Peripheral Quantitative Computed Tomography: Review of Evidence and Recommendations for Image Acquisition, Analysis and Reporting, Among Individuals with Neurological Impairment

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Running title: Recommendations for pQCT assessment

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ABSTRACT
In 2015, the International Society for Clinical Densitometry (ISCD) position statement regarding peripheral quantitative computed tomography (pQCT) did not recommend routine use of pQCT, in clinical settings until consistency in image acquisition and analysis protocols are reached, normative studies conducted, and treatment thresholds identified. To date, the lack of consensus-derived recommendations regarding pQCT implementation remains a barrier to implementation of pQCT technology.

Thus, based on description of available evidence and literature synthesis, this review recommends the most appropriate pQCT acquisition and analysis protocols for clinical care and research purposes, and recommends specific measures for diagnosis of osteoporosis, assigning fracture risk and monitoring osteoporosis treatment effectiveness, among patients with neurological impairment. A systematic literature search of MEDLINE, EMBASE©, CINAHL and PubMed for available pQCT studies assessing bone health was carried out from inception to August 8th, 2017. The search was limited to individuals with neurological impairment (spinal cord injury, stroke and multiple sclerosis) as these groups have rapid and severe regional declines in bone mass. Of 923 references, we identified 69 that met review inclusion criteria. The majority of studies (n = 60) used the Stratec XCT 2000/3000 pQCT scanners as reflected in our evaluation of acquisition and analysis protocols. Overall congruence with the ISCD Official Positions was poor. Only 11% (n = 6) studies met quality reporting criteria for image acquisition and 32% (n = 19) reported their data analysis in a format suitable for reproduction.

Therefore, based on current literature synthesis, ISCD position statements standards and the authors’ expertise, we propose acquisition and analysis protocols at the radius, tibia and femur sites using Stratec XCT 2000/3000 pQCT scanners among patients with neurological impairment.
for clinical and research purposes in order to drive practice change, develop normative datasets and complete future meta-analysis to inform fracture risk and treatment efficacy evaluation.

**Key words:** pQCT, image acquisition, neurological impairment, spinal cord injuries, diagnosis, systematic review, treatment
INTRODUCTION

Advances in medical imaging (i.e., quantitative computed tomography and magnetic resonance imaging) during the last three decades have: enabled more comprehensive *in vivo* analysis of bone macro- and micro-structure; increased our overall knowledge and understanding of bone anatomy and physiology; and, improved diagnostic determination of the presence or absence of disease (osteoporosis) \(^{(1,2)}\). Nevertheless, in the clinical realm, diagnostic determination of the presence of low bone mass (osteoporosis), and the associated risk of non-vertebral and vertebral fragility fractures continues to rely predominantly on dual-energy X-ray absorptiometry (DXA) measures of areal bone mineral density (aBMD) and associated risk prediction tools (e.g., FRAX®, CAROC) as the current clinical “gold standard” \(^{(3–6)}\).

DXA is low cost, widely available, with simple usability - lower aBMD values are associated with a higher likelihood of fragility fracture, and a greater likelihood the patient will benefit from medical therapy \(^{(7,8)}\). Despite these appealing features, the reliability of aBMD can be compromised by inherent inaccuracies and ambiguities in DXA interpretation \(^{(9–11)}\). The aBMD assessments do not consider bone size and, subsequently, a larger bone may appear more dense than a smaller one \(^{(2)}\). Furthermore, aBMD is derived from the assumption that the region of interest contains only calcified hard tissue and homogeneous soft tissues \(^{(10)}\). Further, DXA is currently unable to provide reliable estimations of three-dimensional bone geometry and structure, that are necessary for the assessment of bone strength \(^{(12)}\) and associated fracture risk \(^{(13–15)}\). These limitations often lead to spuriously elevated absolute aBMD values among patients with bone disorders, such as osteoarthritic spondylosis and/or diffuse idiopathic skeletal hyperostosis \(^{(16)}\).
In contrast to DXA measurements of aBMD, peripheral quantitative computed tomography (pQCT) and high resolution pQCT (HRpQCT) allow measurement of volumetric BMD (vBMD) independent of bone size. These scanners conduct sequential scanning (translation – rotation motion) in acquisition mode and acquire single-slice (pQCT) or multi-slice (HRpQCT) cross-sectional images. Further, pQCT scanners offer the means to assess bone cross-sectional geometry, and to separate bone into its trabecular and cortical compartments (17). However, due to the narrow diameter of the scanner gantry, they cannot be applied to vertebral or proximal femur sites. Nonetheless, pQCT does provide information on apparent structural traits from appendicular bones, similar to data provided by clinical QCT at the lumbar spine and proximal femur (18–20). Furthermore, pQCT scanners do not require transfer of patients onto the scanner bed, which is particularly appealing among individuals with neurological impairments who require gait aids or a manual or power wheelchair to move about their home or community (21).

Notwithstanding the aforementioned limitations of DXA assessment, the discrepancies in DXA and pQCT distribution throughout the world (22), and the volume of pQCT studies (23), the current official positions of the International Society for Clinical Densitometry (ISCD) (4,6,24,25), does not recommend routine use of pQCT for diagnosis of osteoporosis, fracture risk prediction or monitoring of treatment effectiveness. This position is in part due to incompatibility of pQCT data with DXA derived T-scores, inconsistency in measurement sites, acquisition and analysis protocols, lack of normative studies, and specific treatment thresholds (4,23,24,26,27). The following research questions were specified by ISCD (2007 ISCD Official Positions (4)) to determine the generalizability of pQCT modalities in clinical settings: “1) What are the technical
limitations of pQCT assessment for specific patient groups? 2) Which are the optimum anatomical sites to scan? and most importantly, 3) Which parameter(s) should be measured and for which intervention (diagnosis, fracture risk prediction, or treatment monitoring)”. These knowledge gaps constitute barriers to advancement of pQCT practice and routine clinical implementation of pQCT technology.

It is well recognized that disuse related declines in bone mass (e.g., after sustaining a spinal cord injury, SCI) are more rapid and severe than age or postmenopausal related bone deterioration. Consequently, monitoring time intervals of changes in bone traits (e.g., size, shape, density, structure) as detected by peripheral scanners are shorter in duration, when compared to the general aging population. As a result, this impairment group represents a unique model for determination of the most appropriate pQCT measures based on their clinimetric properties for diagnosis, fracture risk prediction and monitoring of therapy. Finally, individuals with SCI tend to fracture at the distal femur and proximal tibia rather than the spine or proximal femur, so pQCT scans may be more clinically relevant.

Thus, due to the current lack of consensus derived recommendations/guidelines for clinicians/researchers regarding pQCT implementation, we conducted a systematic literature search. Based on synthesis of the literature identified and the authors’ expertise, we evaluated the quality reporting of pQCT methods according to the ISCD Official Positions’ and available evidence to recommend the most appropriate pQCT acquisition and analysis protocols, measures for diagnosis of osteoporosis, assigning fracture risk and monitoring the effectiveness of osteoporosis therapy among individuals with neurological impairment. Considering the
variety of pQCT-based studies, in-vivo human studies among individuals with neurological impairment, including SCI, stroke and multiple sclerosis (MS), were the focus of this review.

METHODS

Methodology

A systematic literature search for peer-reviewed articles was conducted in four databases: MEDLINE (OVID interface), EMBASE®, CINAHL and PubMed. The search included all published reports from 1946 (MEDLINE and PubMed), 1947 (EMBASE©) and 1937 (CINAHL) until August 8th, 2017. The search strategy used the following terms to capture the key concepts: SCI, Stroke, Multiple Sclerosis, pQCT, HR-pQCT, long bones, bone loss and bone traits. The search strategy employed an algorithm for each term, which was refined for each database, maximizing the use of available filters and qualifiers in order to maximize manuscript capture and minimize inclusion of irrelevant records (Appendix 1).

A total of 923 references were identified; 156 (MEDLINE), 358 (EMBASE), 40 (CINAHL) and 369 (PubMed). However, the search failed to identify some articles on related topics known to the authors; these articles were also included in the review process.

Selection process

The primary author (TC) eliminated duplicate records (n = 301). Following a first level review of the abstract title and body of the remaining studies, the primary author eliminated animal studies not excluded by the search strategy (n = 26), ex vivo studies (n = 13), and studies unrelated to the imaging modalities of interest (i.e., modalities that cannot be directly used for densitometric measurements) and/or to the desired sites of assessment including the radius, tibia or femur anatomic sites (n = 480).
Following a second level review of the method sections of all remaining studies (n = 103), the primary author excluded study protocols (n = 1), studies irrelevant to the populations of interest (n = 8) and modality of interest (n = 21), and review papers (n = 4). Of the remaining 69 studies, 67 used pQCT and 2 HRpQCT for bone health assessment. The article screening process is illustrated in Figure 1.

Appraisal of evidence

The following data were abstracted from the selected manuscripts: (i) the material and methods sections were searched for references regarding study design (observational/interventional, cross-sectional/longitudinal), patient population, scanner type, reference lines used, imaging site(s) selection, voxel size, slice thickness, method used for data analysis; and, (ii) the results and discussion sections were hand searched for references regarding bone traits that showed significant changes over the study duration or significant between group differences (p<0.05) and their clinimetric properties (i.e. the precision and least significant change), or traits used for bone strength estimation and/or fracture risk prediction. These bone traits were then deemed meaningful for bone assessment by peripheral scanners and recorded. Traits that were reported as significant by at least 20% of studies (with similar study design), were recommended for inclusion in future minimum data sets (research and clinical), required to inform the development of normative datasets.

To guarantee study reproducibility and comparability, the 2015 ISCD Official Positions state that quality reporting of pQCT methods should specify details regarding the pQCT acquisition and analysis (4,24). Specifically, all image acquisition protocols should include: scanner
make/model, bone length measurement methods; reference line selection, voxel size, and slice thickness settings; scanner translation speed, and specification of the imaging sites. Analysis protocols should clearly describe: the software version; analysis modes, and software thresholds used. The following sections describe the available abstracted data regarding pQCT scan acquisition parameters (anatomic site selection, reference line selection, voxel size, etc.), and scan analysis methods (i.e., used contour and peel modes, and specific thresholds) among individuals with SCI, Stroke and MS.

RESULTS

Imaging modalities

The majority of reviewed studies (n = 60) used single-slice scanners, either XCT 2000 or XCT 3000 (Stratec Medizintechnik GmbH, Pforzheim, Germany), with two exceptions, two studies which used the multi-slice XtremeCT (Scanco Medical AG, Bassersdorf, Switzerland) [41,42]. A few studies (n = 6) used predecessors of these scanners e.g., XCT 960, Densiscan 1000/2000 [29,32,38,43–45], and one study used the specially designed OsteoQuant® peripheral scanner [46] (Table 1).

As the search strategy identified only two HRpQCT-based studies [41,42], the evidence abstracted from these studies was considered insufficient for drawing specific conclusions, and therefore was omitted from further synthesis and the article recommendations. Further, the XCT 960 and Densiscan scanners are obsolete and are now sparsely available [Personal communication with Stratec Medizintechnik GmbH and Scanco Medical], and the OsteoQuant® scanner is a unique laboratory product. As newer clinical scanners (XCT 2000/3000 and XtremeCT I/II) are routinely
used for current clinical studies, the further description of these aforementioned outdated scanners was deemed irrelevant for the purpose of this manuscript; thus, no further discussion regarding the XtremeCT (n = 2), XCT 960 (n = 2), Densiscan (n = 4) and OsteoQuant® (n = 1) scanner is included. Of note, technical details of both XCT 2000 and 3000 scanners were abstracted from the manufacturers’ websites and supplemental materials, and are presented in Table 2.

[PREPARED LOCATION OF TABLE 2]

Image acquisition

Anatomic site selection

Of the sixty pQCT studies selected for inclusion in this review, 21 (35%) studies did not report the methodology used for determining bone length and identifying reference lines for each region of interest \(^{(37–39,47–65)}\); further, an additional 25 (42%) studies reported the distal endplate or joint gap as a reference line, without any specific details regarding how these were identified, or the reference lines assigned \(^{(28,63,66–88)}\).

In the remaining fourteen studies (25%) \(^{(30,31,89–100)}\), the radius bone length was measured from the humero-radial joint cleft to the medial aspect of the styloid process, the tibia bone length from the most distal palpable end of the medial malleolus to the most proximal edge of the medial tibial plateau (the medial joint cleft), and the femoral length was either approximated to be equal to tibial length as suggested by Eser et al. \(^{(93)}\), or measured from the most proximal palpable limit of the greater trochanter, to the most distal limit of the lateral femoral condyle.

For the radius and tibia, reference lines were placed at the flattest portion of the plateau of the tibial or radial endplate, respectively. For the proximal tibia imaging, the reference line was
placed on the proximal end of the more distal of the two condyles of the tibia (medial condyle of the tibia). For the femur, the reference line was placed at the distal limit of the lateral femoral condyle.

Imaging sites reported in the selected literature and the rationale for their inclusion is briefly outlined in Table 3. The majority of studies used the manufacturer’s recommended imaging sites for trabecular bone assessment (4% of radius, tibia and femur length), cortical bone assessment (38% of tibia and 25% of femur length) and muscle assessment (66% of radius and tibia length, Table 4, Figure 2).

**[PREFERRED LOCATION OF Figure 1]**

**Voxel size selection**

Despite the importance of reporting voxel sizes in pQCT study methods, 14/60 studies (23%) did not report this important detail. From the remaining studies, the majority used either 0.4 x 0.4 mm (epiphysis) or 0.5 x 0.5 mm (diaphysis) voxel sizes for radial and tibial assessments, and a reduced 0.3 x 0.3 mm voxel sizes for femoral assessment due to a very thin cortical shell at the distal femur sites. The slice thickness varied between 2 – 2.5 mm (Table 4).

Of note, only 6 (10%) studies met quality reporting criteria for image acquisition based on ISCD Official Positions.

**[PREFERRED LOCATION OF Table 3 AND 4]**

**Scan Analysis**

Twenty of the selected studies (33%) in this review, did not report details regarding image analysis. Further, 21 (35%) studies provided incomplete
descriptions (Table 5). Nevertheless, based on the authors' knowledge of the Stratec analysis software, we were able to abstract or infer the following patterns for assessment of epiphyseal sites:

- For the periosteal border (total bone cross-section) detection, all available contour modes were used, with specific research groups selecting their own threshold levels; the following thresholds were used in an almost equal number of studies: 130, 150, 169, 180, and 200 mg/cm$^3$;
- The cortical compartments were not analyzed, with the exception of two studies $^{(66,80)}$, presumably due to the thin cortex in these locations and poor endosteal border detection of cortical bone $^{(101,102)}$;
- Approximately half of the studies used threshold driven selection of the trabecular compartment (Peel mode 2), mostly set to a threshold value of 400 mg/cm$^3$. The remaining studies appear to have used Peel mode 1 with trabecular compartment detection set to 45% of total bone area.

For diaphyseal sites, almost all research groups used similar analysis settings:

- For assessment of total bone cross-section, the vast majority of studies used unspecified contour mode (presumably mode 1) with the threshold set to 280 mg/cm$^3$;
- For assessment of cortical bone cross-section, the vast majority of studies used unspecified separation mode (presumably 1 or 2) with the threshold set to 710 mg/cm$^3$;
- If the stress strain index (SSI) analysis was reported separately (8 studies $^{(31,48,54,68,72,93,94,103)}$), the most frequently used threshold was 280 mg/cm$^3$. 

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Of particular note, only 19 (32%) studies met quality reporting criteria for image analysis based on the ISCD Official Positions.

[PREPARED LOCATION OF TABLE 5]

**Reported bone traits with significant responses**

The most frequently reported bone traits showing significant changes or between-group differences over all reviewed studies are summarized in Table 6. The precision and least significant changes for particular bone traits (Table 6) at each of the manufacturer’s suggested imaging sites are shown in Table 7, which displays the mean values derived from data provided in the following studies \(^{17,31,73,81,83,95,104–108}\).

[PREPARED LOCATION OF TABLE 6 AND 7]

**Observational studies:** The most frequently reported bone traits showing significant changes in observational studies at epiphyseal sites of radius, tibia and femur were total bone mineral content (BMCto), total vBMD (BMDto) and trabecular vBMD (BMDt). At diaphyseal sites, traits demonstrating consistent clinically significant changes within the reviewed studies were BMCto, cortical BMC (BMCC), cortical cross-sectional area (CSAc) and cortical thickness (CoTh).

**Interventional studies:** Interventions featured either a form of exercise (e.g., functional electrical stimulation, partial body-weight supported treadmill training, robotic exoskeleton walking, standing or variety of weight-bearing activities to enhance lower extremities bone strength in stroke survivors) \(^{37,39,40,45,47,51,55,57,62,65,71,72,78,86,89,91,92,109}\) or use of oral or intravenous bisphosphonate therapy \(^{52,77}\).
Similar to observational studies, the traits that showed the largest responses to interventions were BMCto, trabecular BMC (BMCl) and BMDt, and BMCto, BMCl and CoTh at epiphyseal and diaphyseal sites of the radius, tibia and femur, respectively.

**Bone strength and fracture discrimination:** The bone strength traits often showing significant between group differences in the currently reviewed pQCT-based studies were the bone strength index (BSI) and stress-strain index (SSI) at epiphyseal and diaphyseal sites, respectively. The bone traits that were able to distinguish between individuals with, and without, a history of fracture were BMDt and polar moment of inertia (PMI).

**DISCUSSION**

**Imaging modalities**

All pQCT scanners selected for inclusion in this review, have distinct advantages and disadvantages, which limit their usability for particular patient groups, measurement sites, and purposes. The XCT peripheral scanners use the single-slice technology. In contrast to the multi-slice high-resolution technology scanners (HRpQCT), they do not acquire high resolution images, isotropic voxel sizes (the same voxel size in plane and axial direction) and full 3D imaging of the field of view. Nevertheless, these XCT scanners have the advantage of somewhat faster image acquisition times, and consequently a lower frequency of movement artifacts, lower radiation dose (x-ray beam is shaped according to detector size), and calibration prior to projection (the X-ray source and detector move off the field of view, while measurements of the empty field and the dark bias signal are performed).

The XCT 2000 is the lightest and the most portable of these scanners; it can be placed on a moving and height adjustable platform which makes it an ideal device for studies of individuals
with neurological impairment where restricted patient mobility necessitates greater scanner mobility. Operators or technologists can adjust the scanner position according to scan or patient specific needs (21). This scanner can acquire images of the humerus, radius, distal femur and tibia. The reach is, however, limited by the maximal distance of travel (40 cm) and the gantry opening (14 cm). Due to these limitations in the gantry movement, the device does not allow measurements of the entire lower limb in adults. Thus, the patient has to be repositioned for scans of the distal femur and proximal tibia. In addition, the limited gantry opening restricts the use of this scanner to individuals with a smaller limb circumference. Consequently, this reduces the usability of this scanner for muscular or obese patients with a wide calf circumference, or measurement of more proximal femur sites.

The XCT 3000 scanner is larger and heavier than the XCT 2000, necessitating that it remain in place. However, it’s larger gantry opening (30 cm), allows screening of the limbs with larger circumferences and more proximal sites of the femur. Bone traits yielded by both scanners have excellent agreement and are highly correlated; \( r = 0.90–0.99 \) for cortical vBMD (BMDc), with \( r = 0.97–0.99 \) for all other traits across measured sites (110,111). Therefore, these scanners could be used interchangeably particularly during multi-centre clinical trials.

Image acquisition
The image acquisition time for one anatomical site (single-slice) for both pQCT scanners is \(~ 90\) s (depending on limb diameter and scan speed). Short time periods for pQCT data acquisition reduces the appearance of movement artifacts in the resulting image. To avoid negative density values within images, Stratec pQCT scanners are calibrated so that fat tissue is equal to 0 and water \(~ 55 \text{ mg/cm}^3 \) of bone equivalent (112)
Anatomic site selection

The large variability in Stratec scanner settings allows users (researchers/clinicians/technologists) the potential to assess any bone location or region of interest provided that the desired region fits within the scanner gantry. This is especially beneficial when evaluating interventions where anatomically-localized intervention-specific responses are expected. However, the lack of standardized scanning protocols and the freedom to select a variety of anatomical sites restricts inter-study comparison and limits our ability to establish recommendations for routine use of pQCT sites to measure vBMD in clinical practice, or to recommend minimal data elements for inclusion in research settings such as a clinical trial.

A recent study by Rittweger et al. investigated the tibia of individuals with SCI (n = 9) by conducting a series of evenly distributed scans (in steps of 5% of the tibia length) and compared with results acquired from body height, weight and age matched able bodied individuals (n = 9). They found that bone (BMCto) is primarily lost at epiphyseal sites (the largest absolute bone lost being at proximal epiphysis), and the largest reduction (expansion) of periosteal (endosteal) circumference occurs between 30% and 40%, and between 65% and 75% of tibia length. These results suggest that the measurement sites with optimal prognostic capability for clinical practice may be located at these sites. Nevertheless, larger-scale studies are needed to confirm this assumption.

In addition to variability in the region of interest or anatomic site selection, there is variability in the methodology for determining bone length, and identifying reference lines, for each region of interest. This variability in procedures combines to produce additional sources of variability.
in scan acquisition. Accurate and precise measurements of bone length and reference line selection are crucial. In the worst case scenario, as investigated by Shields at al.\textsuperscript{(99)}, the scan location error can be up to ±3 mm. This slice misplacement at the ultra-distal tibia (4% site) can account for mean BMDt differences up to 2.3% and 4.6% in able-bodied individuals and individuals with SCI, respectively\textsuperscript{(99)}. Within the distal femur region of interest, the mean BMDt differences were 2.6% and 2.4% for able-bodied individuals and individuals with SCI, respectively\textsuperscript{(90)}.

In other studies, authors evaluated the influence of a misplaced slice in a follow-up scan\textsuperscript{(113,114)}. Marjanovic et al. reported that slice misplacement at the ultra-distal radius by 1.2 mm can result in mean BMDt and BMDto differences 3.8% and 4.8%, respectively. Further, in a study by Sun et al., the authors conducted an exhaustive investigation of changes in total cross-sectional area and BMDt at the ultra-distal sites of the radius and tibia with changes of slice position up to ±1 mm in 0.1 mm steps. They reported that the cross-sectional area changes by ~20 mm$^2$ for each 0.5 mm slice misplacement in both the radius and tibia. Further, the BMDt, with the same misplacement, changes by 3.3% and 0.8% in the radius and tibia, respectively. In addition, in the radius, slice misplacement by 1 mm proximally (distally) leads to a ~31 mm$^2$ (40 mm$^2$) change in bone cross-section and 5.8% increase (2.6% decrease) in BMDt. They also investigated changes in the precision of BMDt measurement, and suggest that the follow-up location can be considered to be the same location as the baseline measurement, if the total bone cross-section (CSAto) remains within ±10 mm$^2$ and ±20 mm$^2$ at the radius and tibia, respectively.

Thus, site selection and potential errors in slice placement may have a profound impact on the interpretation of the therapeutic effectiveness of interventions. Therefore, to yield clinically
reliable results, uncompromised by the aforementioned issues, it is essential to set rigorous protocols for measurement of bone length and slice assignment particularly for longitudinal evaluation, that do not deviate throughout the study. For Stratec operating software version 5.5 and up, use of an automatic procedure of reference line placement by matching the baseline scan scout view and follow-up measurements for longitudinal studies is recommended. Ideally, the same acquisition protocols should be used in all pQCT studies. Of note, in longitudinal evaluations, bone length measurement should not be repeated after the baseline measurement in adults with a mature skeleton, to avoid further measurement errors.

**Voxel size selection**

The main disadvantage of Stratec pQCT scanners is low image resolution. Spatial resolution of the scanner is determined by the size of the smallest possible feature that can be detected. Resolution is typically represented by a point spread function (PSF). The PSF describes the response of an imaging system to a small point object (e.g., small bead), with the spread of the point object in the image characterizing the PSF. However, voxel size is commonly used to indicate differences in spatial resolution between different imaging modalities, given that the voxel size is greater than the PSF, not equivalent to the PSF. While standard XCT scanners have adjustable voxel size in range 0.2 – 1.0 mm and fixed slice thickness in range of 2.0 – 2.5 mm, the XCT Research+ scanners can theoretically reach voxel sizes down to 0.1 mm, with a slice thickness of 0.5 mm. This setting improves scanner spatial resolution and decreases partial volume effects, however, at the cost of a higher noise level, due to a finite number of X-rays quanta produced by the X-ray source. With smaller voxel size – less X-ray quanta are detected to create an image. Therefore, longer imaging (exposure) time, or increased X-ray quanta
energy, both increasing radiation dose, are key considerations when optimizing image quality. Of note, reducing slice thickness by a factor 5, assuming the radiation dose remains unchanged, will increase the noise by a factor of $\sqrt{5}$ \(^{(115)}\). Obviously, increasing the radiation dose is not a desired option in any setting and longer exposure times increase the potential for movement artifacts. This is especially important during radius measurements where even a subtle movement can radically decrease the reliability \(^{(116)}\) and measurements among patients with neurological impairment who may have spasticity, tremor, clonus or other involuntary movements difficult to inhibit for prolonged periods of time.

Nevertheless, reducing the slice thickness from 2.2 mm to 0.6 mm while reducing scanning speed (≈increasing radiation dose) to keep the same noise level, did not improve accuracy of assessed bone traits in a cadaver study conducted by Lala and colleagues \(^{(117)}\).

These voxel size settings (0.4 x 0.4 mm or 0.5 x 0.5 mm for assessment of the radius and tibia, and 0.3 x 0.3 mm for assessment of the femur) allow sufficiently accurate determination of bone densities of both bone compartments \(^{(108,118)}\) and detection of cortical bone thicker than 2.0 – 2.5 mm \(^{(101,119)}\). With voxel size reduced to 0.2 x 0.2 mm for epiphyseal sites; with use of a dedicated software, bone micro-architecture (bone volume fraction, trabecular number, trabecular separation and trabecular thickness) can be roughly estimated \(^{(73,74,117,120)}\).

Nevertheless, these apparent micro-architecture traits differ substantially from traits obtained via high-resolution pQCT \(^{(117)}\), and at this time there seems to be no additional diagnostic value, or clinical utility over standard pQCT-measured vBMD \(^{(121)}\).

Data Analysis
Since introduction of the Stratec pQCT scanner, almost three decades ago, researchers have tried to determine the optimal means of analyzing the acquired images. The common approach is based on manufacturer-provided simple density threshold contour detection and peeling procedures. This practice comes not only from its technical simplicity, but also from the need for reproducible results in clinical and research settings. However, these clinical needs are not always met by threshold based analyses, mainly due to partial volume effects, a relatively low signal to noise ratio, or the presence of movement artefacts. Therefore, proper reporting of analysis modes and the threshold levels used, are the key reporting criteria to ensure reproducibility of future studies and assure inter-study comparability.

We found substantial variability in analysis parameters. It has been suggested that thresholds 169 mg/cm$^3$ and 130 mg/cm$^3$ are the optimal settings for assessment of able-bodied individuals and individuals with SCI, respectively, yet a variety of thresholds are in use for periosteal border detection. However, the main discrepancy between studies stems from the selection of the peel mode. Dudley-Javoroski and Shields found that the peel mode 1 (set to 45%) reduces mean BMDt by an average of 17.3% and 8% in comparison with threshold driven peel mode for subjects with SCI and able-bodied subjects, respectively. Further, for subjects with low BMDt, peel mode 1 yielded differences up to 30% from the value obtained with the threshold driven peel method. For subjects with higher density BMDt, differences between the two modes were smaller (~10%). Sievanen et al. [17] compared BMDt data obtained from both peel mode 1 and contour detection algorithm (peel mode 2, contour mode 2) and found large discrepancies (up to ±36 mg/cm$^3$) between the analysis methods. This data suggests results
from studies using different peel modes cannot be combined or directly compared. The peel mode 1 can be used in scenarios where investigators desire to compare similar bone regions between study cohorts, assuming that the trabecular deterioration occurs mainly in the center of the bone cross-section. This latter assumption, however, may not be true, as the trabecular bone adaptations to interventions vary across anatomical regions of the bone cross-section (71,92,126).

Although the threshold for cortical bone assessment was set to 710 mg/cm³ (manufacturer’s recommended value) in the majority of reviewed studies, it has been recognized that this threshold should be set to a lower value (~600-661 mg/cm³) to correctly determine cortical bone geometry (e.g., CSAc) (101,108,118,124,125,127). The manufacturer’s recommended threshold also underestimates the BMDc value by ~10-15% (101) and a higher value (~1200 mg/cm³) should be used to accurately determine BMDc (101,127). Therefore, two distinct thresholds should be used to correctly assess CSAc and BMDc. The lower threshold value (661 mg/cm³), however, provides BMDc values similar to those yielded by HRpQCT (mean error = -0.6%) (128), despite different density calibrations of the two modalities (112,129).

To date, two more sophisticated and reliable, threshold-free approaches have been developed to reduce dependence on threshold based analysis for pQCT data assessment, OsteoQ (130) and OBS (131,132). Nevertheless, these methods are not routinely available for clinical use. The former is proprietary software developed by Gordon et al. and customers are charged an hourly rate for data analysis, and the latter was developed by Cervinka et al., available on request, for cortical bone detection at epiphyseal sites. In addition, the current evidence supporting their use in clinical studies is limited (126,133,134).
Reported bone traits with significant responses

Observational studies

Although only a limited number of reported bone traits showed clinically significant changes or important between group differences across the reviewed articles, these findings are not unexpected (Table 6). First, all of the reviewed studies used the manufacturer’s threshold-based protocols that preclude accurate detection of cortical bone at epiphyseal sites \(^{(101,131)}\). Second, as the trabecular compartment accounts for the majority of bone cross-section at the epiphyseal site, all traits are likely to be directly affected by changes in trabecular structure. Third, at diaphyseal sites, where the bone is composed predominantly of thicker cortical bone, bone traits related to cortical bone cross-section or amount of bone mineral (BMCc), not density (BMDc), are the key parameters to monitor. Obviously, one can speculate whether the assessment of BMDc at diaphyseal sites would provide any additional information as suggested by radial and polar BMDc assessment in young men \(^{(135)}\) or postmenopausal athletes \(^{(136)}\). Nevertheless, to date, there is no evidence requiring bone anatomical sector analysis in individuals with neurological impairments and current evidence shows that BMDc only slightly decreases (2-4\%) during the first 2-5 years post SCI or stroke \(^{(31,32,54,81)}\), and recovers thereafter \(^{(31,54,95)}\). This decrease may be caused by intra-cortical remodeling (increased cortical porosity) as reported in HRpQCT-based study by Kazakia et al. \(^{(137)}\) where cortical porosity was found to have the largest and most persistent response to 6 weeks of immobilization. Cortical porosity, however, cannot be detected by low resolution pQCT. Therefore, it seems that after sufficient cortical bone deterioration at the endocortical surface – bone adaptation to the new loading conditions, only reduced (more compact) cortical
bone cross-section is detected. Perhaps, including a total vBMD trait at diaphyseal sites in future studies may provide an explanation; if total bone cross-section remains stable, bone loss across the whole cross-section, would likely infer bone deterioration at the endocortical surface.

**Interventional studies**

In interventional studies, the observed changes have been presumed to be related to bone adaptation processes in the trabecular compartment and cortical bone cross-section at epiphyseal and diaphyseal sites, respectively. However, the mean numbers yielded from the whole bone cross-section may not provide the full picture, regarding the adaptation processes; specifically, in cortical and trabecular compartments or in anatomical directions. The actual benefit(s) resulted from a specific treatment may be lost in the analysis of the whole bone cross-section; whereas, anatomical sector analysis might improve sensitivity to longitudinal changes as reported by Dudley-Javoroski and Shields (71,92) and also suggested by Rantalainen et al. (138), Cervinka et al. (126) and Evans et al. (139) in able-bodied individuals. Consequently, treatments imposing a positive effect in a specific anatomical bone sector could result in a type two error (false negative results) based on whole cross-section assessment, although a simple regional or sector treatment modification may reveal positive effects on whole bone structure.

**Bone strength and fracture risk prediction**

The key role BSI and SSI traits play in estimation of long bone strength could be presumed as these traits reflect the strength of bone structure against compressive forces at the distal ends of long bones (140) and the torsional rigidity of the long bone shaft, respectively (124,141). Nevertheless, only a limited number of studies presented thresholds for selected bone traits
(BMDt and PMI) intended to distinguish patients who are at high risk of fracture according to vBMD values\textsuperscript{(48,75,94)}.

In a retrospective study, Eser et al.\textsuperscript{(94)} suggested using BMDt with thresholds set to 70 mg/cm\textsuperscript{3} and 110 mg/cm\textsuperscript{3} for distal tibia and femur, respectively. These thresholds were able to correctly determine, in one sample, 79% and 67% of patients with history of fracture in tibia and femur, respectively. Biggin et al.\textsuperscript{(48)} evaluated distal tibia in pediatric patients and reported that patients did not sustain a fracture when their BMDt was higher than 100 mg/cm\textsuperscript{3}. However, a later study by Lala et al.\textsuperscript{(75)} introduced data suggesting that this threshold may be placed even higher as patients with previous fracture(s) had mean (standard deviation - SD) BMDt equal to 84.4 (33.3) mg/cm\textsuperscript{3}. They also suggested that PMI was able to distinguish the patients with history of fracture from those without fracture. The mean PMI was equal to 32000 mm\textsuperscript{4} and 47000 mm\textsuperscript{4} in patients with fractures and without fractures, respectively, and the adjusted odds ratio (3.2) was significant (p = 0.038)\textsuperscript{(75)}.

**Recommendations**

The following recommendations stem from the described review, currently available data, and the authors’ opinions/expertise.

**Length measurement**

Based on the abstracted evidence, we suggest that future studies should strictly measure bone length between following landmarks:

(i) the medial aspect of the styloid process and the humero-radial joint cleft for the radius;
(ii) the most distal palpable end of the medial malleolus and the most proximal edge of
the medial tibial plateau (the medial joint cleft) for the tibia; and,

(iii) the most distal limit of the lateral femoral condyle and the most proximal palpable
limit of the greater trochanter.

Data acquisition – clinical studies

For measurement alignment, we suggest using the following reference lines (see Figure 2):

(i) the superior aspect of the cortical shell at the most distal and flattest portion of the
plateau of the tibial or radial endplate;

(ii) the proximal end of the medial condyle of the tibia for proximal tibia imaging; and,

(iii) the distal limit of the lateral femoral condyle for imaging of femur.

To date, there are no available sensitivity studies, describing optimal imaging site/sites for
assessment of bone responsiveness to interventions. Therefore, based on currently available
knowledge, we propose that the following imaging sites be included in future clinical studies, as
a part of minimum image acquisition protocol allowing interstudy comparability, should
comprise:

(i) 4% and 66% for radius;

(ii) 4%, 38% and 66% for the tibia; and,

(iii) 4% and 25% for the femur.

In the event of interest in knee region imaging, imaging of the proximal tibia (96%) site may be
used, keeping repeatability limits of this site in mind (Table 7).
Prior to completion of longitudinal analyses, clinicians and scientists should ensure that the CSA to in follow up scans does not differ by more than ±10 mm² (radius) and ±20 mm² (tibia) from the baseline scan, prior to conducting the analysis.

The 0.5 x 0.5 mm voxel size is sufficient for assessment of key bone traits (see Table 6) in radial, tibial and femoral diaphysis. A smaller voxel size of 0.4 x 0.4 mm should be used for assessment of the distal radius and tibia, and an even smaller voxel size 0.3 x 0.3 mm for measurements of femoral epiphysis as cortical bone is thinnest at this site.

The slice thickness, if applicable (all XCT Research+ scanners), should be selected within the range of 2 – 2.5 mm. The standard XCT scanners cannot reach thinner image slices (manufacturer pre-set slice thickness lies between 2 – 2.5mm) and therefore this range allows comparability between XCT scanners.

Data acquisition – clinical practice

In terms of screening patients for the presence or absence of osteoporosis, although their prognostic capability requires further validation, we recommend that the minimal image acquisition protocol should comprise the tibia 4%, 38% and 66% sites. The reference line should be placed at the superior aspect of the cortical shell at the most distal and flattest portion of the plateau of the tibial endplate (see Figure 2). The voxel size of 0.4 x 0.4 mm and 0.5 x 0.5 should be used for bone traits assessment in tibial epiphysis and diaphysis, respectively. The slice thickness should be selected within the range of 2 – 2.5 mm.

Summary of recommendations for pQCT image acquisition in clinical and research setting is appended in Table 8.

[PREFERRED LOCATION OF TABLE 8]
Data analysis selection

For bone detection at epiphyseal sites, locations mainly used for trabecular bone assessment, we recommend the use of contour mode 3 with thresholds set to 169 mg/cm³ (able bodied subjects) and 130 mg/cm³ (subjects with neurological impairment), and peel mode 2 set to 400 mg/cm³. These settings will guarantee proper bone periosteal contour detection and clear separation of trabecular from subcortical bone, and assure comparability across studies.

At diaphyseal sites, we suggest the use of separation mode 4 with outer threshold set to 200 mg/cm³ and inner threshold 650 mg/cm³ to yield accurate cortical cross-sectional bone area.

Diagnosis

Clearly, large normative datasets are needed for diagnosis of osteoporosis based on Z-scores; a robust reference data set of this nature does not currently exist \(^{(4,24)}\), partially due to the large variability in presented bone traits and measurement sites \(^{(23)}\). Therefore, based on the reviewed studies, we suggest reporting the following traits for radius, tibia and femur at the above suggested sites, as a future minimum data set to inform the development of normative datasets.

Epiphyseal sites:

- BMCto and BMDt

Diaphyseal sites:

- BMCto, BMCc, CSAc and CoTh

Although, BMDc, assessed at diaphyseal sites, was also reported as a trait consistently showing significant changes or between group differences in a large portion of reviewed studies (n = 21), we do not recommend use of this trait because of limitations provided in Discussion.
**Monitoring therapies**

For future longitudinal studies, we suggest monitoring the following bone traits that showed significant responses to intervention in reviewed studies.

Epiphyseal sites:

- BMCto and BMDt,

Diaphyseal sites:

- BMCto, BMCc and CoTh

Nevertheless, if feasible, future studies should also include anatomic regional analysis of cortical and trabecular compartments to improve sensitivity of bone assessment to longitudinal changes. Such a regional analysis is freely available as part of BoneJ for diaphyseal sites \(^{(135)}\).

**Bone strength and fracture risk prediction**

Although some pQCT-based studies suggested use of a “hole” size in trabecular compartment \(^{(130,142)}\) or cortical traits \(^{(143)}\) as the optimal measures for fracture discrimination in the able-bodied population, the current review suggests that future pQCT-based studies should focus on establishing cut-off or threshold values to estimate risk of future fracture for BMDt and BSI, and PMI and SSI at epiphyseal and diaphyseal sites, respectively. Of note, based on current evidence \(^{(75)}\), individuals with SCI with BMDt (measured at 4% site of tibia) above 120 mg/cm\(^3\) are unlikely to sustain a fragility fracture.

**Limitations**

Some limitations warrant further discussion. When evaluating quality reporting of included studies, we used the recommendations imbedded in the 2015 ISCD Official Position Statement. However, there may be circumstances (e.g., word count restrictions imposed by journal editors)
in which authors reduce explicit details of their methodology (i.e., acquisition and data analysis protocols) by referring to their prior work or the standard methods used in their setting or laboratory. As source references were not considered in current review, these studies may have been evaluated as not fulfilling the quality reporting criteria because of the review criteria.

Further, the recommendations for land marking and measurement of bone length may be difficult or infeasible in some patients with neurological impairment due to body habitus, contracture, restricted range of motion, prior surgical intervention or fragility fracture in a region of interest, or changes in bone shape due to absence of muscle contraction or inability to weight bear.

Furthermore, prior to generalizing the aforementioned recommendations, there are several issues that require further consideration. First, despite efforts to identify all available literature concerning pQCT imaging used among populations with neurological impairment, the number of identified studies was relatively low, leaving the potential for biased evaluation of image acquisition and analysis protocols as well as bone traits that showed consistently significant changes or between group differences over all reviewed studies. Second, although all studies including SCI, stroke and MS populations were used for the abstraction of pQCT image acquisition and analysis protocols, the majority of evidence appraisal discussing issues relate to improper setting of these protocols are based on data derived from the SCI population; predominantly, from published literature regarding men with motor complete paraplegia. Therefore, following recommendations concerning image acquisition and analysis protocols may only be valid for this population. Nevertheless, we believe, the same standards can also be employed among individuals with other forms of neurological impairment such as MS, Stroke,
Parkinson’s disease, Spina Bifida or Cerebral Palsy. The authors trust that data to validate, refine or revise our recommendations from others in the field, will follow publication of the enclosed recommendations.

CONCLUSIONS

The lack of consensus regarding scan acquisition and analysis protocols has been recognized by many authors \(^{(4,17,23,24,144)}\) and remains a primary barrier to routine clinical implementation of pQCT technology. However, to our knowledge, no study evaluated what would be the most appropriate anatomic site and outcomes for determining the diagnosis of osteoporosis, predicting regional fracture, and monitoring of therapy efficacy/effectiveness for patients with neurological impairment. This lack of consensus limits implementation; creation of a robust age, sex, race and body size specific reference database is required to advance pQCT practice \(^{(23,24,26)}\). Despite the small number of selected studies for review inclusion, and the potential for biased recommendations, we have proposed minimum standard acquisition protocols, for use in both clinical practice and research settings, and analysis protocols for pQCT scanners among patients with neurological impairment for specific clinical indications including diagnosis of low bone mass, assigning fracture risk and determining therapy effectiveness. We anticipate that adherence to these recommendations would substantially advance the field and allow for future data synthesis (meta-analysis).

APPENDIX 1: Search strategies

MEDLINE search strategy

\[\text{(exp Spinal Cord Injuries OR exp Paraplegia OR exp Quadriplegia OR hemiplegia OR exp paresis OR Spinal Cord Compresion OR (spinal cord injur* OR SCI).tw,kw OR (spinal cord adj3 (contusion* OR} \]
trauma* OR transection* OR laceration* OR compression*)).tw,kw OR (paraplegia* OR quadriplegia* OR quadriparesis OR locked-in syndrome OR tetraplegia* OR hemiplegia* OR hemiparesis OR paresis).tw,kw OR exp Multiple Sclerosis OR exp Stroke OR (multiple sclerosis OR stroke*).tw,kw, kw OR (cerebrovascular adj3 (accident* OR apoplexy)).tw,kw) AND (exp Tomography, X-Ray Computed OR peripheral quantitative computed tomography.tw,kw OR (peripheral adj2 computed tomography).tw,kw, OR (pQCT* or HR-pQCT*).tw,kw) AND (radius OR femur OR tibia OR Bone Density OR ((bone* OR radius OR tibia* OR femur*) adj3 (health* OR quality OR density OR loss OR morphology OR strength OR recovery OR disease* OR status OR adapt* OR respon* OR geomet* OR structur* OR properties)).tw,kw OR (long adj2 bone*).af NOT (animals NOT (humans AND animals)).sh) limit to English language

EMBASE® search strategy

(exp Spinal Cord Injury OR Paraplegia OR Quadriplegia OR Hemiplegia OR paresis OR (spinal cord injur* OR SCI).tw,kw OR (spinal cord sdj3 contusion* OR trauma* OR transection* OR laceration* OR compression*)).tw,kw OR (paraplegia* OR quadriplegia* OR quadriparesis OR locked-in syndrome OR tetraplegia* OR hemiplegia* OR hemiparesis OR paresis).tw,kw OR exp Multiple Sclerosis OR exp cerebrovascular accident OR (multiple sclerosis OR stroke*).tw,kw OR (cerebrovascular adj3 (accident* OR apoplexy)).tw,kw) AND (exp computer assisted tomography OR peripheral quantitative computed tomography.tw,kw OR (peripheral adj2 computed tomography).tw,kw, OR (pQCT* or HR-pQCT*).tw,kw) AND (exp long bone OR radius OR femur OR tibia OR Bone Density OR ((bone* OR radius OR tibia* OR femur*) adj3 (health* OR quality OR density OR loss OR morphology OR strength OR recovery OR disease* OR status OR adapt* OR respon* OR geomet* OR structur* OR properties)).tw,kw OR (long adj2 bone*).af NOT (animals NOT (humans AND animals)).sh) NOT (Conference Review.pt OR Conference Abstract.pt OR Short Survey.pt OR editorial.pt OR letter.pt OR note.pt) limit to English language

CINAHL search strategy

((MH “Spinal Cord Injuries+”) OR (MH “Paraplegia+”) OR (MH “Quadriplegia”) OR (MH “Hemiplegia”) OR (MH “Spinal Cord Compression”) OR TI (spinal cord injur* OR SCI) OR AB (spinal cord injur* OR SCI) OR TI (spinal cord N3 (contusion* OR trauma* OR transection* OR laceration* OR compression*)) OR AB (spinal cord N3 (contusion* OR trauma* OR transection* OR laceration* OR compression*)) OR TI (paraplegia* OR quadriplegia* OR quadriparesis OR locked-in syndrome OR tetraplegia* OR hemiplegia* OR hemiparesis OR paresis) OR AB (paraplegia* OR quadriplegia* OR quadriparesis OR locked-in syndrome OR tetraplegia* OR hemiplegia* OR hemiparesis OR paresis) OR (MH “Multiple Sclerosis”) OR (MH “Stroke+”) OR (TI (multiple sclerosis OR stroke*) OR AB (multiple sclerosis OR stroke*)) OR (TI (cerebrovascular N3 (accident* OR apoplexy)) OR AB (cerebrovascular N3 (accident* OR apoplexy))) AND ((MH “Tomography, X-Ray Computed+”) OR (TI peripheral quantitative computed tomography OR AB peripheral quantitative computed tomography) OR (TI (peripheral N2 computed tomography) OR AB (peripheral N2 computed tomography)) OR (TI (pQCT* OR HR-pQCT*) OR AB (pQCT* OR HR-pQCT*)))
PubMed search strategy

REFERENCES

1. Ito M. 2011 Recent progress in bone imaging for osteoporosis research. J Bone Miner Metab. 29:131–140.


60. Totosy de Zepetnek JO, Craven BC, Giangregorio LM. 2012 An evaluation of the muscle-
bone unit theory among individuals with chronic spinal cord injury. Spinal Cord. 50:147–
152.

61. Varzi D, Coupaud SAF, Purcell M, Allan DB, Gregory JS, Barr RJ. 2015 Bone morphology of
the femur and tibia captured by statistical shape modelling predicts rapid bone loss in


63. Coupaud S, Gislason MK, Purcell M, Sasagawa K, Tanner KE. 2017 Patient-specific bone
mineral density distribution in the tibia of individuals with chronic spinal cord injury,
derived from multi-slice peripheral Quantitative Computed Tomography (pQCT) - A cross-

64. Gibbs JC, Brown ZM, Wong AKO, Craven BC, Adachi JD, Giangregorio LM. 2017 Measuring
Marrow Density and Area Using Peripheral Quantitative Computed Tomography at the
Tibia: Precision in Young and Older Adults and Individuals With Spinal Cord Injury. J Clin
Densitom. 25.

65. Karelis AD, Carvalho LP, Castillo MJ, Gagnon DH, Aubertin-Leheudre M. 2017 Effect on
body composition and bone mineral density of walking with a robotic exoskeleton in


88. Ireland A, Capozza RF, Cointry GR, Nocciolino L, Ferretti JL, Rittweger J. 2017 Meagre effects of disuse on the human fibula are not explained by bone size or geometry. Osteoporos Int. 28:633–641.


142. MacIntyre NJ, Adachi JD, Webber CE. 2003 In vivo measurement of apparent trabecular bone structure of the radius in women with low bone density discriminates patients with recent wrist fracture from those without fracture. J Clin Densitom. 6:35–43.


Figure captions:

Figure 1: PRISMA flow chart for article inclusion process.
Figure 2: Imaging site recommended by Stratec for various long bones. Blue lines depict locations of the reference lines, red lines depict location of particular imaging sites. Detailed images and scout scans are on the right.

Table 1: Imaging modalities included in the literature review

<table>
<thead>
<tr>
<th>Technology</th>
<th>Scanner</th>
<th>Number of publications</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-slice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XCT 2000</td>
<td></td>
<td>20</td>
<td>(26,47,48,57,58,60,64,66,71,73–75,77,78,80,85,86,88,90,98–100)</td>
</tr>
<tr>
<td>XCT 3000</td>
<td></td>
<td>34</td>
<td>(28,30,31,39,40,49–56,61,63,65,67–72,76,81–84,87,89–96)</td>
</tr>
<tr>
<td>XCT 960</td>
<td></td>
<td>2</td>
<td>(32,38)</td>
</tr>
<tr>
<td>OsteoQuant©</td>
<td></td>
<td>1</td>
<td>(46)</td>
</tr>
<tr>
<td>Multi-slice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XtremeCT</td>
<td></td>
<td>2</td>
<td>(41,42)</td>
</tr>
<tr>
<td>Densiscan 2000</td>
<td></td>
<td>2</td>
<td>(29,45)</td>
</tr>
<tr>
<td>Densiscan 1000</td>
<td></td>
<td>2</td>
<td>(43,44)</td>
</tr>
</tbody>
</table>
Note: In studies Sherk et al. (59), Gibbons et al. (62) and Dudley-Javoroski and Shields (37), the authors did not report which type of XCT scanner they used and in study Dudley-Javoroski and Shields (71) the authors used both XCT 2000 and 3000 scanners.

Table 2: Technical specifications of the Stratec 2000/3000 peripheral QCT scanners

<table>
<thead>
<tr>
<th>Scanner</th>
<th>Dimensions (l/w/h) [cm]</th>
<th>Weight [kg]</th>
<th>Distance of travel [cm]</th>
<th>Gantry opening [cm]</th>
<th>Scanning time* [s]</th>
<th>Voxel size [mm]</th>
<th>Slice thickness [mm]</th>
<th>Radiation dose [mSv]</th>
</tr>
</thead>
<tbody>
<tr>
<td>XCT 2000</td>
<td>128 x 55 x 62</td>
<td>45</td>
<td>40</td>
<td>14</td>
<td>90</td>
<td>0.1 - 1.0</td>
<td>0.5 - 2.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>XCT 3000</td>
<td>128 x 74 x 91</td>
<td>90</td>
<td>40</td>
<td>30</td>
<td>90</td>
<td>0.2 - 1.0</td>
<td>2.0 - 2.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*actual scanning times depend on scan parameters (e.g., size of imaged object and scanning speed) and whether or not a scout scan is done

Table 3: Imaging sites reported and the clinical rationale for their inclusion

<table>
<thead>
<tr>
<th>Bone</th>
<th>Site</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius</td>
<td>4%</td>
<td>Predominantly trabecular bone, this compartment has higher metabolic activity per unit mass, in contrast to the cortical compartment located at shafts of long bones (145)</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>Standard imaging location to assess cortical bone for older XCT 960 scanner (32,38)</td>
</tr>
<tr>
<td></td>
<td>30/33%</td>
<td>Anatomical proximity to the origin/insertion of many muscle groups (e.g., Abductor pollicis longus, extensor pollicis brevis and pronator teres) and a presumption of larger effects of muscles on cortical bone cross-sectional area at this site (66,68)</td>
</tr>
<tr>
<td></td>
<td>65/66%</td>
<td>Largest muscle circumferences and muscle cross-sectional area (146)</td>
</tr>
<tr>
<td>Tibia</td>
<td>4/5%</td>
<td>Predominantly trabecular bone, this compartment has higher metabolic activity per unit mass, in contrast to the cortical compartment located at shafts of long bones (145)</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>vBMD and bending strength are the lowest in general population (85,147,148) suggesting a potential important correlation with fracture risk</td>
</tr>
<tr>
<td></td>
<td>30/38%</td>
<td>Anatomical proximity to the origin/insertion of lower limb muscle groups (e.g., tibialis anterior, extensor hallucis longus, and soleus) and a presumption of larger effects of these muscles on cortical bone cross-sectional area at this site</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>Middle of the tibia shaft</td>
</tr>
<tr>
<td></td>
<td>66%</td>
<td>Largest muscle circumferences and muscle cross-sectional area (146,147)</td>
</tr>
<tr>
<td></td>
<td>85/86%</td>
<td>Presumably the most susceptible site to changes in the muscle-bone unit (30)</td>
</tr>
<tr>
<td></td>
<td>95/96/98%</td>
<td>Predominantly trabecular bone, this compartment has higher metabolic activity per unit mass, in contrast to the cortical compartment located at shafts of long bones</td>
</tr>
</tbody>
</table>
Predominantly trabecular bone, this compartment has higher metabolic activity per unit mass, in contrast to the cortical compartment located at shafts of long bones (145).

Common fracture site (149,150)

Most proximal scan site due to insufficient hip abduction in patients with neurological impairments, absent or impaired lower extremity voluntary movement (31), and somewhat poorer image quality of more proximal sites (17).

Note, images from 25% site of the femur cannot typically be acquired by XCT 2000 in a majority of individuals due to small gantry opening; although it can often accommodate the limbs of individuals with neurologic impairment and significant atrophy. For healthy individuals with thigh circumferences (diameter > 14 cm) and long limbs, the XCT 3000 is required due to its larger gantry.

Table 4: Voxel sizes and slice thicknesses at various imaging sites reported in studies included in this review.

<table>
<thead>
<tr>
<th>Bone</th>
<th>Site</th>
<th>N</th>
<th>Voxel size [mm]</th>
<th>Slice Thickness [mm]</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 x 0.5</td>
<td>0.4 x 0.4</td>
<td>0.3 x 0.3</td>
</tr>
<tr>
<td>Radius</td>
<td>4%</td>
<td>12</td>
<td>x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(32,38,48,57,66–68,77,81–83,100)</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>2</td>
<td>x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(66,98)</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>2</td>
<td>x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(61,83,84)</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>3</td>
<td>x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(48,68,77,100)</td>
</tr>
<tr>
<td></td>
<td>65/66%</td>
<td>4</td>
<td>x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(28,30,31,47–49,53–55,59,60,63,67,68,70–74,76–78,80,86,87,91,93–96,99,100,117)</td>
</tr>
<tr>
<td>Tibia</td>
<td>4/5%</td>
<td>34</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(28,31,49,63,69,70,89)</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>6</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(79)</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>1</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(28,31,49,53–55,59,63,68–70,72,86,89,93,94)</td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td>26</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(47,78)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>2</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(28,30,40,48,50,59,60,63–65,73–77,86,87,89,93,95–97,100)</td>
</tr>
<tr>
<td></td>
<td>66%</td>
<td>24</td>
<td>x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x</td>
<td>(28,30,40,48,50,59,60,63–65,73–77,86,87,89,93,95–97,100)</td>
</tr>
<tr>
<td>Site</td>
<td>Radius Protocol</td>
<td>N</td>
<td>Study</td>
<td>Tibia Protocol</td>
<td>N</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------</td>
<td>----</td>
<td>-------</td>
<td>-------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>85/86%</td>
<td>CSA to CSA: C3P2 (130-400)</td>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>95/96/98%</td>
<td>3 x x x x x x (30,58,91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>4%</td>
<td>12</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>(28,31,51,53–55,61,67,68,72,89,93,94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12/15%</td>
<td>6</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>(30,51,52,58,90–92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>10</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>(28,31,53–55,61,67,68,72,89,93,94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Analysis protocols used in reviewed studies at the radius, tibia and femur

<table>
<thead>
<tr>
<th>Site</th>
<th>Radius Protocol</th>
<th>N</th>
<th>Study</th>
<th>Tibia Protocol</th>
<th>N</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>CSA to CSA: C3P2 (130-400)</td>
<td>1</td>
<td>[66]</td>
<td>CSA to CSA: C3P2 (280-400)</td>
<td>5</td>
<td>[78,73,75,99]</td>
</tr>
<tr>
<td></td>
<td>CSA to CSA: C3P2 (169-400)</td>
<td>3</td>
<td>[81-83]</td>
<td>CSA to CSA: C3P2 (130-400)</td>
<td>2</td>
<td>[78,73,75,99]</td>
</tr>
<tr>
<td></td>
<td>CSA to C1P1 (280-45%)</td>
<td>1</td>
<td>[48]</td>
<td>CSA to CSA: C2P2 (169-400)</td>
<td>5</td>
<td>[78,80,87,95,96]</td>
</tr>
<tr>
<td></td>
<td>CSA to CxP1 (150-45%)</td>
<td>2</td>
<td>[67,68]</td>
<td>CSA to C1P1 (169-45%)</td>
<td>1</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>CSA to CxP1 (180-45%)</td>
<td>1</td>
<td>[100]</td>
<td>CSA to C1P1 (180-45%)</td>
<td>9</td>
<td>[31,54,67,68,72,89,93,94,100]</td>
</tr>
<tr>
<td></td>
<td>CSA to C1 (169)</td>
<td>1</td>
<td>[57]</td>
<td>CSA to M4 (169-400)</td>
<td>1</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: M4 (169-710)</td>
<td>1</td>
<td>[66]</td>
<td>Osteo-Q architectural analysis</td>
<td>1</td>
<td>[73]</td>
</tr>
<tr>
<td>14%</td>
<td>CS Ac: M4 (169-710)</td>
<td>2</td>
<td>[81,83,84]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: M1 (710)</td>
<td>3</td>
<td>[81,83,84]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: Cx (280)</td>
<td>1</td>
<td>[89]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td>30/33%</td>
<td>CS Ac: M4 (710-710)</td>
<td>2</td>
<td>[81,83,84]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: M1 (710)</td>
<td>3</td>
<td>[81,83,84]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td>38%</td>
<td>CS Ac: M4 (169-710)</td>
<td>1</td>
<td>[66]</td>
<td>CS Ac: Mx (280)</td>
<td>7</td>
<td>[31,54,67,68,72,89,93,94]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: Mx (710)</td>
<td>6</td>
<td>[81,83,84]</td>
<td>CS Ac: Mx (710)</td>
<td>6</td>
<td>[31,54,67,68,72,89,93,94]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: M1 (711)</td>
<td>1</td>
<td>[86]</td>
<td>CS Ac: M1 (711)</td>
<td>1</td>
<td>[86]</td>
</tr>
<tr>
<td>50%</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
<td>CS Ac: M4 (710-710)</td>
<td>1</td>
<td>[78]</td>
</tr>
<tr>
<td>65/66%</td>
<td>CS Ac: M1 (710)</td>
<td>1</td>
<td>[48]</td>
<td>CS Ac: M1 (280)</td>
<td>1</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: Cx (280)</td>
<td>3</td>
<td>[67,68,100]</td>
<td>CS Ac: M1 (280)</td>
<td>1</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: Mx (710)</td>
<td>2</td>
<td>[67,68,100]</td>
<td>CS Ac: Mx (280)</td>
<td>4</td>
<td>[30,68,93,100]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: Mx (710)</td>
<td>4</td>
<td>[67,68,100]</td>
<td>CS Ac: Mx (280)</td>
<td>4</td>
<td>[30,68,93,100]</td>
</tr>
<tr>
<td></td>
<td>CS Ac: M1 (710)</td>
<td>8</td>
<td>[48,64,73,75,86,87,95,96]</td>
<td>CS Ac: M1 (280)</td>
<td>8</td>
<td>[48,64,73,75,86,87,95,96]</td>
</tr>
</tbody>
</table>
Table 5: Analysis protocols used in reviewed studies in various imaging sites of radius, tibia and femur (continued)

<table>
<thead>
<tr>
<th>Site</th>
<th>Femur Protocol</th>
<th>N</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>CSAto/CSAt: CxP1 (120-650)</td>
<td>1</td>
<td>(58)</td>
</tr>
<tr>
<td></td>
<td>CSAto: CxP1 (130-45%)</td>
<td>2</td>
<td>(67,89)</td>
</tr>
<tr>
<td></td>
<td>CSAto: CxP1 (150-45%)</td>
<td>7</td>
<td>(31,54,61,68,92,93,94)</td>
</tr>
<tr>
<td>12%</td>
<td>CSAto/CSAt: CxPx (200-400)</td>
<td>4</td>
<td>(30,90-92)</td>
</tr>
<tr>
<td></td>
<td>CSAto: CxP1 (200-45%)</td>
<td>1</td>
<td>(90)</td>
</tr>
<tr>
<td>15%</td>
<td>CSAto/CSAt: CxP1 (120-650)</td>
<td>1</td>
<td>(58)</td>
</tr>
<tr>
<td>25%</td>
<td>CSAto: Mx (280)</td>
<td>7</td>
<td>(31,54,68,72,89,93,94)</td>
</tr>
<tr>
<td></td>
<td>CSAc: Mx (710)</td>
<td>7</td>
<td>(31,54,68,72,89,93,94)</td>
</tr>
</tbody>
</table>

x denotes unknown number of contour (C) or peel (P) mode (M), CSAto – total cross-sectional area, CSAc – cortical cross-sectional area, CSAt – trabecular cross-sectional area, N – number of studies

Table 6: Key bone traits.

<table>
<thead>
<tr>
<th>Scanner</th>
<th>Imaging site</th>
<th>Observational studies</th>
<th>Intervention studies</th>
<th>Fracture risk prediction and bone strength traits</th>
</tr>
</thead>
<tbody>
<tr>
<td>pQCT</td>
<td>Epiphysis</td>
<td>BMCto</td>
<td>BMCto</td>
<td>BMDt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMDt</td>
<td>BMDt</td>
<td>BSI</td>
</tr>
</tbody>
</table>
Diaphysis | BMCto | BMCto | PMI
---|---|---|---
BMCc | BMCc | SSI
CSAc | CoTh | CoTh


Table 7: Precision and least significant changes of key traits for particular bones and sites as measured by Stratec pQCT (17,31,73,81,83,95,104–108)

<table>
<thead>
<tr>
<th>Site</th>
<th>Trait</th>
<th>CV_{%RMS} [%]</th>
<th>LSC [%]</th>
<th>Site</th>
<th>Trait</th>
<th>CV_{%RMS} [%]</th>
<th>LSC [%]</th>
<th>Site</th>
<th>Trait</th>
<th>CV_{%RMS} [%]</th>
<th>LSC [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>BMCto</td>
<td>3.0</td>
<td>8.3</td>
<td>4%</td>
<td>BMCto</td>
<td>1.0</td>
<td>2.7</td>
<td>4%</td>
<td>BMCto</td>
<td>1.1</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>BMDto</td>
<td>3.9</td>
<td>10.8</td>
<td></td>
<td>BMDto</td>
<td>1.3</td>
<td>3.5</td>
<td></td>
<td>BMDto</td>
<td>2.0</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>BMCt</td>
<td>4.7</td>
<td>13.0</td>
<td></td>
<td>BMCt</td>
<td>2.1</td>
<td>5.8</td>
<td></td>
<td>BMCt</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>BMDt</td>
<td>2.1</td>
<td>5.8</td>
<td></td>
<td>BMDt</td>
<td>1.1</td>
<td>3.2</td>
<td></td>
<td>BMDt</td>
<td>2.3</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>BSI</td>
<td>5.4</td>
<td>15.0</td>
<td></td>
<td>BSI</td>
<td>2.0</td>
<td>5.5</td>
<td></td>
<td>BSI</td>
<td>6.0</td>
<td>16.6</td>
</tr>
</tbody>
</table>

| 33%  | BMCto | 2.5           | 6.9    | 38%  | BMCTo | 0.6           | 1.6    | 25%  | BMCto | 2.0           | 5.6    |
|      | BMCCc | 0.8           | 2.2    |      | BMCCc | 0.9           | 2.5    |      | BMCCc | 2.6           | 7.2    |
|      | CSAc  | 1.8           | 4.9    |      | CSAc  | 1.1           | 3.1    |      | CSAc  | 2.9           | 8.0    |
|      | CoTh  | 1.6           | 4.3    |      | CoTh  | 1.2           | 3.3    |      | CoTh  | 3.6           | 10.0   |
|      | PMI   | 2.2           | 6.1    |      | PMI   | 2.0           | 5.4    |      | PMI   | 1.7           | 4.7    |
|      | SSI   | 2.1           | 5.8    |      | SSI   | 1.6           | 4.5    |      | SSI   | 4.1           | 11.2   |

| 66%  | BMCto | -             | -      | 66%  | BMCto | 0.8           | 2.1    | 66%  | BMCto | 0.8           | 2.1    |
|      | BMCCc | 3.4           | 9.5    |      | BMCCc | 0.9           | 2.5    |      | BMCCc | 1.1           | 3.0    |
|      | CSAc  | 3.1           | 8.6    |      | CSAc  | 1.1           | 3.8    |      | CSAc  | 1.4           | 3.8    |
|      | CoTh  | -             | -      |      | CoTh  | 1.4           | 3.8    |      | CoTh  | -             | -      |
|      | PMI   | -             | -      |      | PMI   | 1.4           | 3.8    |      | PMI   | -             | -      |
|      | SSI   | 4.0           | 11.1   |      | SSI   | 1.8           | 4.9    |      | SSI   | -             | -      |

| 96%  | BMCto | 3.5           | 9.7    |      | BMDto | 3.1           | 8.6    |      | BMDto | 2.1           | 5.8    |
|      | BMCCc | -             | -      |      | BMCCc | -             | -      |      | BMCCc | -             | -      |
|      | CSAc  | -             | -      |      | CSAc  | -             | -      |      | CSAc  | -             | -      |
|      | CoTh  | -             | -      |      | CoTh  | -             | -      |      | CoTh  | -             | -      |
|      | PMI   | -             | -      |      | PMI   | -             | -      |      | PMI   | -             | -      |
|      | SSI   | -             | -      |      | SSI   | -             | -      |      | SSI   | -             | -      |

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BMCto – total bone mineral content, BMCc – cortical bone mineral content, BMCt – trabecular bone mineral content, BMDto – total bone mineral density, BMDt – trabecular bone mineral density, CSAc – cortical cross-sectional area, CoTh – cortical thickness, BSI – bone strength index (resistivity in compression), PMI – polar moment of inertia (resistivity in bending), SSI – stress strain index (resistivity in bending), CV\%RMS – relative coefficient of variation (short-term precision), LSC – least significant change. The clinimetric properties (the precision and least significant changes) for selected bone were abstracted from the available literature known to authors using the same imaging sites described in this review. Where feasible, the CV\%RMS and LSC were calculated from the available published data as CV\%RMS = LSC/2.77 and LSC = 2.77*CV\%RMS, respectively.

Table 8: Recommendations for minimal image acquisition protocols for clinical and research settings using Stratec pQCT scanners.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Region of interest</th>
<th>Length measurement</th>
<th>Reference line placement</th>
<th>Imaging sites</th>
<th>Voxel size [mm]</th>
<th>Slice thickness [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Settings</td>
<td>Radius</td>
<td>Measure from the medial aspect of the styloid process to the humero-radial joint cleft</td>
<td>Place at the superior aspect of the cortical shell at the most distal and flattest portion of the plateau of the endplate</td>
<td>4%</td>
<td>0.4 x 0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>(Humans)</td>
<td>Tibia</td>
<td>Measure from the most distal palpable end of the medial malleolus to the most proximal edge of the medial tibial plateau (the medial join cleft)</td>
<td>Place at the superior aspect of the cortical shell at the most distal and flattest portion of the plateau of the endplate</td>
<td>4%</td>
<td>0.4 x 0.4</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>Measure from the most distal limit of the lateral femoral condyle to the most proximal palpable limit of the greater trochanter</td>
<td>Place at the distal limit of the lateral femoral condyle</td>
<td>4%</td>
<td>0.3 x 0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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| Clinical Practice Settings | Tibia | Measure from the most distal palpable end of the medial malleolus to the most proximal edge of the medial tibial plateau (the medial joint cleft) | Place at the superior aspect of the cortical shell at the most distal and flattest portion of the plateau of the endplate | 4% 0.4 x 0.4 | 38% 0.5 x 0.5 | 66% 0.5 x 0.5 | 2 – 2.5 |