT

Muscle CSA is an important determinant of muscle force, and the latter is a strong determinant of bone mass and strength. Therefore, assessing both muscle force and an indicator of bone strength (such as bone strength index) in osteoporotic patients may give useful information as to the cause of low bone mass. Based on this premise, several groups have assessed muscle CSA at forearm and calf by pQCT as a surrogate measure of muscle strength of the upper and lower limb, respectively, and have evaluated the relationship between muscle CSA and cortical bone CSA or moment of inertia at the same site. As expected, a close relationship linked the muscle and bone parameter both in children and in adults ($R2 = 0.60$-$0.95$) (32). A few studies suggest that osteopenic states may be further characterized by investigating the proportionality between muscle and bone mass. In fact, according to this view, bone loss following a hypomobility condition associated with sarcopenia would give origin to a "concordant" or "armonic" osteopenia, in which both muscle mass and bone mass are reduced and the ratio between them remains constant. On the other hand, a bone loss caused by an endocrino-metabolic disorder, such as a "true" osteoporosis or hyperparathyroidism, would lead to a "discordant" or "disarmonic" osteopenia, in which muscle mass is preserved or is reduced to a lesser extent than bone mass. In one study osteoporotic patients with fractures had a similar degree of osteopenia as age-matched healthy postmenopausal women, however, in the fracture patients the ratio between tibia cortical CSA and muscle CSA at the calf was reduced compared with the controls (33). Other studies in children obtained similar results (34). These findings raise the possibility of diagnosing patients with osteoporosis and high fracture risk from osteopenic individuals whose low bone mass is merely a consequence of frailty. Based on these patho-physiological considerations, the mainstay of treatment of these patients is an appropriate "sarcogenic" and "osteogenic" form of physical exercise, such as vibration training, not an antiresorptive drug (35, 36).

## Advantages and disadvantages of pQCT, compared to planar densitometry and axial QCT

Compared to conventional planar densitometry and axial QCT, pQCT presents several practical and safety advantages, including low space requirement and transportability of the device. Moreover, compared to axial QCT pQCT has a lower cost, and much lower irradiation to operator and patient. Compared with DXA, pQCT is more reliable since the availability of cross-sectional images allows for immediate recognition of errors due to incorrect positioning and movements of the patients. On the other hand, in DXA measurements an incorrect positioning of the patient may be evident only at a follow-up examination, when differences in the BMD values are too high to have a biological cause, or may never be appreciated if the baseline and follow-up have consistent, albeit incorrect figures (37). This often neglected source of inaccuracy and imprecision in DXA measurements may influence the decision on whether to begin or continue a treatment.

However, the use of pQCT also has limitations. Among these, a high level of dependence on the operator and the numerosity and complexity of the parameters that can be obtained may have prevented a wider use of this method in the clinical practice. Another limitation is the need to assess multiple sites in order to "sample" the most suitable sources of information in the skeleton. In my experience, radial metaphysis for trabecular bone and tibial diaphysis for cortical bone are the ideal sites for obtaining thorough, accurate, and informative measurements. An often cited limitation of pQCT is the lack of assessment of the most common fracture sites (spine and hip). However, Colles fracture is a common osteoporotic fracture, which often occurs many years before other osteoporotic fractures. Moreover, age- and menopause-related bone loss usually occurs at all skeletal sites, albeit at different rates, and osteoporosis is certainly a systemic condition. Consistently, peripheral bone mass measurements have been recently shown in the NORA study to effectively predict bone loss and occurrence of osteoporotic fractures in both early postmenopausal and older women (38).

## Conclusions

As shown in this review, compared to both DXA and axial QCT, pQCT is a more versatile technique, allowing for selective assessment of trabecular and cortical bone components, accurate assessment of bone geometry, assessment of muscle mass and muscle/bone relationships.

PQCT has not been evaluated as thoroughly as DXA in clinical research; therefore the availability of normative data is scant and mostly limited to trabecular vBMD. Likewise, prospective

studies indicating prediction of fracture risk are needed in order to develop recommendations on pQCT measurements in the clinical practice. However, recent studies on representative populations in the USA and Italy have yielded normative data on trabecular and cortical bone vBMD, and geometry parameters obtained by pQCT at multiple skeletal sites (13, 39).
In the Italian study tibial pQCT parameters have been obtained in more than 1200 subjects spanning from 20 to 102 years of age; these data could provisionally be used as reference values by physicians to detect patients with osteopenia, assess their bone strength, and to plan appropriate, patho-physiologically based treatment (13, 14).

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