Axial and Peripheral QCT

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Contents

Abstract

While Dual *X*-ray absorptiometry (DXA) is considered as the standard technique to measure bone mineral density (BMD), quantitative computed tomography (QCT) measures true volumetric and not areal BMD and has a number of advantages over DXA, which makes QCT an attractive alternative technique for certain indications.

1 Introduction

While Dual *X*-ray absorptiometry (DXA) is considered as the standard technique to measure bone mineral density (BMD), quantitative computed tomography (QCT) measures true volumetric and not areal BMD and has a number of advantages over DXA, which makes QCT an attractive alternative technique for certain indications. Interestingly, QCT was introduced and studied prior to DXA at the end of the 1970s (Genant and Boyd 1977; Genant et al. 1983). A large number of studies were performed subsequently establishing QCT as one of the first techniques for quantitative musculoskeletal imaging (Cann and Genant 1980; Genant et al. 1982, 1983; Cann et al. 1985; Sandor et al. 1985; Firooznia et al. 1986; Kalender et al. 1987; Kalender and Süss 1987). Normative data were made available and imaging techniques were optimized with new calibration devices and better image analysis algorithms. Also in addition to single slice techniques, volumetric techniques were developed which have superior precision and thus improve monitoring of therapy.

However, with the development of DXA, QCT lost ground and the number of studies validating and establishing DXA as a standard technique has superseded these performed with QCT. QCT studies have shown the technique's ability to differentiate subjects with and without osteoporotic fractures and to monitor therapy; however, studies proving that QCT can indeed also predict osteoporotic fractures are limited and have been found to be a major

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limitation in evaluating the technique. Also access to CT scanners always appeared limited, while DXA scanners are now widely available in the US and Europe. An additional issue with QCT is the lack of well-established normative data allowing to define individuals as osteopenic or osteoporotic based on their BMD. The WHO criteria using T-scores of lower than −2.5 as osteoporotic are only used for DXA and not QCT nor for any other technique to assess osteoporosis.

QCT techniques are used to measure BMD at the lumbar spine and proximal femur defined as axial QCT, while peripheral QCT measures BMD at the distal radius and tibia. In the subsequent chapters, we will discuss strengths and weaknesses of both techniques and also identify specific clinical indications for QCT as compared to DXA. It should be noted that QCT is currently not the standard technique to measure BMD, but it is useful as a problem solving technique for a number of clinical indications. Also at institutions where DXA is not available, QCT will provide pertinent information on bone strength and monitoring therapy.

2 Axial QCT

QCT uniquely allows the separate estimation of trabecular and cortical BMD and provides a true volumetric density in mg/cm^3, rather than the "areal density" (mg/cm^2) of DXA. Since trabecular bone has a higher metabolic turnover, it is more sensitive to changes in BMD. A big advantage of QCT is that it is not as susceptible to degenerative changes of the spine as DXA. Osteophytes and facet joint degeneration as well as soft tissue calcifications (in particular of aortic calcification) do not falsely increase BMD in QCT. As in DXA, however, fractured or deformed vertebrae must not be used for BMD assessment since these vertebrae usually have an increased BMD.

QCT may be performed at any CT-system; however, a calibration phantom is required and dedicated software improves the precision of the examination. The patient is examined supine, lying on the phantom usually with a water or gel-filled cushion in between to avoid artifacts due to air gaps. Calibration phantoms are required to transform the attenuation measured in HU (Hounsfield units) into BMD (mg hydroxyapatite/ml). The patient and the phantom are examined at the same time, which is defined as simultaneous calibration. The Cann-Genant phantom with five cylindrical channels filled with K_2HPO_4 solutions (of known concentrations) was the first phantom in clinical use (Cann and Genant 1980; Genant et al. 1983). However, due to the limited long-term stability of these solutions solid-state phantoms with densities expressed in mg calcium hydroxyapatite/ml were developed, which do not change with time and are more resistant to damage. Two of the most frequently used phantoms include (1) the solid-state "Cann-Genant" phantom (Arnold 1989) (Figs. 1a and 2) the phantom developed by Kalender et al. (1987; Kalender and Süss 1987) (Fig. 1b). The latter phantom has a small cross section and is constituted of only two density phases: a 200 mg/ml calcium hydroxyapatite phase and a water equivalent phase.

Thorough *quality control* is critical to acquire meaningful BMD QCT data and should be performed according to the Guidelines of the International Society of Clinical Densitometry as published by Engelke et al. (2008). This includes the following: (1) In vivo precision of new QCT techniques must be established. However, due to radiation considerations, it is not recommended to reconfirm in vivo precision for each clinical facility. Instead, precision of acquisition should be established with phantom data; analysis precision should be established by reanalysis of patient data. (2) The scanner stability should be controlled longitudinally by scanning a quality assurance (QA) phantom at least once a week whenever patients are to be scanned. (3) The scan protocol must be kept constant for all visits of an individual patient.

Currently, 2-D resp. single slice and 3-D resp. volumetric measurements are used for QCT. While the 2-D measurement is only used for the lumbar spine 3-D measurements may also be performed at the proximal femur.

2.1 Single Slice QCT

Single Slice QCT has been established for BMD measurements at the lumbar spine; using the standard technique single sections of the first to third lumbar vertebrae are scanned. Typically, slice thicknesses are in the order of 8–10 mm, the mid-vertebral portion is examined and a dedicated gantry tilt is used (Fig. 2a). Single mid-vertebral slice positions of L1-3 parallel to the vertebral endplates are selected in the lateral digital radiograph resp. scout view (Fig. 2b). An automated software, selecting the mid-vertebral planes may be useful to reduce the precision error (Kalender et al. 1988).

Low energy protocols in the order of 80 kVp (or 120 kVp) and 120 mAs (or 150–200 mAs) result in effective doses of <200 microSv (Engelke et al. 2008). Felsenberg et al. described a low energy, low dose protocol with 80 kVp, and 146 mAs resulting in effective doses down to 50–60 μSv, including the digital radiograph (Felsenberg and Gowin 1999). Bone marrow fat increases with age and may falsely decrease BMD. Thus, the actual BMD may be underestimated by 15–20 %. Due to age-matched data bases, however, the clinical relevance of this fat error is small (Glüer and Genant 1989). A dual energy QCT technique was described to reduce the fat error. However, since this technique has an increased radiation exposure and a decreased precision, its

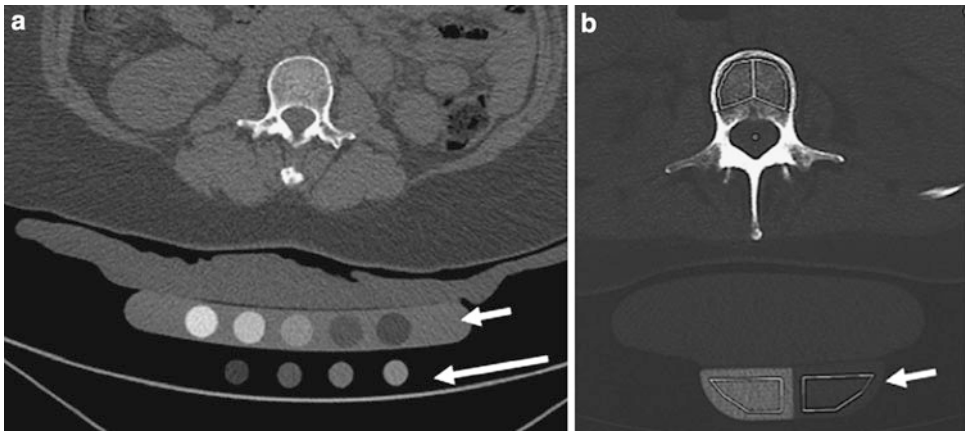

Fig. 1 BMD calibration phantoms. **a** Shows the solid-state Mindways (*short arrow*) and Image Analysis (*long arrow*), phantoms which are based on the original "Cann-Genant" phantom. **b** Depicts the two element phantom developed by Kalender et al. (1987; Kalender and Süss 1987) (*arrow*)

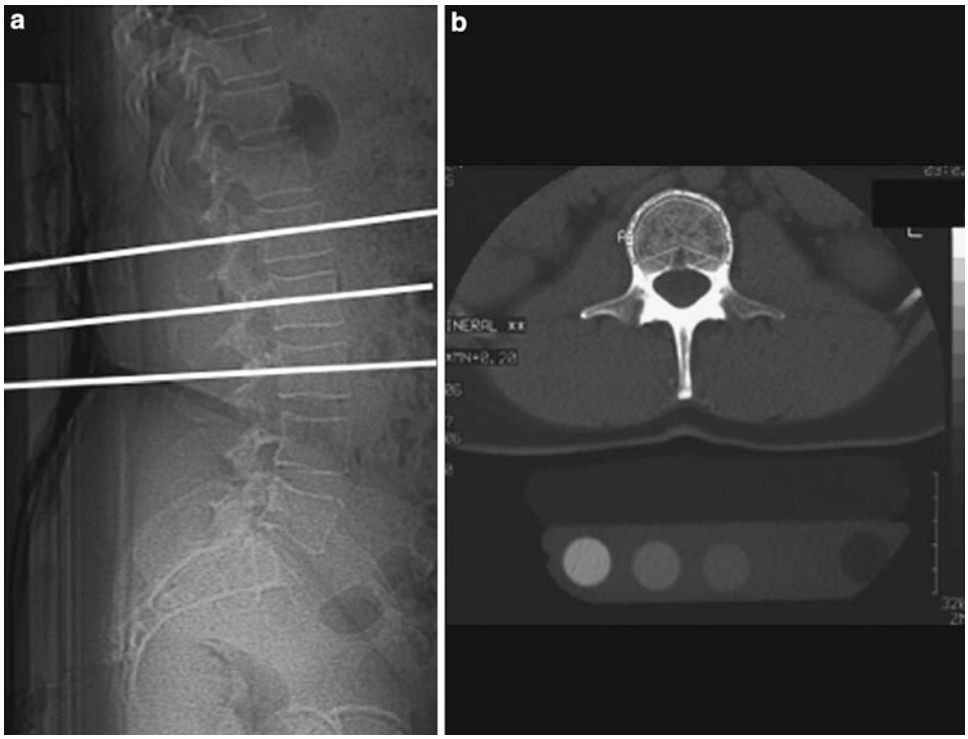

Fig. 2 Lateral digital radiogram (scout view) (**a**) shows mid-vertebral positions of the sections in L1-3, which are used to measure single slice QCT BMD. In (**b**) a mid-vertebral image of L2 demonstrates a "Pacman" or peeled region of interest (ROI) used to measure trabecular and "cortical" BMD (**b**). The cortical BMD measurement is an approximate measurement as the cortex of the vertebral body is below the spatial resolution of the axial CT image and subjected to partial volume effects

use was limited to research purposes (Genant and Boyd 1977; Felsenberg and Gowin 1999).

A number of different region of interest (ROI) shapes and techniques have been used to determine the BMD in the axial sections of the vertebral bodies. Manually, placed elliptical ROIs and automated image evaluation with elliptical and peeled or "Pacman" ROIs (Fig. 3) have been described (Kalender et al. 1987; Steiger et al. 1990). The ROI developed by Kalender et al. uses an automatic contour tracking of the cortical shell to determine a ROI analyzing trabecular and cortical (as visualized by CT) BMD separately (Kalender et al. 1987). The use of an automated ROI improves the precision of BMD measurements (Sandor et al. 1985; Kalender et al. 1987). Steiger et al. have shown that elliptical and peeled ROIs yield similar results and have a very high correlation ($r = 0.99$) (Steiger et al. 1990).

Measurements should not be performed in fractured or deformed vertebral bodies and great care should be taken to avoid performing QCT after intravenous contrast application (e.g., after a standard contrast-enhanced CT). Also it is critical to analyze all images including the scout images for abnormalities in the bone and soft tissue windows. Vertebral fractures (scout images) and soft tissue abnormalities such as renal tumors or abnormally enlarged lymph nodes must not be missed as they may have an impact on patient management or may have legal consequences.

BMD-data obtained by QCT are compared to an age-, sex-, and race-matched database (Block et al. 1989; Kalender et al.

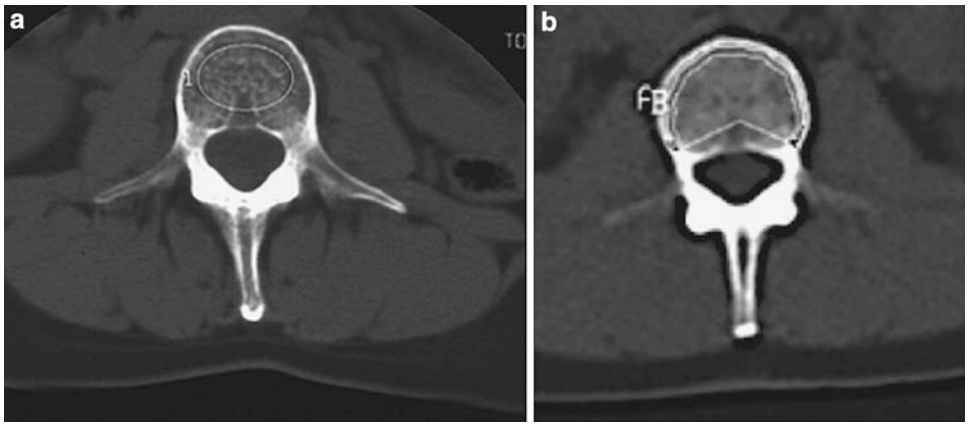

Fig. 3 ROIs used for BMD measurements include manually (**a**) or automatically placed (**b**) regions, which may be either oval shaped (**a**) or peeled ("Pacman" shaped ROI) (**b**)

1989). T-scores used for the assessment of osteoporosis according to the WHO definition have been established for DXA but not for QCT, though they may be given by the software of the manufacturers. If these T-scores are used to diagnose osteoporosis, a substantially higher number of individuals compared to DXA will be diagnosed as osteoporotic, since BMD measured with QCT shows a faster decrease with age than DXA. In order to facilitate the interpretation of QCT results, the American College of Radiology has in 2008 published guidelines for the performance of QCT; based on these guidelines BMD values from 120 to 80 mg/ml are defined as osteopenic and BMD values below 80 mg/ml as osteoporotic, which would correspond to a T-score of approximately −3.0.

A substantial disadvantage of 2-D QCT is its lower precision compared to that of DXA (1.5–4 vs. 1 %), which results in a larger least significant change required to detect significant changes in BMD (6–11 vs. 3 %). However, since the metabolic activity of trabecular bone is higher, a lower precision is adequate for single slice QCT to monitor longitudinal changes that are in the same range as those found with DXA.

2.2 Volumetric QCT

With spiral and multislice CT acquisition of larger bone volumes, such as entire vertebrae and the proximal femur, is feasible within a few seconds (<10 s). These data sets can be used to obtain 3-D-images, which provide geometrical and volumetric density information (Fig. 4). As an alternative to volumetric QCT (vQCT) the term three dimensional (3-D) QCT may be used. Contiguous sections with a slice thickness of 1–3 mm and no CT scanner angulation are typically obtained. The lumbar spine protocols typically only include L1 and L2, as the exposure dose is relatively high. Typically, kVp is in the order of 80–120 and mAs between 100 and 200. Using these parameters, the exposure dose has been estimated to be as high as 1.5 mSv for the spine, and 2.5–3 mSv for the hip (Engelke et al. 2008). The primary advantage of volumetric QCT of the spine is an improved precision for trabecular BMD measurements, which is in the order of 1–2.5 % (Engelke et al. 2008). Different analysis techniques have been applied to quantify BMD in the volumetric ROIs; in addition to the standard midvertebral trabecular volume of interest (VOI) that in size and location is similar to the volume analyzed in single slice mode, various additional VOI can be measured by 3-D QCT. However, to date there is no agreement on the locations, sizes, or shapes of VOIs (Engelke et al. 2008). Currently, two manufacturers offer volumetric QCT software with calibration phantoms (QCT Pro, Mindways Software, Inc., Austin, TX and Image Analysis Inc., Columbia, KY).

Because of the complex anatomy of the proximal femur, single slice QCT is not feasible but volumetric approaches have been found to have good reproducibility. The scan region typically starts 1–2 cm above the femoral head and extends a few centimeters below the lesser trochanter. Typically, kVp is in the order of 120 and mAs between 100 and 330 (Engelke et al. 2008). Algorithms to process volumetric CT images of the proximal femur and to measure BMD in the femoral neck, the total femur, and the trochanteric regions are available and include two commercial and a few advanced university-based research tools (Lang et al. 1997). Proximal femur 3-D QCT has a high precision of 0.6–1.1 % for trabecular bone and may also be used to determine geometric measures such as the cross-sectional area of the femur neck and the hip axis length. These measurements may be useful in optimizing fracture prediction of the proximal femur.

While WHO criteria are not applicable to volumetric QCT measurements of the lumbar spine, it should be noted that the American College of Radiology guidelines for the performance of QCT for single slice QCT are also applicable to volumetric QCT: BMD values of 120–80 mg/ml are defined as osteopenic and below 80 mg/ml as osteoporotic. One of the manufacturers also provides BMD ranges to quantify

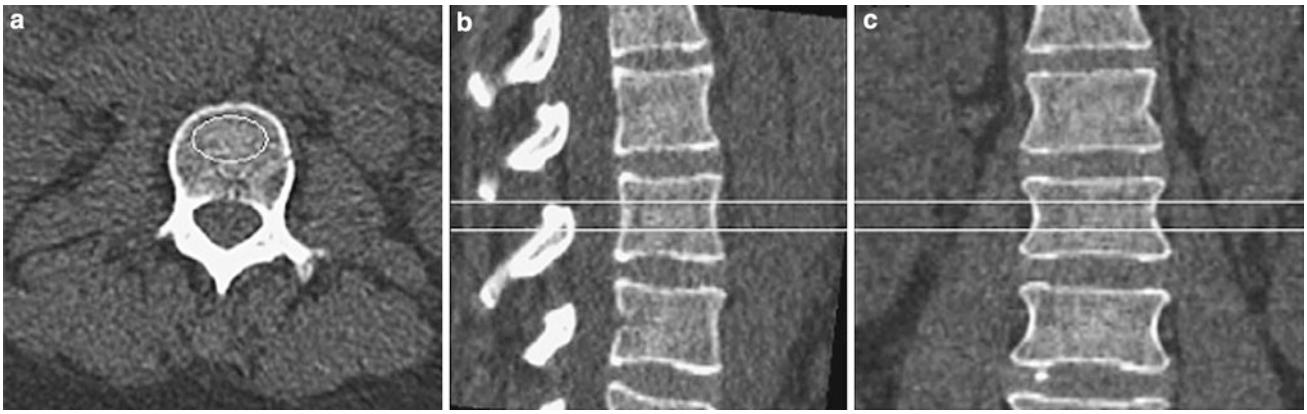

Fig. 4 Volumetric or 3-D QCT of the lumbar spine demonstrating an axial CT image of L2 (**a**) as well as sagittally (**b**) and coronally (**c**) reconstructed images indicating the volume of interest used for the volumetric BMD measurement

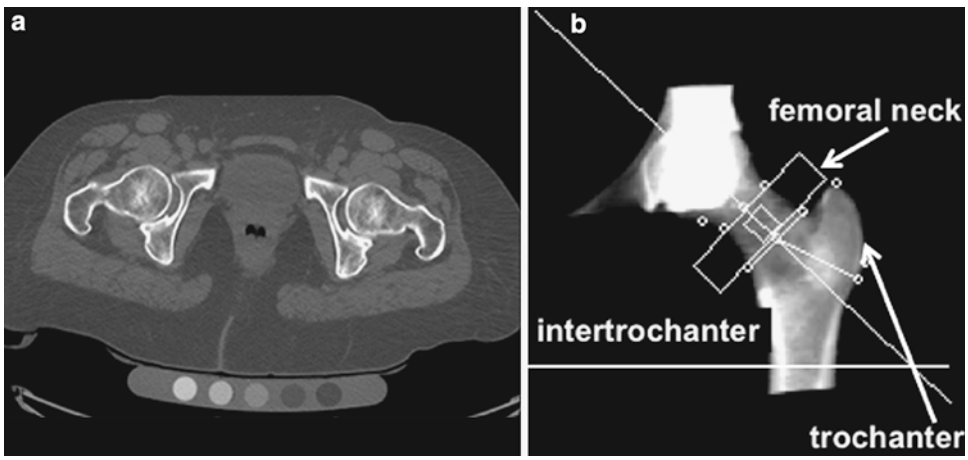

Fig. 5 Volumetric QCT of the hip: axial CT image of bilateral hip joints on a Mindways calibration phantom (**a**) and DXA like, 2-D, reconstructed CT image with femoral neck (*small arrow*), trochanteric (*long arrow*), and intertrochanteric ROIs (**b**)

increase in fracture risk: a BMD of 110–80 mg/cc is described to indicate a mild increase in fracture risk, BMD values of 50–80 mg/cc indicate a moderate increase in fracture risk and a BMD lower than 50 mg/cc indicates a severe increase in fracture risk.

For the proximal femur, 3-D datasets may be used to derive a projectional 2-D image of the proximal femur and in this image standard DXA-equivalent ROIs may be placed (Fig. 5). This so-called QCT-derived DXA equivalent aBMD (QCT(DXA) aBMD) can be calculated using CTXA Hip software (Mindways Software Inc., Austin, TX, USA). In the ROIs, BMD values are determined in g/cm^2. Since the correlations between these calculated BMD values of the proximal femur and those obtained by DXA are extremely high, the WHO classification may be applied to those BMD values in post-menopausal women (Khoo et al. 2009). Thus, a T-score $\leq$2.5 derived from those datasets indicates osteoporotic BMD.

2.3 Advantages and Disadvantages of Axial QCT versus DXA

In addition to the true volumetric measurements, QCT has several important advantages over DXA. As DXA is a projectional technique, structures overlying the vertebral body and proximal femur will impact and limit the measurements. Thus, aortic and femoral artery calcifications will artificially increase BMD measurements, as will degenerative disc disease, diffuse idiopathic skeletal hyperostosis (DISH), and facet arthropathy. In addition surgical clips, contrast within the bowel and status post spine surgery (in particular laminectomies) will alter BMD measurements. All of this will have less impact on QCT measurements. A recent study comparing DXA and QCT in older men with DISH demonstrated that QCT was better suited to differentiate men with and without vertebral fractures (Diederichs et al. 2011); DISH is a condition which is frequently found in

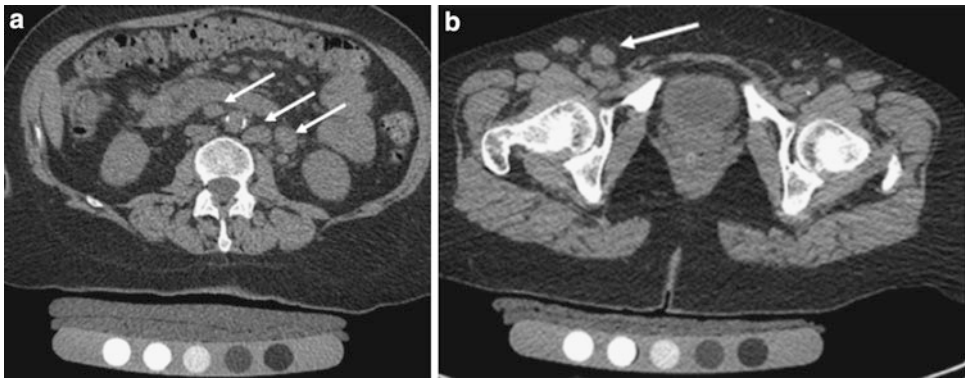

Fig. 6 Volumetric QCT of the spine and hip showing nonenhanced abdominal and pelvic source images. In the para-aortic region (**a**) and the right inguinal region (**b**) there are multiple large lymph nodes (*arrows*), which were an incidental finding. Further clinical work-up led to the diagnosis of Non-Hodgkin's Lymphoma

Table 1 ACR guidelines for the performance of QCT, result interpretation

Density in mg Hydroxyapatite/ml	Definition
>120 mg/ml	Normal
120–80 mg/ml	Osteopenic
<80 mg/ml	Osteoporotic

older individuals and a higher number of vertebral fragility fractures were shown in these individuals.

In addition, QCT provides purely trabecular bone measurements which are more sensitive to monitoring changes with disease and therapy. In a randomized, double-blind clinical study of parathyroid hormone and alendronate to test the hypothesis that the concurrent administration of the two agents would increase bone density more than the use of either one alone, Black et al. found that changes in BMD demonstrated with QCT in patients treated with PTH and alendronate were 2–3 times higher than those found with DXA (Black et al. 2003).

Cross-sectional studies have shown that QCT BMD of the spine allows better discrimination of individuals with and without fragility fractures (Yu et al. 1995; Bergot et al. 2001). Bergot et al. found significantly higher ($p < 0.05$) receiver operator characteristics analysis (ROC) values for QCT compared to DXA not only for vertebral fractures (0.85 vs. 0.79), but also for peripheral fractures (0.72 vs. 0.67) in 508 European women.

In addition, QCT is better suited for examining obese patients as DXA has limitations in measuring BMD in patients with a BMD over 25–30 kg/m^2; in obese patients superimposed soft tissue will elevate measured BMD due to attenuation of the *X*-ray beams and beam hardening artifact as shown in previous studies (Tothill et al. 1997; Weigert and Cann 1999; Binkley et al. 2003).

However, a number of pertinent disadvantages of QCT also have to be considered. Most of all, the higher radiation dose (0.06–3 mSv) is of concern in particular in younger individuals (e.g., peri-menopausal women). Also, there are a limited number of longitudinal scientific studies assessing how QCT predicts fragility fractures and most of the pharmacological therapy studies have been performed using DXA. Another major problem with QCT is that T-scores should not be used to define osteoporosis and osteopenia. A T-score threshold of −2.5 for QCT would identify a much higher percentage of osteoporotic subjects, and has therefore never been established for clinical use. Currently, volumetric QCT techniques are state-of-the-art (Lang et al. 1999; Bousson et al. 2006; Farhat et al. 2006a, b) and in clinical routine absolute measurements of volumetric BMD to characterize fracture risk have been used (110–80 mg/cm^3 = mild increase in fracture risk, 80–50 mg/cm^3 = moderate increase in fracture risk and below 50 mg/cm^3 = severe increase in fracture risk). Also, more importantly, according to the "American College of Radiology (ACR) Guidelines for QCT" a density range of 120–80 mg/cm^3 is defined as osteopenic BMD and BMD values below 80 mg/cm^3 as osteoporotic BMD (ACR Practice Guideline for the Performance of QCT Bone Densitometry; 2008) (Table 1).

Currently, DXA of the spine and proximal femur is the preferred imaging text for making therapeutic decisions, but if not available QCT may also be used (Engelke et al. 2008). According to expert opinion from Japan, the US, the United Kingdom, and Germany for Siemens QCT scanners, a treatment threshold for spinal trabecular BMD of 80 mg/cm^3 without additional risk factors may be used (Engelke et al. 2008).

Concerning image interpretation, it should be noted that volumetric QCT takes substantially longer to report compared to DXA as the limited CT of the pelvis and abdomen may show a number of abnormalities of the internal organs, the spine, bony pelvis, and muscles, which should not be missed. Analysis of nonenhanced CT images is challenging, yet failure to report abnormalities such as kidney tumors and enlarged lymph nodes may have legal consequences (Fig. 6).

Table 2 Clinical Indications for volumetric QCT

Clinical indication for QCT	Rationale
1. Very small or large patients	Volumetric measurement, not impacted by patient size such as DXA (projectional measurement)
2. Advanced degenerative spine disease (degenerative disc disease, facet arthropathy, and DISH)	Only trabecular part of vertebral body is measured and osteophytes have limited impact on measurement
3. Obese subjects (BMI > 30)	DXA incompletely removes soft tissue
4. If high sensitivity to monitor metabolic bone change is required	Trabecular is metabolically more active

2.4 Clinical Indications for Axial QCT

The most important clinical indications for QCT are outlined in Table 2. Recommendations for the use of QCT instead of DXA are (1) very small or large individuals (DXA may suggest abnormally low BMD in small individuals), (2) older individuals with expected advanced degenerative disease of the lumbar spine or morphological abnormalities (in particular men and individuals with DISH), (3) if high sensitivity to monitor metabolic bone change is required such as in patients treated with parathyroid hormone or corticosteroids. Also, QCT should be considered and (4) in obese subjects, as dual energy in DXA only incompletely removes error due to fat.

2.5 Advanced QCT Technologies and Applications

Standard BMD measurements have limitations in assessing fracture risk; in the 2000 NIH consensus conference, the expert panel agreed to not only include BMD as a test to diagnose fracture risk, but also include measures of bone quality (NIH Consensus Development Panel on Osteoporosis Prevention 2001). Bone quality includes bone architecture, micro- and macrostructure and researchers have subsequently developed technologies to characterize bone quality. In addition to high-resolution peripheral QCT (HR-pQCT), multidetector CT (MD-CT) was investigated to image bone structure as it can be used in clinical practice and has superior spatial resolution compared to previous spiral CT scanners. For imaging of trabecular bone structure; however, spatial resolution is still limited given a minimum slice thickness in the order of 0.6 mm with minimum in plane spatial resolution of approximately 0.25–0.3 mm^2 (Link et al. 2003). Using this spatial resolution, imaging of individual trabeculae (measuring approximately 0.05–0.2 mm in diameter) is subject to significant partial volume effects; however, it has been shown that trabecular bone parameters obtained from this technique correlate with those determined in contact radiographs from histological bone sections and μCT (Issever et al. 2002; Link et al. 2003).

An advantage of MD-CT compared to HR-pQCT is access to central regions of the skeleton such as the spine and proximal femur, sites at risk for fragility fractures, where monitoring of therapy may be most efficient. However, in order to achieve adequate spatial resolution and image quality, the required radiation exposure is substantial, which offsets the technique's applicability in clinical routine and scientific studies (Graeff et al. 2007; Damilakis et al. 2010). High-resolution MD-CT requires considerably higher radiation doses compared with standard techniques for measuring BMD. Compared with the 0.001–0.05 mSv effective dose associated with DXA in adult patients and 0.06–0.3 mSv delivered through 2-D QCT of the lumbar spine, protocols used to examine vertebral microstructure with high-resolution MD-CT provide an effective dose of approximately 3 mSv (Ito et al. 2005; Graeff et al. 2007).

Clinical studies have demonstrated that MD-CT derived structure measures at the proximal femur and lumbar spine improve differentiation of osteoporotic patients with proximal femur fractures and normal controls (Rodriguez-Soto et al. 2010) (Fig. 5) as well as individuals with and without osteoporotic spine fractures (Ito et al. 2005). In addition, the technique was shown to be well suited for monitoring teriparatide-associated changes of vertebral microstructure (Graeff et al. 2007). Recently, Keaveny et al. used finite element analysis to study vertebral body strength and therapy-related changes in MD-CT datasets of the spine and proximal femur (Keaveny et al. 2008; Mawatari et al. 2008; Keaveny 2010); the results of this work suggested improved monitoring of treatment effects compared to DXA and greater sensitivity in fracture risk assessment.

A number of studies have suggested to use clinical contrast and noncontrast-enhanced abdominal and pelvic CT to measure BMD, which would greatly enhance the availability of BMD information in larger patient populations with no extra radiation or cost. In a feasibility study, Link et al. analyzed BMD in standard single slice QCT studies and compared these measurements with those obtained in clinical spiral CT studies. They found highly significant correlations between BMD measurements using both techniques and concluded that by using a conversion factor, BMD measurements can be determined with routine abdominal spiral CT scans (Link et al. 2004). Subsequently,

BMD measurements obtained from volumetric QCT of the spine and hip were correlated with those derived from non-dedicated contrast-enhanced standard MD-CT datasets to derive a conversion factor for volumetric QCT (Bauer et al. 2007). Based on linear regression, a correlation coefficient of $r = 0.98$ was calculated for lumbar BMD with the equation BMD(QCT) = 0.96 × BMD(MD-CT) −20.9 mg/mL and a coefficient of $r = 0.99$ was calculated for the proximal femur with the equation BMD(QCT) = 0.99 × BMD(MD-CT) −12 mg/cm2 ($p < 0.01$). Both standard volumetric QCT and contrast-enhanced MD-CT datasets could be used to differentiate post-menopausal women with and without fragility fractures; no significant differences were found between both techniques' performance in differentiating fracture and nonfracture cohorts. The investigators concluded that with the conversion factors, reliable volumetric BMD measurements can be calculated for the hip and the spine from routine abdominal and pelvic MD-CT datasets (Bauer et al. 2007). Similar results were also found by other studies (Lenchik et al. 2004; Papadakis et al. 2009; Baum et al. 2011, 2012), which confirms the potential of standard MD-CT abdominal and pelvic studies to provide clinically pertinent BMD information if performed with the patient located on a calibration phantom.

3 Peripheral QCT

Dedicated peripheral QCT (pQCT) scanners have been developed to assess the BMD of the distal radius and tibia (Butz et al. 1994). These scanners have a low radiation dose, a high precision with a short examination time, but have the same limitations as peripheral DXA in the monitoring of patients with osteoporosis. While this technique is potentially suited to predict fracture risk, studies have shown the limitations of this technique in predicting spine fractures and proximal hip fractures compared to other bone densitometry techniques (Grampp et al. 1997; Augat et al. 1998a, b).

Standard pQCT scanners work in step and scan mode, operating either with single slice or multislice acquisition. The forearm measurement locations are defined with respect to the length of the radius and measured from the radio-carpal joint surface to the olecranon. Typically, scan locations with single slice CT scanners are distal sites (4% of radius length) containing mainly trabecular bone and a shaft location (15%–65% of radius length) consisting predominantly of cortical bone, while multislice scanners use a distal site between 4 and 10 % of the length of the radius and also a shaft location (Engelke et al. 2008). The most frequently used peripheral scanners for the distal radius are the Stratec Scanners (Stratec Medizintechnik, Pforzheim, Germany).

Previous cross-sectional studies have demonstrated that pQCT can differentiate patients with hip fragility fractures and normal controls (Augat et al. 1998a, b), while findings were more controversial for spine fragility fractures (Formica et al. 1998; Clowes et al. 2005). While absolute BMD threshold values are available for axial QCT to differentiate patients with normal, osteopenic, and osteoporotic BMD, those threshold values are not available for pQCT. Given these limitations, using pQCT to initiate osteoporosis treatment is problematic; however, once initiated, pQCT can be used to monitor treatment (Engelke et al. 2008). Please note that as in axial QCT, measurements between different scanners should not be compared.

3.1 HR-pQCT

One of the most promising developments to assess bone architecture over the last 10 years has been the introduction of high-resolution peripheral QCT (HR-pQCT) (Boutroy et al. 2005; Burghardt et al. 2008; Burrows et al. 2009; Burghardt et al. 2010a; Krug et al. 2010) (Fig. 7). The dedicated extremity imaging system designed for imaging of trabecular and cortical bone architecture is currently available from a single manufacturer (Xtreme CT, Scanco Medical AG, Brüttisellen, Switzerland) and was developed based on experimental MicroCT technology. This device has the advantage of significantly higher signal to noise ratio (SNR) and spatial resolution compared to MD-CT, MRI, and other pQCT devices (nominal isotropic voxel dimension of 82 μm) (Krug et al. 2010). By comparison, MD-CT has a maximum in plane spatial resolution of 250–300 and MRI of 150–200 μm with slice thicknesses of 0.5–0.7 and 0.3–0.5 mm, respectively. Furthermore, the effective radiation dose is substantially lower compared to whole-body MD-CT, and primarily does not involve critical, radiosensitive organs (effective dose <3 microSv). The scan time for HR-pQCT is approximately 3 min for each scan of the tibia and femur.

There are several disadvantages to this technology; most notably, that it is limited to peripheral skeletal sites, and therefore can provide no direct insight into bone quality in the lumbar spine or proximal femur—common sites for osteoporotic fragility fractures (Krug et al. 2010). Only a limited region of the distal radius and tibia may be scanned in one pass (9.02 mm in length with 110 slices). In addition, the scanner tube has a limited life span and motion artifacts sometimes limit morphological analysis of the bone architecture.

The advantages of the system are that it allows acquisition of BMD, trabecular, and cortical bone architecture at the same time. A semi-automatic standard protocol provided by the manufacturer is used for image analysis; the segmentation

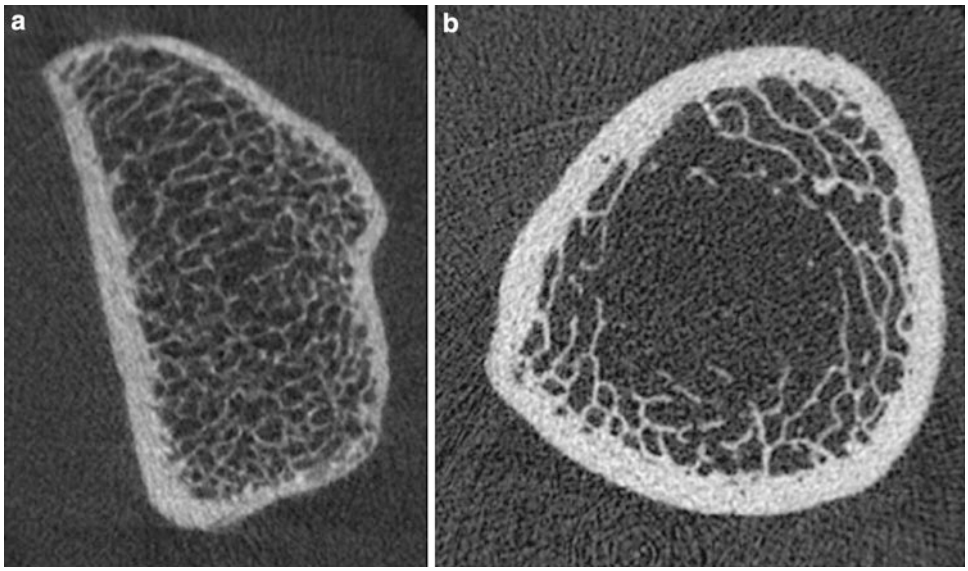

Fig. 7 HR-pQCT images of the distal radius (**a**) and the distal tibia (**b**). Images impressively demonstrate trabecular bone architecture, which is well interconnected in (**a**) and shows central loss of trabeculae in (**b**)

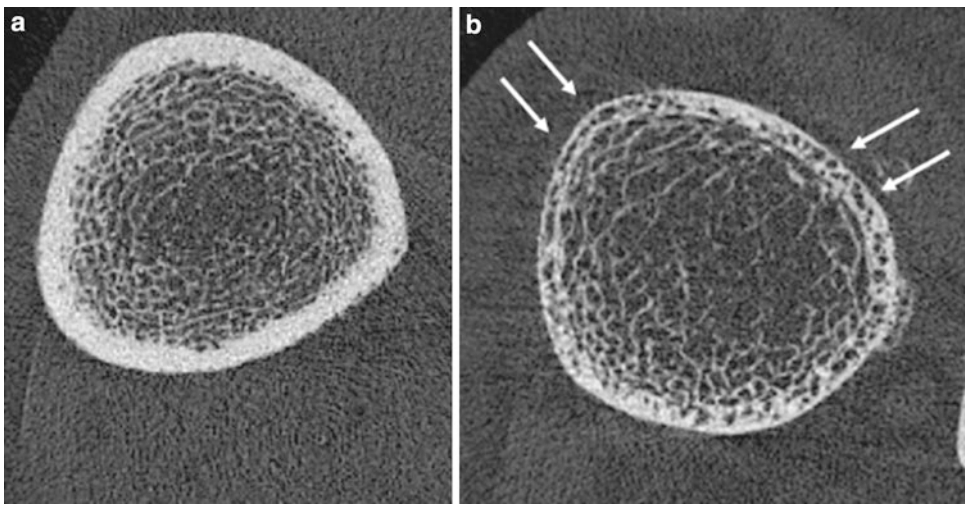

Fig. 8 HR-pQCT images of the distal tibia in a healthy control (**a**) and a patient with Diabetes and a fragility fracture in (**b**), note impressive increase in cortical porosity in the fracture patient (*arrows*)

process is initiated by the operator and automatically adjusted using an edge detection process to precisely identify the periosteal boundary. The cortical bone compartment is segmented using a 3-D Gaussian smoothing filter followed by a simple fixed threshold. The trabecular compartment is identified by digital subtraction of the cortical bone from the region enclosed by the periosteal contours. Based on this semi-automated contouring and segmentation process, the trabecular, and cortical compartments are segmented automatically for subsequent densitometric, morphometric, and biomechanical analyses (Link 2012).

A 5 cylinder hydroxyapatite calibration phantom is used to generate volumetric BMD separately for cortical and trabecular bone compartments, similarly to central QCT. Morphometric indices analogous to classical histomorphometry as well as connectivity, structure model index (a measure of the rod or plate-like appearance of the structure), and anisotropy can be calculated from the binary images of the trabecular bone (Link 2012). In addition, finite element analysis (FEA) can be applied to these datasets and apparent biomechanical properties (e.g., stiffness, elastic modulus) can be computed by decomposing the trabecular bone structure into small cubic elements (i.e., the voxels) with assumed mechanical properties (Macneil and Boyd 2008a; Burghardt et al. 2010b; Liu et al. 2010). Reproducibility of HR-pQCT densitometric measures is high (coefficient of variation <1 %), while biomechanical and morphometric measures typically have a coefficient of variation of 4–5 % (Boutroy et al. 2005; MacNeil and Boyd 2008b; Burghardt et al. 2010b).

A number of clinical studies have been performed which have shown promising results in differentiating post-menopausal females and older men with and without fragility fractures (Boutroy et al. 2005; Szulc et al. 2010) as well as in

monitoring therapeutic interventions (Burghardt et al. 2010c; Li et al. 2010). It was also found that trabecular and cortical subregional analysis may provide additional information in characterizing gender and age-related bone changes (Sode et al. 2010).

Recently, structural analysis of cortical bone has been introduced to the study of HR-pQCT datasets and cortical porosity measurements have been developed (Burghardt et al. 2010d). A recent study suggested that cortical porosity measurements may be useful to assess increased fracture risk in patients with diabetes (Burghardt et al. 2010d) (Fig. 8). Patients with type II diabetes are at higher risk for fragility fractures, yet DXA BMD in diabetes patients is increased, and is therefore not well suited to diagnose fracture risk (Schwartz and Sellmeyer 2004).

4 Conclusion and Future Developments

In summary, while DXA is the standard technique to measure BMD, QCT has some important advantages over DXA which are useful for a number of clinical applications including (1) BMD in small, large, or obese patients, (2) when rapid information on treatment effects is required and (3) when degenerative disease, arterial calcifications, or artifacts limit evaluation of DXA scans. QCT also has a number of disadvantages including the higher radiation dose, limited applicability of WHO criteria, and overall less experience with fracture prediction, treatment initiation, and response with QCT compared to DXA.

Given the deficits of QCT in relation to DXA, future research needs to focus on prospective studies clearly providing evidence that QCT also predicts fragility fractures of the spine, proximal femur, and appendicular skeleton and better treatment thresholds need to be defined; those for spine QCT are currently based on expert opinion and for pQCT no good recommendations exist. While central QCT of the spine is relatively well-established QCT of the hip and pQCT of the distal radius and tibia are still substantially less developed. HR-pQCT is currently a promising research tool, but not suited for larger scale clinical applications.

Research currently targets improved evaluation of bone strength using structure analysis techniques and finite element modeling has a central role in this arena; in addition, there is an increasing body of knowledge on cortical bone structure and its significance in predicting bone strength, which may change our algorithms in how to interpret the risk of fragility fractures in individual patients.

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