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Position Statement

Peripheral Quantitative Computed Tomography in Children and Adolescents: The 2007 ISCD Pediatric Official Positions

Babette Zemel,[*,1,a] *Shona Bass,*[2,b] *Teresa Binkley,*[3,b] *Gaele Ducher,*[2,b] *Heather Macdonald,*[4,b] *Heather McKay,*[4,b] *Laurie Moyer-Mileur,*[5,b] *John Shepherd,*[6,b] *Bonny Specker,*[3,b] *Kate Ward,*[7,b] *and Didier Hans*[8,c]

[1]*The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA;* [2]*Deakin University, Melbourne, Australia;* [3]*South Dakota State University, Brookings, SD, USA;* [4]*University of British Columbia, Vancouver, BC, Canada;* [5]*University of Utah, Salt Lake City, UT, USA;* [6]*University of California at San Francisco, CA, USA;* [7]*University of Manchester Imaging Science & Biomedical Engineering, Manchester, UK; and* [8]*Geneva University Hospital, Geneva, Switzerland*

Abstract

Peripheral quantitative computed tomography (pQCT) has mainly been used as a research tool in children. To evaluate the clinical utility of pQCT and formulate recommendations for its use in children, the International Society of Clinical Densitometry (ISCD) convened a task force to review the literature and propose areas of consensus and future research. The types of pQCT technology available, the clinical application of pQCT for bone health assessment in children, the important elements to be included in a pQCT report, and quality control monitoring techniques were evaluated. The review revealed a lack of standardization of pQCT techniques, and a paucity of data regarding differences between pQCT manufacturers, models and software versions and their impact in pediatric assessment. Measurement sites varied across studies. Adequate reference data, a critical element for interpretation of pQCT results, were entirely lacking, although some comparative data on healthy children were available. The elements of the pQCT clinical report and quality control procedures are similar to those recommended for dual-energy X-ray absorptiometry. Future research is needed to establish evidence-based criteria for the selection of the measurement site, scan acquisition and analysis parameters, and outcome measures. Reference data that sufficiently characterize the normal range of variability in the population also need to be established.

Key Words: Bone mineral density; children; peripheral quantitative computed tomography.

Introduction

The concept that osteoporosis prevention begins during childhood is well-accepted *(1)*. Bone fragility throughout the life-cycle is determined in large part by bone density and "geometry", those characteristics that relate to the dimensions and biomechanical properties of bones. Most pediatric bone studies have relied on dual-energy X-ray absorptiometry (DXA) to assess bone mineral content (BMC) and density. However, DXA provides areal bone mineral density (BMD) measurements which, in children, are inherently biased by the size of the child, and have required software modifications due to the smaller size of the bones and surrounding soft tissue in younger children *(2)*. In recent years, there has been growing interest in the use of peripheral Quantitative Computed Tomography (pQCT) as an imaging tool because of its ability to assess both density and geometry, although it remains within the realm of research for pediatric

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*Address correspondence to: Babette Zemel, PhD, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, 3535 Market Street, Room 1560, Philadelphia, PA 19104-4399, USA. E-mail: zemel@email.chop.edu
[a]Task Force Chair.
[b]Task Force Member.
[c]Task Force Liaison.

patients. Unlike DXA, which is a two-dimensional imaging technique, pQCT provides authentic three-dimensional measures of trabecular and cortical volumetric BMD. Trabecular and cortical bone respond differently to stimuli such as pubertal changes, mechanical forces, and disease-related stresses. Therefore, it holds promise for more specific classification of abnormalities of bone mineral acquisition during childhood. Peripheral quantitative computed tomography also measures the geometric properties of long bones, offering measures of cortical dimensions and strength. Scan acquisition is rapid and radiation exposure is low, which are important characteristics for pediatric assessment. The limitations of pQCT use in children, and its utility in clinical assessment of osteoporosis in the pediatric population have not been established.

Dedicated pQCT devices are table top-sized pieces of equipment designed to measure peripheral sites such as the radius or tibia. The metaphyseal regions of long bones are rich in trabecular bone. The shafts of the long bones are almost entirely cortical bone. Peripheral quantitative computed tomography can easily obtain information from multiple regions of the long bone, with minimal radiation exposure. Since the majority of childhood fractures occur in the long bones, there is good rationale for obtaining measures of bone density and structure at these sites.

Peripheral quantitative computed tomography measurements in children present unique challenges due to smaller bone size; the presence of the growth plate; the changing size of the metaphysis with growth; and the problem of obtaining measurements in the same location in longitudinal studies of growing bone. In addition, since pQCT has mainly been used as a research tool at individual centers, scan acquisition procedures, analysis protocols, and outcome measures have not been standardized.

To assess the utility of pQCT in diagnostic assessment of children, the pQCT task force addressed the following general areas of concern:

I. What is the clinical application of pQCT in children and adolescents?
II. What are the important elements to be included in a pQCT report?
III. How should quality control be monitored?

Methodology

The task force developed a comprehensive bibliography of the pQCT literature in children. A literature search using PubMed was performed using the keywords, ''peripheral quantitative comput* tomography children'' to identify references. Further information was obtained from searching the abstracts from the American Society for Bone Mineral Research over the past 3 yr. Based on the literature review, preliminary position statements were developed by the task force and presented to an expert panel for evaluation. The methods used to develop, and the grading system applied to the International Society of Clinical Densitometry (ISCD) Official Positions, are presented in the Executive Summary that accompanies this paper. In brief, all positions were rated by the Expert Panel on quality of evidence (good; fair; poor: where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or information), strength of the recommendation (A; B; C: where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion), and applicability (worldwide = W or variable, according to local requirements = L). Necessity was also considered with a response of ''necessary'' indicating that the indication or procedure is ''necessary'' due to the health benefits outweighing the risk to such an extent that it must be offered to all patients and the magnitude of the expected benefit is not small.

What is the Clinical Application of pQCT in Children and Adolescents?

ISCD Official Positions

- Reference data are not sufficient for the clinical use of pQCT for fracture prediction or diagnosis of low bone mass.
  Grade: Fair-C-W-Necessary
- When the forearm is measured, the non-dominant forearm should be used.
  Grade: Fair-A-W-Necessary
- Measurements sites should include the metaphysis and diaphysis.
  Grade: Good-C-W-Necessary

Rationale

pQCT Devices and Software. The majority of pQCT studies in children have used Stratec XCT devices (model numbers XCT900, XCT2000, XCT3000). Only one study used the Stratec XCT3000 in children/adolescents. A smaller number of studies have used the Densiscan peripheral micro-CT device, but there are no pediatric studies that have used the newest generation scanner, the high resolution XTreme CT (Scanco Medical AG). Axial CT devices can also be used to measure the peripheral skeleton. Software used on the Stratec devices includes Versions 5.4 and 5.5 but whether there are differences in results obtained from different software versions (as in DXA) is not known. The BonAlyse software has also been applied to scans obtained on Stratec devices, but is used less commonly. The Densiscan device uses its own software. The Stratec and BonAlyse software permit the selection of analysis modes and thresholds. The

analysis modes and thresholds impact scan results (3), but are often not reported; consequently, comparisons between studies can be problematic.

Presently, there are no studies that have compared manufacturers, devices, and software versions for their impact on pediatric bone assessment. Their comparability is unknown. A comparison of results obtained on 19 adults measured using the Stratec XCT900 and XCT2000 devices showed variable agreement ($r = 0.82$ for the cross-sectional area; 0.81 for total vBMD; 0.97 for trabecular vBMD; 0.99 for total BMC; and 0.86 for polar stress strain index (SSI) at the 4% radius) (4). Another study of 87 adult women comparing the Stratec XCT900 and the XCT1400 obtained quite similar correlation coefficients (5). However, the amount of unexplained variance for some of the measures is a point of concern, and both studies demonstrated a consistent and significant difference between scanners. The impact of these important technical aspects on pediatric bone assessment is unknown.

pQCT Outcome Measures. Multiple outcome measures have been reported in pQCT studies of children. Table 1 defines the most commonly used outcome measures. The outcome measures are the same for the radius and tibia. The choice of an outcome measure depends on whether it is a metaphyseal or diaphyseal measurement. For example, trabecular bone can only be measured at the metaphysis as there is no trabecular bone at diaphyseal sites. There is no consensus as to which are the best outcome measures or measurement sites for pQCT.

Historically, the radius was measured by pQCT measurements because of its accessibility and vulnerability to fractures. However, the bones of children are smaller and thinner than those of adults, and are more subject to partial volume effects. Partial volume effect is related to the resolution of the image and the size of the object being measured. As depicted in Fig. 1, the bone image is compiled from the attenuation values of the X-ray beam for each voxel in the scan field (like grid sections). Voxels that are close to the edge of the bone are more likely to be comprised of both bone and soft tissue and will have a lower attenuation value than the voxels that are within the bone envelope and attenuated by bone only. Smaller bones will have a higher proportion of voxels that are close to the bone edge and may thereby appear to have a lower density. The tibia is larger than the radius, so some investigators have chosen the tibia for their measurement site to reduce partial volume effects. The tibia is also a weight-bearing limb and is less susceptible to movement artifacts, so there are several reasons why the tibia may be chosen for measurement.

Insufficiency of Reference Data. Available reference data: Optimally, pediatric reference data should meet several criteria. The sample should consist of healthy children who are representative of the population, with adequate representation of age and gender groups to characterize the range of normal variation. The data should be collected in more than one geographical site to be generalizable, and analyzed using appropriate statistical techniques to describe the distribution of values in the population. There are no pQCT reference data that meet these criteria. Published studies based on large groups of healthy children can be used for comparative purposes, but do not meet the criteria for reference data.

There are no studies that have evaluated the differences between pQCT devices by manufacturer or different models by the same manufacturer. Nor have differences in software been evaluated. The use of published data, even for comparative purposes, should be done with care; the same manufacturer, scan acquisition, and analysis protocols should be used. There are no data to determine which regions of interest are optimal for use in children for determining fracture risk, or identifying disease or treatment-related effects on bone health. Nevertheless, the published comparative data offer values, based on healthy children, at sites located in the metaphysis and diaphysis of the radius and tibia.

The published pediatric pQCT data that can be used for comparative purposes are summarized in Table 2 and described below.

The DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) Study (6–10) obtained measurements at the distal (4% site), and proximal (65% site) radius, using the Stratec XCT2000, in 371 Caucasian children in Germany ages 6–23 yr. Measurements in the distal radius included total cross-sectional area (CSA), total volumetric BMD, trabecular volumetric BMD, and cortical plus subcortical BMD. Measurements in the proximal radius included total CSA; cortical CSA; marrow CSA (equivalent to total CSA minus cortical CSA); total bone mineral content (BMC); total volumetric BMD; cortical BMC; cortical BMD; muscle CSA; and stress-strain index (SSI). These measures were generated by the manufacturer's software.

Data from the UK (11) (Abstract only) are based on 435 Caucasian subjects, 5 to 18 yr of age, with measurements obtained at the distal and mid-shaft sites (exact site not reported in abstract). The distal radius total and trabecular volumetric BMD were reported.

In the US, Binkley et al. (12) published reference data using the XCT2000 in 231 mostly Caucasian children, 5 to 22 yr of age, at the 20% distal tibia site. Centile curves based on the same statistical methodology used to construct the Centers for Disease Controls 2000 growth charts (13) were published for periosteal and endosteal circumferences and cortical volumetric BMD. Curves for cortical volumetric BMD were only produced for a subset ($n = 138$) that had mean cortical thickness greater than 2 mm, due to concerns regarding partial volume effects.

Several other studies offer data on samples with limited age ranges. These include Wang et al. (14–17) and Suuriniemi et al. (18,19) with distal radius (4% site) and tibial shaft (60% site) data on 207 girls, 10–13 yr of age, with the following measurements of the distal radius: total CSA; total BMC; total volumetric BMD; and trabecular volumetric BMD; and tibial shaft; total CSA; total BMC; total volumetric BMD; cortical CSA; cortical thickness; cortical volumetric BMD; marrow CSA (defined as the region in the center of the bone area with a density less than 100 mg/cm^3); cortical and marrow proportion (the ratio of cortical CSA to total CSA and the ratio of marrow

Table 1
pQCT Outcome Measures and Their Meaning

Name	Meaning
Bone mineral content and bone mineral density parameters	
Total content	Total bone mineral content [mg]
Total density	Total volumetric bone mineral density [mg/cm^3]
Trabecular content	Bone mineral content [mg] of the trabecular bone (metaphyseal sites only)
Trabecular density	The volumetric bone mineral density [mg/cm^3] of trabecular bone (metaphyseal sites only). Note that this includes the bone marrow fat that is interspersed within the trabecular bone
Cortical content	Bone mineral content [mg] of the cortical bone
Cortical density	Volumetric bone mineral density [mg/cm^3] of the cortical bone
Geometric parameters	
Total area	Total cross sectional area [mm^2] of the bone
Trabecular area	Cross sectional area [mm^2] of the trabecular portion of the total bone area
Cortical area	Cross sectional area [mm^2] of the cortical portion of the total bone area
Cortical thickness	The average thickness [mm] of the cortical shell
Marrow cross-sectional area	Total area minus cortical area, [mm^2]
Periosteal circumference	Periosteal circumference [mm] or outer diameter of bone
Endosteal circumference	Endosteal circumference [mm] or inner diameter of bone
Cross sectional moment of inertia	Cross-sectional moment of inertia [mm^4]: $\pi/4(R_o^4 - R_i^4)$, where R_o = the outer radius and R_i = the inner radius, indicative of bending strength
Polar moment of inertia	Polar moment of inertia [mm^4]: $\pi/2(R_o^4 - R_i^4)$, where R_o = the outer radius and R_i = the inner radius, indicative of strength in torsion
Section modulus	Section modulus [mm^3]: Polar moment of inertia/max distance to the centroid, indicative of shearing strength
Strain strength index	Strain Strength Index [mm^4]: Density weighted polar moment of inertia
Bone strength index	Total area $\times$ Total density^2

CSA to total CSA, respectively); muscle cross-sectional area (MCSA); and cross-sectional moment of inertia (CSMI). Macdonald et al. *(20)* and Kontulainen et al. *(21,22)* report on the tibial midshaft (50% site) for 128 multi-ethnic children ages 10−12 yr followed over 20 mo. Their primary outcomes were total CSA, cortical CSA, cortical volumetric BMD, cortical thickness, section modulus, and MCSA. Macdonald et al. *(23,24)* also reported on the distal tibia (8% site) and tibial shaft (50 and 66% sites) in 424 children, 9−11 yr of age. Distal measures included total CSA, total volumetric BMD, bone strength index (BSI), and tibial shaft measures included cortical CSA, cortical volumetric BMD, SSI, and MCSA.

The comparative data described above have several shortcomings. The measurement sites and protocols are not always well-described or standardized, and the majority of studies either have a large representation of children in a narrow age range, or a large age range with small sample sizes within each chronological age/sex category. The degree to which these samples are representative is not known. It should also be noted that the samples are composed mainly of Caucasian children, and maturity data are not available for all studies.

Use of the Dominant vs Non-Dominant Limb. The majority of studies of the radius measured the non-dominant forearm. Studies of the tibia report either the left limb *(12,14−30)*, the non-dominant limb *(31−37)* or the right limb *(38)*. A number of studies did not report which limb was scanned *(39−42)*. Studies of athletes have documented differences in pQCT-derived bone properties between dominant and non-dominant limbs *(43,44)*. Anthropometric data indicate greater asymmetry for the upper limbs with a systematic right-bias in all dimensions (lengths, breadths), while lower limbs have biases close to zero *(45)*.

The studies of athletes suggest that for the forearm, the non-dominant limb should be measured, however there is no supporting evidence for limb choice based on the clinically important outcome of fracture. For the tibia, there is inadequate evidence to support the use of the dominant vs non-dominant limb for the tibia, and there is little difference between them. Further research is needed to determine whether the dominant vs non-dominant limb is optimal for clinical assessment.

Measurement Sites at the Metaphysis and Diaphysis. Unlike DXA, pQCT has the ability to obtain distinct estimates of trabecular and cortical bone. Measures of trabecular density are obtained from the metaphyseal sites of the radius or tibia, and cortical measures are derived from the diaphyseal sites. Trabecular and cortical bone respond differently to the influences

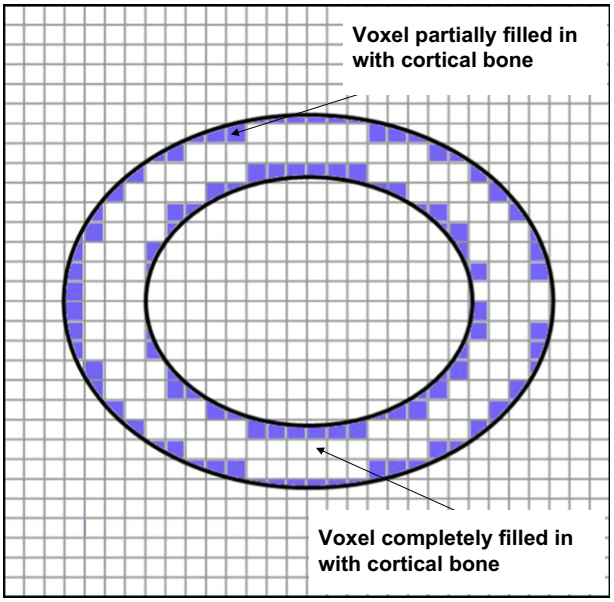

Fig. 1. Partial volume effect is due to the fact that voxels located close to the bone edge are more likely to be comprised of both bone and soft tissue. Voxels that overlap bone and soft tissue will have a lower density value than the voxels that are attenuated by bone only within the bone envelope. Smaller bones will have a higher proportion of voxels close to the bone edge and may thereby appear to have a lower density due to this artifact.

of growth, maturation, physical activity, disease processes, and treatments, so clinical assessment should include measurements in both of these long-bone regions. As noted above, there is no consistency in the literature regarding the optimal site for the regions of interest for either the radius or the tibia in children. One study of adult subjects showed that the precision of pQCT measurements varied by site, limb, and outcome measure. Using phantoms, they also showed that the surrounding soft tissue altered the precision of the measurements, especially for volumetric BMD and BMC outcomes *(46)*. Precision, sources of error and clinical relevance should all be considered in the choice of an optimal outcome.

Animal *(47–49)* and human ex vivo studies with mature bone *(50,51)* elucidate the clinical relevance of pQCT estimates of bone strength such as the BSI and polar SSI, which incorporate measures of bone geometry (CSA or CSMI) and volumetric BMD at various sites using breaking or bending tests as a criterion. At the tibial midshaft, bone geometry measures (total or cortical CSA, section modulus) were strongly associated with failure load of cadaveric specimens from elderly individuals, whereas cortical volumetric BMD was not associated with failure *(52)*. At the radius, mechanical properties (compressive strength, bending strength) were closely associated with either total or cortical BMC *(50,53,54)*. The only study to compare pQCT parameters in children with and without fractures was conducted in otherwise healthy girls with forearm fractures. The study demonstrated that trabecular volumetric BMD in the radius did not differ between fracture and non-fracture patients, however cortical cross-sectional area provided good fracture discrimination *(55)*. It is not known if this finding is generalizable to children with bone deficits due to chronic disease.

Use and interpretation of cortical measures should be done with care since cortical bone is subject to partial volume effect at measurement sites where the cortical thickness is less than 2.5 mm *(25,56,57)*, and a voxel size of 0.4 mm is used in the scan acquisition. At the distal radius, the cortical thickness is too small for meaningful measurements of cortical volumetric BMD. Several techniques have been proposed for adjusting for partial volume effect in estimating cortical density *(58–60)*, however none have been validated. Bone turnover rates also affect cortical volumetric BMD: greater turnover is associated with lower density *(61)*.

Although trabecular volumetric BMD at peripheral sites has not been associated with fracture discrimination, it can be useful in identifying disease-related deficits and treatment effects. Reduced trabecular volumetric BMD has been reported in some pediatric disease groups *(31,62–64)*. It is important to note that trabecular volumetric BMD measurements are sensitive to the site of measurement. Lee et al. *(65)* demonstrated that the length of the tibia metaphysis is highly variable in children, and trabecular volumetric BMD varied from 0.41 to 7.2 mg/cm^3 along the length of the metaphysis. For the distal radius, Rauch et al. *(66)* also found highly significant differences in total and trabecular volumetric BMD, CSA and BMC among adjacent pQCT slices close to the 4% site. These data underscore the importance of identifying the optimal and most consistent site for measuring trabecular volumetric BMD and adherence to strict protocol guidelines.

In summary, pQCT measurements of the metaphysis and diaphysis have both been shown to be associated with fracture load or fracture discrimination in pediatric and adult clinical studies, and in experimental animal and cadaver studies. Trabecular density can be useful in assessing disease or treatment related effects on trabecular bone. The measurements obtained at the metaphysis and diaphysis offer distinct and valuable kinds of information about bone structure and strength. Further research is needed to determine the performance of pQCT to identify children at risk of fracture and the optimal measurement parameter(s).

Discussion

Peripheral quantitative computed tomography has mainly been used as a research tool in children. The research to date has not provided much of the information needed to establish pQCT as a diagnostic tool for pediatric patients. The comparability of pQCT devices and software versions is unknown. In the research setting, this may be of little consequence in study designs involving a local control group or changes within individuals over time. However, in the clinical setting, reference data are needed to interpret pQCT results in growing children. Most centers are not able to take on the time and expense of developing local reference data and are

Table 2
Published pQCT Values for Healthy Children

Studies	Age and gender distribution	Skeletal site	pQCT manufacturer and model	Reference data
Ref (9) Neu Bone 2001	186 ♀, 185 ♂ 6-23 years	4% distal radius (non dominant) 2 mm slice Voxel size 0.4 mm, scan speed: 15 mm/s	Stratec XCT2000	Girls: 6-7 yr TotBMD 290 ± 36, TrBMD 191 ± 31, CortBMD 370 ± 45; 8-9 yr 283 ± 22, 186 ± 23, 362 ± 32; 10-11 yr 281 ± 36, 191 ± 36, 355 ± 44; 12-13 yr 295 ± 39, 197 ± 32, 376 ± 54; 14-15 yr 303 ± 37, 179 ± 25, 407 ± 53; 16-17 yr 350 ± 57, 186 ± 26, 483 ± 95; 18-23 yr 371 ± 50, 195 ± 35, 516 ± 74 Boys: 6-7 yr TotBMD 306 ± 34, TrBMD 206 ± 32, CortBMD 388 ± 42; 8-9 yr 294 ± 34, 189 ± 34, 380 ± 41; 10-11 yr 290 ± 33, 194 ± 32, 368 ± 41; 12-13 yr 292 ± 38, 201 ± 36, 366 ± 47; 14-15 yr 293 ± 35, 201 ± 33, 369 ± 47; 16-17 yr 349 ± 56, 217 ± 30, 458 ± 86; 18-23 yr 401 ± 60, 220 ± 42, 549 ± 83 Total CSA (mm²): Girls / Boys 6-7 yr 164 ± 30 / 174 ± 31 8-9 yr 185 ± 25 / 211 ± 31 10-11 yr 237 ± 39 / 245 ± 37 12-13 yr 260 ± 55 / 289 ± 47 14-15 yr 297 ± 32 / 351 ± 70 16-17 yr 300 ± 45 / 358 ± 49 18-23 yr 295 ± 42 / 377 ± 64 Data also available according to pubertal stage (Tanner Stage 1 to 5)
Ref (69) Schoenau JCEM 2000	159 ♀, 159 ♂ 6-22 years	65% proximal radius	Stratec XCT2000	No numerical data
Ref (6) Schoenau Bone 2002	185 ♀, 177 ♂ 6-23 years 159 ♀, 151 ♂ 6-23 years Tanner stage (TS) 1 to 5	65% proximal radius 2 mm slice Voxel size 0.4mm	Stratec XCT2000	Girls: 6-7 yr Cort BMD 942 ± 47, Cortical thickness 1.15 ± 0.39; 8-9 yr 1004 ± 50, 1.68 ± 0.35; 10-11 yr 1021 ± 37, 1.84 ± 0.40; 12-13 yr 1037 ± 47, 2.14 ± 0.51; 14-15 yr 1093 ± 27, 2.38 ± 0.35; 16-17 yr 1106 ± 26, 2.42 ± 0.31; 18-23 yr 1134 ± 27, 2.42 ± 0.34; TS1 981 ± 54, 1.44 ± 0.41; TS2 1010 ± 33, 1.81 ± 0.23; TS3 1035 ± 48, 2.02 ± 0.30; TS4 1068 ± 24, 2.34 ± 0.33; TS5 1112 ± 30, 2.50 ± 0.34 Boys: 6-7 yr Cort BMD 975 ± 45, Cortical thickness 1.45 ± 0.31; 8-9 yr 1008 ± 31, 1.71 ± 0.21; 10-11 yr 1025 ± 37, 1.78 ± 0.26; 12-13 yr 1018 ± 42, 1.85 ± 0.28; 14-15 yr 1031 ± 50, 2.27 ± 0.46; 16-17 yr 1172 ± 32, 2.63 ± 0.35; 18-23 yr 1116 ± 32, 2.74 ± 0.44; TS1 998 ± 47, 1.58 ± 0.31; TS2 1024 ± 40, 1.80 ± 0.27; TS3 1027 ± 33, 1.96 ± 0.42; TS4 1020 ± 39, 2.16 ± 0.31; TS5 1077 ± 48, 2.61 ± 0.47
Ref (7) Schoenau JCEM 2001	185♀, 177 ♂ 6-23 years 158♀, 151♂ 6-23 years Tanner stage (TS) 1 to 5	65% proximal radius Single slice 2 mm Voxel size 0.4 mm	Stratec XCT2000	Cortical BMC (mg/mm): Girls / Boys 6-7 yr 29 ± 8 / 36 ± 8 8-9 yr 43 ± 10 / 47 ± 6 10-11 yr 52 ± 12 / 53 ± 9 12-13 yr 64 ± 19 / 58 ± 9 14-15 yr 76 ± 11 / 75 ± 18 16-17 yr 81 ± 11 / 90 ± 15 18-23 yr 81 ± 13 / 105 ± 16 TS1 40 ± 12 / 46 ± 12 TS2 50 ± 15 / 59 ± 9 TS3 55 ± 8 / 60 ± 10 TS4 70 ± 8 / 71 ± 14 TS5 82 ± 12 / 94 ± 20 Data available for polar movement of inertia, section modulus and strength strain index

(*Continued*)

Table 2
(Continued)

Studies	Age and gender distribution	Skeletal site	pQCT manufacturer and model	Reference data
Ref (8) Neu OI 2001	185 ♀, 177 ♂ 6-23 years Tanner stage only: 162 ♀, 153 ♂ 6-23 years Tanner stage (TS) 1 to 5	65% proximal radius Single slice 2 mm Voxel size 0.4 mm	Stratec XCT2000	Girls: Co.Th (mm) / BMC (mg/mm) / BMD (mg/cm²) 6-7 yr: 1.15 ± 0.39 / 47 ± 6 / 517 ± 84 8-9 yr: 1.68 ± 0.35 / 57 ± 9 / 615 ± 90 10-11 yr: 1.84 ± 0.40 / 65 ± 12 / 619 ± 89 12-13 yr: 2.14 ± 0.51 / 77 ± 19 / 662 ± 97 14-15 yr: 2.38 ± 0.35 / 89 ± 11 / 722 ± 88 16-17 yr: 2.42 ± 0.31 / 94 ± 12 / 717 ± 66 18-23 yr: 2.42 ± 0.34 / 93 ± 12 / 749 ± 78 TS1: 1.50 ± 0.43 / 55 ± 10 / 577 ± 93 TS2: 1.81 ± 0.39 / 65 ± 14 / 607 ±102 TS3: 1.98 ± 0.30 / 68 ± 10 / 648 ± 72 TS4: 2.33 ± 0.34 / 82 ± 9 / 713 ± 85 TS5: 2.49 ± 0.34 / 95 ± 13 / 739 ± 75 Boys: Co.Th (mm) / BMC (mg/mm) / BMD (mg/cm²) 6-7 yr: 1.45 ± 0.31 / 52 ± 8 / 579 ± 70 8-9 yr: 1.71 ± 0.21 / 61 ± 6 / 601 ± 57 10-11 yr: 1.78 ± 0.26 / 68 ± 9 / 596 ± 68 12-13 yr: 1.85 ± 0.28 / 73 ± 9 / 589 ± 82 14-15 yr: 2.27 ± 0.46 / 91 ± 17 / 645 ± 92 16-17 yr: 2.63 ± 0.35 / 105 ± 16 / 720 ± 66 18-23 yr: 2.75 ± 0.41 / 121 ± 16 / 719 ± 82 TS1: 1.64 ± 0.32 / 61 ± 11 / 593 ± 70 TS2: 1.88 ± 0.31 / 74 ± 9 / 597± 79 TS3: 1.84 ± 0.35 / 75 ± 8 / 574 ± 80 TS4: 2.22 ± 0.32 / 87 ± 16 / 640 ± 66 TS5: 2.61 ± 0.47 / 111 ± 19 / 700 ± 90 Data available for cortical area, marrow area, outer bone radius, and marrow radius
Ref (10) Schoenau JBMR 2002	183 ♀, 166 ♂ 6-19 years Tanner stage (TS) 1 to 5	65% proximal radius (ND) Single slice 2 mm Voxel size 0.4 mm	Stratec XCT2000	Height / Girls muscle CSA (cm²) / Boys muscle CSA (cm²) 120 - 129 cm: 15.8 ± 1.4 / 17.1 ± 2.0 130 - 139 cm: 18.1 ± 2.4 / 20.3 ± 2.5 140 - 149 cm: 20.8 ± 2.5 / 22.4 ± 3.7 150 - 159 cm: 24.8 ± 3.0 / 24.6 ± 4.0 160 - 169 cm: 27.4 ± 3.5 / 30.5 ± 4.8 170 - 179 cm: 28.0 ± 3.3 / 36.6 ± 6.3 180 - 189 cm: / 40.8 ± 5.1 Ratio BMC (mg/mm) / muscle CSA (cm²) Girls / Boys 6-7 yr: 2.59 ± 0.29 / 2.54 ± 0.34 8-9 yr: 2.62 ± 0.38 / 2.55 ± 0.31 10-11 yr: 2.59 ± 0.35 / 2.58 ± 0.43 12-13 yr: 2.64 ± 0.40 / 2.47 ± 0.43 14-15 yr: 2.90 ± 0.35 / 2.39 ± 0.32 16-17 yr: 2.91 ± 0.31 / 2.36 ± 0.26 18-19 yr: 2.96 ± 0.36 / 2.44 ± 0.26
Ref (95) Rauch and Schoenau 2005	173 ♂ and 185 ♀, under 21	See Neu 2001	Stratec XCT2000	Reference curves
Ref (11) Ashby suppl JBMR 2006	6-17 years			Unpublished
Ref (12) Binkley 2002	107 ♂ and 124 ♀ 5-22 years	20% distal tibia (no scout view)	Stratec XCT2000 2000 Stratec software 5.40 Rev. B Scanning parameters fixed at the time the scan is taken	Centile curves (using the LMS st atistical method) for endosteal and periosteal circumferences, total cortical area, cortical density No numeric data provided
Ref (17) Wang JCEM 2004	248 ♀ 10-13 years Mean ± SD: 11.2 ± 0.7 yrs	60% tibial shaft 2mm slice, voxel size 0.59 mm (60% of lower leg length up from the lateral malleolus) Left side Bonalyse 1.3	Stratec XCT2000 Stratec software 5.40	Total CSA (mm²): 364 ± 54 Cortical CSA (mm²): 198 ± 31 Cortical thickness (mm): 3.45 ± 0.40 Total vBMD (mg/cm³): 665 ± 48 Cortical vBMD (mg/cm³): 1042 ± 54
Ref (14) Wang JCEM 2006	258 ♀ 10-13 years	60% tibial shaft 2 mm slice, voxel size 0.59 mm	Stratec XCT2000 Stratec software 5.40	No numeric data provided

(*Continued*)

Table 2
(Continued)

Studies	Age and gender distribution	Skeletal site	pQCT manufacturer and model	Reference data
Ref (15) Wang ScJMSS 2005	242 ♀ 10-12 years Tanner Stage 1 and 2	60% tibial shaft 2 mm slice, voxel size 0.59 mm	Stratec XCT2000 Stratec software 5.40	Data reported for Tanner 1 and 2 and according to the loading of favourite activity Tanner Stage 1 — Low-impact — High -impact CSA (mm^2) 259 ± 33 — 268 ± 38 BMC (mg) 225 ± 28 — 238 ± 36 vBMD (mg/cm^3) 853 ± 41 — 868 ± 31 Polar moment inertia (g.mm) 1639 ± 443 — 1754 ± 587 CoBMD (mg/cm^3) 975 ± 34 — 989 ± 28 Co.Th (mm) 3.27 ± 0.38 — 3.46 ± 0.37 Tanner Stage 2 — Low-impact — High -impact CSA (mm^2) 301 ± 36 — 299 ± 27 BMC (mg) 264 ± 31 — 262 ± 26 vBMD (mg/cm^3) 857 ± 37 — 848 ± 32 Polar moment inertia (g.mm) 2266 ± 550 — 2201 ± 439 CoBMD (mg/cm^3) 980 ± 31 — 970 ± 27 Co.Th (mm) 3.57 ± 0.37 — 3.56 ± 0.33 Data also available according to the amount of physical activity (low, moderate, high)
Ref (94) Wang JBMR 2005	258 ♀ 10-13 years	4% distal radius + 60% tibial shaft 2 mm slice, voxel size 0.59 mm	Stratec XCT2000 Stratec software 5.40	Distal radius — Mean (95% CI) Total CSA (mm^2) 270 (176-364) BMC (mg/mm) 77.3 (55.6-98.0) Total vBMD (mg/cm^3) 290 (221-358) Tibial shaft — Mean (95% CI) Total CSA (mm^2) 415 (319-511) Total BMC (mg/mm) 294 (226-362) Total vBMD (mg/mm^3) 709 (615-803) Cortical CSA (mm^2) 238 (181-295) Cortical thickness (mm) 3.97 (3.23-4.71) Cortical vBMD (mg/mm^3) 1081 (1039-1133)
Ref (18) Suuriniemi Bone 2006	247 ♀ 10-13 years	4% distal radius 60% tibial shaft (60% of lower leg length up from the medial malleolus)	Stratec XCT2000 BonAlyse software	Results reported according to polymorphism COL1A1 gene (GG n=175, GT n=68 or TT n=4) Tibia — GG — GT — TT CSA (mm^2) 370 ± 2 — 377 ± 4 — 352 ± 16 Co.Th (mm) 3.46 ± 0.02 — 3.43 ± 0.04 — 3.23 ± 0.16 vBMD (mg/cm^3) 667 ± 4 — 658 ± 6 — 654 ± 24 Radius — GG — GT — TT CSA (mm^2) 227 ± 3 — 228 ± 5 — 219 ± 20 vBMD (mg/cm^3) 288 ± 3 — 286 ± 4 — 264 ± 18 TrBMD (mg/cm^3) 226 ± 2 — 225 ± 3 — 199 ± 14
Ref (19) Suuriniemi JBMR 2004	245 ♀ 10-13 years	4% distal radius 60% tibial shaft	Stratec XCT2000 BonAlyse software	No numeric data
Ref (20) Macdonald Bone 2005	69 ♀ 11.9 ± 0.6 yrs 60 ♂ 12.0 ± 0.6 yrs	50% tibial midshaft (50% proximal to the distal endplate) Slice 2.3 ± 0.2 mm Voxel size 0.5 mm^2 Scan speed 30 mm/s	Stratec XCT2000	Results reported according to maturity status ♀ early: premenarcheal at baseline and 20 months later (11.6 ± 0.5 years) ♀ peri: premenarcheal at baseline, postmenarcheal at 20 months (11.9 ± 0.6 years) ♀ post: postmenarcheal at baseline (12.3 ± 0.5 years) ♂ early: advanced to Tanner Stage 2 or 3 during follow-up (11.7 ± 0.6 yrs) ♂ peri: advanced to Tanner Stage 4 during follow-up (12.0 ± 0.6 years) ♂ post: advanced to Tanner Stage 5 during follow-up (12.3 ± 0.4 years) Girls — ToA (mm^2) — CoA (mm^2) — Co.Th (mm) Early 310.8 ± 56.0 — 201.1 ± 33.2 — 4.1 ± 0.5 Peri 361.1 ± 61.4 — 239.3 ± 44.4 — 4.5 ± 0.6 Post 360.0 ± 52.6 — 244.8 ± 41.7 — 4.7 ± 0.6 Boys — ToA (mm^2) — CoA (mm^2) — Co.Th (mm) Early 329.8 ± 45.9 — 211.0 ± 31.3 — 4.1 ± 0.5 Peri 377.2 ± 50.9 — 246.5 ± 35.8 — 4.5 ± 0.5 Post 415.8 ± 97.2 — 270.6 ± 67.3 — 4.7 ± 0.8 Data also available for the section modulus, CoA/MCSA and strength index/MCSA
Ref (22) Kontulainen JCEM 2006	68 ♀, 59 ♂ 11.9 ± 0.6 yrs	50% tibial midshaft	Stratec XCT2000	Cortical density (mg/cm^3) — Girls — Boys Early 1027.8 ± 33.9 — 1007.0 ± 38.2 Peri 1018.5 ± 37.9 — 993.1 ± 32.1 Post 1063.5 ± 24.2 — 971.9 ± 31.4

(*Continued*)

Table 2
(Continued)

Studies	Age and gender distribution	Skeletal site	pQCT manufacturer and model	Reference data
Ref (24) Macdonald JBMR 2007	65 ♀ 10.3 ± 0.5 yrs 64 ♂ 10.3 ± 0.6 yrs	8% distal tibia (8% from the distal endplate) 50% tibial shaft	Stratec XCT2000	Distal tibia only (for the shaft: see Ref 45, 47 and 48) Girls / Boys CSA (mm^2) 503.4 ± 80.0 / 548.1 ± 88.1 ToD (mg/cm^3) 292.8 ± 32.3 / 311.6 ± 32.2 Bone Strength Index (mg^2/mm^4) 4351.2 ± 1136.0 / 5322.7 ± 1136.7 Data available for the polar strength-strain index at the midshaft
Ref (23) MacDonald Bone 2006	424 pre- and early pubertal boys and girls 9-11 yrs	8% distal tibia 50% tibial shaft Left tibia 2.3 mm slice Voxel size 0.4 mm^2, scan speed 30 mm/s Muscle CSA at 66% proximal tibia	Stratec XCT2000	Data reported according to pubertal stage Pre: Tanner Stage 1; E arly: Tanner Stage 2 or 3 Distal tibia (Bone Strength Index also available) CSA (mm^2) Girls / Boys Pre 489.9 ± 71.1 / 541.6 ± 85.3 Early 526.3 ± 76.4 / 559.2 ± 90.4 ToD (mg/cm^3) Girls / Boys Pre 286.4 ± 32.7 / 309.8 ± 30.8 Early 297.7 ± 34.7 / 303.7 ± 31.9 Tibial midshaft (Strength Strain Index also available) CoA (mm^2) Girls / Boys Pre 174.2 ± 28.7 / 196.2 ± 34.0 Early 196.2 ± 27.9 / 200.5 ± 29.3 CoD (mg/cm^3) Girls / Boys Pre 1060.4 ± 30.2 / 1046.8 ± 36.6 Early 1052.5 ± 32.3 / 1045.6 ± 31.4 Tibia 66% Muscle CSA (mm^2) Girls / Boys Pre 3120.4 ± 495.0 / 3418.4 ± 523.7 Early 3445.2 ± 539.9 / 3444.4 ± 495.6
Ref (32) Ward Bone 2005	22 ♀ 8.7 ± 1.7 yrs 20 ♂ 8.9 ± 1.6 yrs	4% and 50% radius Tibia: 10 mm proximal to the distal surface of the distal metaphysis + 65% tibial shaft Non dominant	Stratec XCT2000	Shafts Radius / Tibia ToA (mm^2) 73 ± 12 / 328 ± 63 CoA (mm^2) 45.5 ± 7.2 / 153 ± 30 CoD (mg/cm^3) 1035 ± 33 / 973 ± 28 Co.Th (mm) 1.88 ± 0.27 / 2.80 ± 0.45 MedA (mm^2) 27.7 ± 8.9 / 175 ± 46 Muscle CSA (mm^2) 1400 ± 260 / 3530 ± 700 Epiphyses Radius / Tibia TrD (mg/cm^3) 167 ± 28 / 203 ± 26 ToD (mg/cm^3) 328 ± 41 / 282 ± 27 ToA (mm^2) 142 ± 32 / 580 ± 122
Ref (38) Heinonen Osteopor Int 2000	62 pre- (11.0 ± 0.9 yrs) and postmenarcheal (13.7 ± 1.0 yrs) girls	50% tibial midshaft	Stratec XCT3000	Girls Premenarcheal / Postmenarcheal CoD (mg/cm^3) 1024.7 ± 32.3 / 1066.4 ± 25.0 CoA (mm^2) 196.1 ± 24.6 / 245.9 ± 36.5 Bone Strength Index (mm^3) 936.5 ± 166.4 / 1313.0 ± 297.4

therefore dependent on published data. Under these circumstances, the comparability of devices and software versions are of the utmost importance, since poor agreement between devices or software versions can lead to misdiagnosis of children with bone deficits.

Childhood growth experts are well aware of the requirements for reference data for clinical interpretation *(67)*. Like many other aspects of childhood growth, bone density, geometry, and architecture increase as children grow, and the variability in these measures also changes with age. Presently, there are no reference data for pQCT outcome measures that are based on a sufficiently large representative sample of healthy children to adequately characterize the age and gender-specific distributions of BMD, bone geometry, and strength. Many published studies are available that include healthy children and an assortment of outcome measures. These represent comparative data, but should not be considered reference data.

A wide array of pQCT outcome measures have been reported. Generally, these fall into the broad categories of bone density, bone geometry, and bone strength. For the researcher, this broad selection offers opportunities for assessing many aspects of bone deficits, but in the clinical setting a reduced number of relevant outcome measures with guidelines for their interpretation are needed. Deficits of cortical and trabecular bone may have different etiologies and respond differently to treatment. Accordingly, we recommend measurements at the metaphysis and diaphysis so that both bone compartments are assessed as part of the pQCT assessment. The optimal site for measurement has yet to be determined, and many regions of interest have been described. The rationale for the selection of measurement sites is frequently overlooked. The radius is easily accessible, a site of common fracture, and has been described in comparative studies of healthy children and children with chronic diseases. However, the smaller bone of the radius is subject to partial

volume effect, to the extent that the cortical density measure is not usable in young children or children with thin bones. When measuring the radius, the non-dominant limb should be measured because of the asymmetry that can develop in the upper limbs due to handedness. The tibia is a weight-bearing limb with no dominant vs non-dominant bias. It is also a larger bone that is less susceptible to partial volume effect. However, further research is needed to determine the site of measurement and the outcome measure that yields the most clinically relevant information.

What are the Important Elements to be Included in a pQCT Report?

ISCD Official Positions

pQCT reports should include:

- Manufacturer, model and software version
- Referring physician
- Patient age, gender, race/ethnicity, weight, and height
- Relevant medical history including previous fractures
- Indication for measurement
- Bone age results, if available
- Measurement site
- Limb length
- Scan acquisition and analysis parameters.
  (specific to this recommendation only; Grade: Fair-B-W-Necessary)
- Scan technical quality.
  (specific to this recommendation only; Grade: Fair-B-W-Necessary)
- Reference data source for Z-score calculation.
  (specific to this recommendation only; Grade: Fair-B-W-Necessary)
- Metaphyseal total and trabecular volumetric BMD and Z-scores
- Diaphyseal BMC; cortical volumetric BMD; cortical thickness; cross-sectional moment of inertia; SSI results; and Z-scores (specific to this recommendation only; Grade: Fair-B-W-Necessary)
- Adjustments made for growth and maturation
- Interpretation

Grade: Good-C-W-Necessary.

Rationale

Very few centers currently use pQCT for clinical evaluations. Generally, a pQCT report should contain the same patient information that is required of a DXA report since these elements are important for interpretation of results with pediatric patients.

General information should include date of test and dates of previous tests (if any), and the referring physician. Patient specific information should include demographic information (age, gender, race), growth assessment (height; height percentile; weight; weight percentile; body mass index; BMI percentile; limb length; Tanner stage; and/or bone age), and medical information (relevant medical history; indication for measurement; medications; age; and site of previous fracture). Technical aspects of scan acquisition, analysis parameters, technical quality, and limitations should also be reported. The reporting of results should include the reference data source; metaphyseal total and trabecular volumetric BMD and Z-score; diaphyseal; BMC; CSA; volumetric BMD; cortical thickness; CSMI; SSI; and Z-scores.

Key Elements

pQCT Devices and Software

As noted above, the most widely used pQCT devices are the Stratec XCT devices (model numbers XCT900, 2000, 3000), but other pQCT devices are also available. The comparability of pQCT devices and software versions is unknown. Until further studies are done and the impact of these important technical aspects of pediatric bone assessment are known, it is essential to report the device and software used for scan acquisition, processing, and analysis.

Growth and Development

Growth assessment is an absolutely essential element of the pQCT evaluation since bone length is a significant determinant of cortical measures *(41,68)*. Measures of bone size and geometry are proportional to the length of the bone, so children with smaller bones will have lower values for measures such as cortical thickness, periosteal and endosteal circumference, and SSI. Most reference data are presented relative to age rather than limb length however, so interpretation of size-dependent pQCT measures in children with advanced or delayed growth is problematic. Characterizing overall growth status through the use of height, weight, and BMI percentiles is useful for identifying patients with growth abnormalities and interpreting pQCT results. Sexual and skeletal maturation also aid in the interpretation of pQCT results. Density of the distal radius increases with menarche in girls *(16)*, and as puberty progresses in boys *(60)*. Cortical measures are also influenced by pubertal stage *(69)*. Although there are little data available on skeletal age, epiphyseal closure is associated with an increase in cortical volumetric BMD *(60,70)*. Skeletal age is also a good marker of the biological age of the patient and therefore can aid in the overall interpretation of bone results.

The expected changes in pQCT measures attributable to growth and development necessitate the use of reference data for interpretation of pQCT results. Because pQCT measures change as children age and growth proceeds, a test result is of little value unless it is compared to a reference to determine whether it is within a normal range. As noted above, there are no sources of data that meet the requirements of appropriate ''reference'' data, but there are data describing healthy children that can be used for comparative purposes. Extreme care should be used in the scan protocol to be sure that the equipment; software; limb length measurements; reference line placement; region of interest site; scan acquisition; and analysis parameters are the same as those used to generate the comparative data.

The reference data source and Z-scores relative to gender and age or body size should be reported.

Scan Acquisition and Analysis Parameters

There are numerous aspects of scan acquisition and analysis that affect pQCT outcomes. The first concern is the region of interest, which needs to be consistent with the reference or comparison data being used, and with any previous assessment of the patient. Identifying the region of interest for the pQCT image is complex and challenging in the immature skeleton.

Regions of interest are obtained in fixed (i.e., millmeters (mm)) or relative distances (i.e., percent of bone length) from a reference line. For consistency in identifying relative distances, standardized and accurate procedures for measuring the limb length are required. This should be done with proper instruments and by trained personnel. A reference point on the scout view also needs to be clearly defined and identifiable so that relative distances from the reference point can be accurately measured. The developmental changes that occur in the epiphysis with skeletal maturation make it difficult to identify the same reference point among children of different ages and maturational stages, and for the same child over time. Skilled technicians familiar with these developmental changes are needed for pediatric assessments.

In pediatric studies, there is a lack of consistency in reference line placement and reporting of landmarks used to identify the reference point. At the radius, the landmarks include the midpoint of the distal endplate *(36,37)*, the radial epiphyseal plate *(71)*, or the most proximal part of the articular surface of the radius *(72)*. One group of investigators set the reference line in a different place according to whether the radial growth plate was open or closed *(9,73)*. Many pQCT studies of the radius did not give sufficient details regarding reference line placement *(6–8,10,32,39,42,60,69,74–85)*. In the radius, investigators have used region of interests at the 4%, 6%, 10%, 15%, 20%, 33%, 50%, and 65% of ulnar length, and at 7 mm from the endplate.

For the tibia, the reference line was set in locations such as the midpoint of the distal tibia endplate *(20,29,33,34,38)*, the distal tibia growth plate *(31)*, the middle of the subchondral bone at the distal tibia *(21,22)*, or the distal surface of the tibial plafond *(23,24)*. Only one study addressed issues of scan acceptability based on the reference line placement, demonstrating that close to 30% of scans were not acceptable due to growth plate interference when the medial end of the distal epiphysis was used as a reference point for scans obtained at the 4% site *(86)*. Many studies fail to report details of reference line placement *(14–19,26–28,30,32,87)*. Tibia measurements have been obtained at the 8%, 10%, 20%, 38%, 50%, 60%, 65%, 66%, and at 10 mm from the distal endplate. For clinical assessment, the reference line placement and site of measurement should be included as part of the scan acquisition component of the report, and match the reference data or comparative data used for the interpretation.

Numerous outcome measures have been reported in pediatric pQCT studies (*see* Table 1). For distal sites (both radius and tibia), these include total CSA; total and trabecular volumetric BMD; total BMC; cortical volumetric BMD; cortical plus sub-cortical volumetric BMD; cortical thickness; and SSI. For mid-shaft sites the outcome measures include cortical thickness; BSI; total and cortical CSA; cortical volumetric BMD; cortical BMC; SSI; polar moment of inertia; marrow CSA; periosteal circumference; and endosteal circumference. Many of these outcome measures are highly correlated and computationally interrelated, but may respond differently to disease processes or treatments. For example, cortical thickness is determined by the periosteal and endosteal circumferences, and the marrow CSA plus the cortical CSA equals total CSA. Inclusion of all variables may not be necessary because of this overlap, but choice of outcome measure may depend on the nature of the disease or treatment effects on bone. For example, it may be important to know whether increased cortical thickness is due to increased periosteal circumference or decreased endosteal circumference.

Several outcome measures are of greatest interest because they have been shown to be associated with fracture load or deficits in children with chronic diseases (see above). At the metaphyses, total and trabecular volumetric BMD should be reported. At the diaphysis, total BMC; cortical volumetric BMD; cortical thickness; cross-sectional moment of inertia; and SSI results are recommended. Z-scores for all measures should also be reported.

The proportion of trabecular and cortical bone varies along the length of long bones. Likewise, trabecular volumetric BMD and bone area vary along the length of the metaphysis, and the cross-sectional shape and thickness of cortical bone vary along the length of the shaft. As a consequence, measurements obtained at different locations along the shaft of the bone are not comparable. Pediatric pQCT studies have not addressed the rationale for specific region of interest locations. Further research is needed to determine the optimal location of the region of interest to achieve consistency across stages of growth and development, and within individuals over time.

Scan acquisition, analysis parameters, technical quality and limitations should also be reported so that follow-up evaluations can be performed in the same manner and compared. The scan images should be evaluated and the report should document appropriate reference line placement, movement or interfering factors, and overall quality.

Discussion

The elements of the pQCT report were selected because of the effects of growth, physical development, and medical history on bone outcomes, and because of the potential for technical limitations to significantly affect the scan acquisition, analysis, and interpretation. Changes in body size and maturational processes are primary determinants of bone dimensions and strength. These changes are mainly captured by age-specific reference data. The use of Z-scores accounts for the expected growth-related changes in pQCT outcomes. Both the measurement and the Z-score are critical elements of the pQCT report. Growth assessment, and accompanying

information about skeletal and sexual maturation are important complementary data to further aide in the interpretation of pQCT Z-scores, since children with advanced or delayed growth may have pQCT Z-scores that are consistent with their growth status.

Differences between pQCT models have been documented, but as yet, the differences in pQCT outcomes attributable to software features is unknown. Until such time as it is established that the devices and their software are interchangeable, it is imperative to document these characteristics of the examination. It is equally important to record the scan acquisition, analysis parameters, and reference data source as these are known to influence the outcome measurements. This is crucial for follow-up evaluations in order to evaluate changes over time in bone outcomes.

How Should Quality Control be Monitored?

ISCD Official Positions

Quality control procedures should be performed as described for central DXA.

Grade: Good-C-W-Necessary

- Determination of the precision error, least significant change (LSC), and monitoring time interval should be performed as described for DXA.

  Grade: Fair-C-W-Necessary

Rationale

Quality Assurance and Quality Control Format for pQCT. Virtually nothing is available in the literature on quality assurance and quality control procedures for pQCT. However, there are basic principles and guidelines that should be followed for all densitometric techniques. The purpose of quality assurance (QA) is to assure that there are quality methods in place to acquire accurate and precise results. Quality control is the process of monitoring the accuracy and data quality to find problems when they occur. The following is a quality assurance checklist that every center performing pQCT should have in place. It is based on expert opinion.

Quality Control and Quality Assurance Checklist for pQCT:

- The site should maintain a site manual for all records regarding the pQCT system including training; maintenance; owner's manual; field service; and site personnel contact information.
- All personnel should be trained on the specific system being used. The manufacturer or a credentialing organization should establish a formal and consistent training program. A special section of the training program must include special issues related to measurements in children, such as optimal patient position, measurement, and analysis protocols for children, identification of the growth plate, placement of reference lines relative to the growth plate, and procedures to minimize movement. This training should be documented for all site personnel.
- The system should be installed and certified by the manufacturer as being in good operation and accurate to factory standards.
- The daily quality control phantom should be calibrated to factory standards by either the manufacturer or by trained personnel.
- A quality control phantom should be used on a periodic basis no less than once a day that scanning is done.
- The center should establish and record the mean and standard deviation (precision) of the principal measures used by the site. This should be done using procedures previously outlined for central DXA. At a minimum, the center should monitor total CSA; cortical CSA; cortical volumetric BMD; and trabecular volumetric BMD.
- The phantom should be evaluated using quality control rules that are sensitive to changes in calibration, such as the Shewhart rules *(88)*.
- A procedure should be in place to identify when calibration errors have occurred, and the steps to be followed to rectify the calibration errors. The manufacturer should be notified if the system is found to be out of calibration, and the site should follow their remedy procedures.
- The primary in vivo system on the US market is the Stratec XCT2000. It is shipped with its own quality control phantom. An alternative quality control phantom is the European Forearm Phantom (EFP) (QRM-Germany).

Cross-Calibration Between pQCT Devices. Cross-calibration for pQCT is similar to other quantitative densitometry modes. Ultimately, cross-calibration is best established using an in vivo population. One study reported an in vivo cross-calibration study of the Stratec XCT900 and XCT2000 systems in adults at the 4% distal radius study. They reported correlation coefficients between the two devices of 0.82 for the CSA; 0.81 for total volumetric BMD; 0.97 for trabecular volumetric BMD; 0.99 for total BMC; and 0.86 for polar SSI. No one has performed a cross-calibration study in children.

The alternative to in vivo cross-calibration is to use a phantom that has been shown to mimic the in vivo relationships between the two devices. The only phantom commercially available to cross-calibrate pQCT systems is the EFP. The EFP is a semi-anthropomorphic phantom, comprised of three hydroxyapatite bone imitations with different densities within the human range, 0.662 g/cm^3 at the highest density level, 0.415 g/cm^3 at the mid-density level, and 0.314 g/cm^3 at the lowest density level *(89)*. It was extensively characterized by Pearson et al. *(90)* in terms of the geometry and density of the regions. However, there are no studies that compared the cross-calibration equations derived in vivo with those based on the EFP. Thus, there is no evidence that the EFP passes the strict criteria of a cross-calibration phantom. However, since the EFP is well characterized, it should be an ideal phantom for cross-calibrating between systems of the same make and model where the only differences expected are due to quality control, not design. Although the procedures for cross-calibration of pQCT are not published, the University of California San Francisco (John Shepherd, personal

communication) and other institutes have developed simple procedures as follows:

- Using the EFP, acquire a scout scan and obtain five axial scans through each of the three portions of the phantom.
- Calculate the mean and standard deviation for all relevant measures for each device.
- Employ linear regression to determine the relationship between the two scanners using one system as the referent, typically the one with the best precision.

Calculation of the Precision Error/Least Significant Change for pQCT Devices. The precision error/least significant change (LSC) should be calculated in the same manner as for DXA. It is calculated as follows:

$$\mathrm{LSC} = \mathrm{CV}(\%) * 2\sqrt{2}$$

e.g., if CV = 1%, then LSC = 2.8% approximately, for a confidence level of 95%.

Monitoring Time Interval (MTI) for pQCT. To determine an appropriate MTI requires a comparison of the magnitude of change (due to growth, intervention, or disease), and the time course of the change relative to the LSC. Longitudinal data assessing skeletal changes using pQCT in children due to growth, disease, or intervention are few. The MTI of 11 published longitudinal studies range from 12 wk to 3.5 yr; most of these have been exercise interventions ($n = 4$) *(24,28,29,38)*; the remaining publications have been longitudinal changes due to (1) growth ($n = 3$) *(16,20,21)*; (2) nutritional assessment ($n = 2$) *(33,91)*; and (3) those with disease ($n = 2$) *(92,93)*. The minimal MTI associated with significant change in BMC, but not in parameters of bone geometry, was reported in an exercise study of 9 mo *(38)*. In one exercise study of 12 mo duration there was a significant effect of exercise on bone geometric parameters and volumetric BMD *(28)*, in contrast similar findings were not reported in a 16-mo exercise intervention *(24)*. Further research is required to determine the MTI for the minimal magnitude change deemed to be clinically important relative to the age and health of the individual or population. This is important because the magnitude of the change in response to growth, disease or intervention will be dependent on the stage of puberty, gender, and linear growth rate. Finally, the MTI may differ for trabecular and cortical sites due to region specific-differences in linear growth and bone modeling.

Discussion

Monitoring equipment performance is essential to obtaining accurate and precise bone densitometry measurements. Peripheral quantitative computed tomography devices are equipped with phantoms that should be scanned regularly and the results monitored for calibration errors and drift in equipment performance. Staff should be appropriately trained, and should be familiar with the special techniques required for obtaining accurate and consistent measurements for children.

The precision of pQCT measurements in children is comparable to adults *(94)*, but the determination of the MTI is complex due to the magnitude of growth-related changes. In all likelihood, the MTI varies by outcome measure and the stage of growth, since the rate of change in bone outcomes fluctuates in childhood and adolescence.

Additional Questions for Future Research

Nearly all aspects of pediatric bone densitometry using pQCT require further research in order to develop evidence-based guidelines for clinical assessment. Hardware and software differences in pQCT devices have the potential to give different results, especially for children because of their smaller size. This is especially important to be sure that technical issues do not interfere with the use of reference or comparison data for clinical interpretation. In this regard, further research is needed to answer the following questions:

- Are there differences between pQCT manufacturers, models and scan analysis software that could have a significant impact on clinical assessment of children?
- Are pediatric reference data specific to the device and software used in its creation, or are they generalizable to other pQCT devices, models, manufacturers and software versions?

Other aspects of scan acquisition and analysis, such as limb length measurement technique; voxel size; scan speed; reference line placement; and region of interest location need to be standardized so as not to introduce any bias when reference or comparison data are used for clinical interpretation. Regions of interest have been described in the literature without rationale or empirical evidence that measurements at particular locations are useful. Further research is needed to determine the optimal measurement sites for assessment of bone density and geometry in children specifically.

- What scan acquisition and analysis techniques, including limb length measurement technique; voxel size; scan speed; reference line placement; region of interest location; and scan analysis parameters are optimal for use in children, in order to obtain consistent, high quality, and interpretable measurements?
- What are the best regions of interest and outcome measures for characterizing bone deficits and capturing clinically significant changes in bone density and dimensions?
- Which regions of interest and outcome measures are the most predictive of fracture risk in healthy children and children with chronic diseases?

Resolution of these research questions and the development of pediatric reference data for pQCT measures are needed to firmly establish pQCT as a clinically useful measure of bone health in pediatric patients.

Summary

Peripheral quantitative computed tomography is an imaging tool that has great potential for clinical evaluation of bone health in children. It is able to obtain information about the density of trabecular and cortical bone, and bone geometry in the long bones, with minimal radiation exposure. However, current published data on healthy children are not sufficient to serve as reference data for the clinical use of pQCT for fracture prediction or diagnosis of low bone mass. Until reference data are established, published reports can be used for comparative purposes, provided the scan acquisition and analysis techniques are comparable. Since cortical and trabecular bone respond differently to disease-related processes and medications, it is important to obtain information from both the diaphysis and the metaphysis for clinical assessment. The elements of the pQCT report are similar to those recommended for DXA, and include demographic information, assessment of growth and development, medical information and the technical aspect of scan acquisition and analysis. Quality assurance and quality control procedures are similar to those for DXA. Further research is needed to determine the optimum scan procedures and outcome measures for fracture risk prediction and diagnosis of low bone mass in children and adolescents.

References

1. NIH. 2000 Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 17(1):1−36.
2. Leonard MB, Zemel BS. 2002 Current concepts in pediatric bone disease. Pediatr Clin North Am 49(1):143−173.
3. Kontulainen S, Liu D, Manske S, et al. 2007 Analyzing cortical bone cross-sectional geometry by peripheral QCT: comparison with bone histomorphometry. J Clin Densitom 10(1):86−92.
4. Rauch F, Tutlewski B, Schoenau E. 2001 Peripheral quantitative computed tomography at the distal radius: cross-calibration between two scanners. J Musculoskelet Neuronal Interact 2(2): 153−155.
5. Grampp S, Nather A, Rintelen B, et al. 2000 Peripheral quantitative CT of the forearm: scanner cross-calibration using patient data. Br J Radiol 73(867):275−277.
6. Schoenau E, Neu CM, Rauch F, et al. 2002 Gender-specific pubertal changes in volumetric cortical bone mineral density at the proximal radius. Bone 31(1):110−113.
7. Schoenau E, Neu CM, Rauch F, et al. 2001 The development of bone strength at the proximal radius during childhood and adolescence. J Clin Endocrinol Metab 86(2):613−618.
8. Neu CM, Rauch F, Manz F, et al. 2001 Modeling of cross-sectional bone size, mass and geometry at the proximal radius: a study of normal bone development using peripheral quantitative computed tomography. Osteoporos Int 12(7):538−547.
9. Neu CM, Manz F, Rauch F, et al. 2001 Bone densities and bone size at the distal radius in healthy children and adolescents: a study using peripheral quantitative computed tomography. Bone 28(2):227−232.
10. Schoenau E, Neu CM, Beck B, et al. 2002 Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res 17(6):1095−1101.
11. Ashby R, Roberts S, Adams J, et al. 2006 DXA and pQCT reference centile curves in healthy children from the United Kingdom, aged 6−17 years. J Bone Miner Res 21(Suppl 1):207.
12. Binkley TL, Specker BL, Wittig TA. 2002 Centile curves for bone densitometry measurements in healthy males and females ages 5−22 yr. J Clin Densitom 5(4):343−353.
13. Ogden CL, Kuczmarski RJ, Flegal KM, et al. 2002 Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 109(1):45−60.
14. Wang Q, Alen M, Nicholson PH, et al. 2006 Differential effects of sex hormones on peri- and endocortical bone surfaces in pubertal girls. J Clin Endocrinol Metab 91(1):277−282.
15. Wang QJ, Suominen H, Nicholson PH, et al. 2005 Influence of physical activity and maturation status on bone mass and geometry in early pubertal girls. Scand J Med Sci Sports 15(2): 100−106.
16. Wang Q, Alen M, Nicholson P, et al. 2005 Growth patterns at distal radius and tibial shaft in pubertal girls: a 2-year longitudinal study. J Bone Miner Res 20(6):954−961.
17. Wang Q, Nicholson PH, Suuriniemi M, et al. 2004 Relationship of sex hormones to bone geometric properties and mineral density in early pubertal girls. J Clin Endocrinol Metab 89(4): 1698−1703.
18. Suuriniemi M, Kovanen V, Mahonen A, et al. 2006 COL1A1 Sp1 polymorphism associates with bone density in early puberty. Bone 39(3):591−597.
19. Suuriniemi M, Mahonen A, Kovanen V, et al. 2004 Association between exercise and pubertal BMD is modulated by estrogen receptor alpha genotype. J Bone Miner Res 19(11):1758−1765.
20. Macdonald HM, Kontulainen SA, MacKelvie-O'Brien KJ, et al. 2005 Maturity- and sex-related changes in tibial bone geometry, strength and bone-muscle strength indices during growth: a 20-month pQCT study. Bone 36(6):1003−1011.
21. Kontulainen SA, Macdonald HM, Khan KM, et al. 2005 Examining bone surfaces across puberty: a 20-month pQCT trial. J Bone Miner Res 20(7):1202−1207.
22. Kontulainen SA, Macdonald HM, McKay HA. 2006 Change in cortical bone density and its distribution differs between boys and girls during puberty. J Clin Endocrinol Metab 91(7):2555−2561.
23. Macdonald H, Kontulainen S, Petit M, et al. 2006 Bone strength and its determinants in pre- and early pubertal boys and girls. Bone 39(3):598−608.
24. Macdonald HM, Kontulainen SA, Khan KM, et al. 2007 Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls? J Bone Miner Res 22(3):434−446.
25. Binkley TL, Specker BL. 2000 pQCT measurement of bone parameters in young children: validation of technique. J Clin Densitom 3(1):9−14.
26. Binkley T, Johnson J, Vogel L, et al. 2005 Bone measurements by peripheral quantitative computed tomography (pQCT) in children with cerebral palsy. J Pediatr 147(6):791−796.
27. Binkley T, Specker B. 2004 Increased periosteal circumference remains present 12 months after an exercise intervention in preschool children. Bone 35(6):1383−1388.
28. Specker B, Binkley T. 2003 Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res 18(5):885−892.
29. Johannsen N, Binkley T, Englert V, et al. 2003 Bone response to jumping is site-specific in children: a randomized trial. Bone 33(4):533−539.
30. Specker BL, Johannsen N, Binkley T, et al. 2001 Total body bone mineral content and tibial cortical bone measures in preschool children. J Bone Miner Res 16(12):2298−2305.
31. Felin EM, Prahalad S, Askew EW, et al. 2007 Musculoskeletal abnormalities of the tibia in juvenile rheumatoid arthritis. Arthritis Rheum 56(3):984−994.

32. Ward KA, Roberts SA, Adams JE, et al. 2005 Bone geometry and density in the skeleton of pre-pubertal gymnasts and school children. Bone 36(6):1012−1018.
33. Moyer-Mileur LJ, Xie B, Ball SD, et al. 2003 Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls. J Musculoskelet Neuronal Interact 3(1):63−70.
34. Moyer-Mileur L, Xie B, Ball S, et al. 2001 Predictors of bone mass by peripheral quantitative computed tomography in early adolescent girls. J Clin Densitom 4(4):313−323.
35. Lee WT, Cheung CS, Tse YK, et al. 2005 Association of osteopenia with curve severity in adolescent idiopathic scoliosis: a study of 919 girls. Osteoporos Int 16(12):1924−1932.
36. Lee WT, Cheung AY, Lau J, et al. 2004 Bone densitometry: which skeletal sites are best predicted by bone mass determinants? J Bone Miner Metab 22(5):447−455.
37. Cheng JC, Qin L, Cheung CS, et al. 2000 Generalized low areal and volumetric bone mineral density in adolescent idiopathic scoliosis. J Bone Miner Res 15(8):1587−1595.
38. Heinonen A, Sievanen H, Kannus P, et al. 2000 High-impact exercise and bones of growing girls: a 9-month controlled trial. Osteoporos Int 11(12):1010−1017.
39. Lettgen B, Hauffa B, Mohlmann C, et al. 1995 Bone mineral density in children and adolescents with juvenile diabetes: selective measurement of bone mineral density of trabecular and cortical bone using peripheral quantitative computed tomography. Horm Res 43(5):173−175.
40. Moilanen P, Nicholson PH, Karkkainen T, et al. 2003 Assessment of the tibia using ultrasonic guided waves in pubertal girls. Osteoporos Int 14(12):1020−1027.
41. Burnham JM, Shults J, Sembhi H, et al. 2006 The dysfunctional muscle-bone unit in juvenile idiopathic arthritis. J Musculoskelet Neuronal Interact 6(4):351−352.
42. Fujita T, Fujii Y, Goto B. 1999 Measurement of forearm bone in children by peripheral computed tomography. Calcif Tissue Int 64(1):34−39.
43. Haapasalo H, Kontulainen S, Sievanen H, et al. 2000 Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. Bone 27(3):351−357.
44. Kontulainen S, Sievanen H, Kannus P, et al. 2003 Effect of long-term impact-loading on mass, size, and estimated strength of humerus and radius of female racquet-sports players: a peripheral quantitative computed tomography study between young and old starters and controls. J Bone Miner Res 18(2): 352−359.
45. Auerbach BM, Ruff CB. 2006 Limb bone bilateral asymmetry: variability and commonality among modern humans. J Hum Evol 50(2):203−218.
46. Sievanen H, Koskue V, Rauhio A, et al. 1998 Peripheral quantitative computed tomography in human long bones: evaluation of in vitro and in vivo precision. J Bone Miner Res 13(5): 871−882.
47. Jamsa T, Jalovaara P, Peng Z, et al. 1998 Comparison of three-point bending test and peripheral quantitative computed tomography analysis in the evaluation of the strength of mouse femur and tibia. Bone 23(2):155−161.
48. Ferretti JL, Capozza RF, Zanchetta JR. 1996 Mechanical validation of a tomographic (pQCT) index for noninvasive estimation of rat femur bending strength. Bone 18(2):97−102.
49. Siu WS, Qin L, Leung KS. 2003 pQCT bone strength index may serve as a better predictor than bone mineral density for long bone breaking strength. J Bone Miner Metab 21(5): 316−322.
50. Muller ME, Webber CE, Bouxsein ML. 2003 Predicting the failure load of the distal radius. Osteoporos Int 14(4):345−352.
51. Ashe MC, Khan KM, Kontulainen SA, et al. 2006 Accuracy of pQCT for evaluating the aged human radius: an ashing, histomorphometry and failure load investigation. Osteoporos Int 17: 1241−1251.
52. Liu D, Manske SL, Kontulainen SA, et al. 2007 Tibial geometry is associated with failure load ex vivo: a MRI, pQCT and DXA study. Osteoporos Int 18:991−997.
53. Louis O, Boulpaep F, Willnecker J, et al. 1995 Cortical mineral content of the radius assessed by peripheral QCT predicts compressive strength on biomechanical testing. Bone 16(3): 375−379.
54. Lochmuller EM, Lill CA, Kuhn V, et al. 2002 Radius bone strength in bending, compression, and falling and its correlation with clinical densitometry at multiple sites. J Bone Miner Res 17(9):1629−1638.
55. Skaggs DL, Loro ML, Pitukcheewanont P, et al. 2001 Increased body weight and decreased radial cross-sectional dimensions in girls with forearm fractures. J Bone Miner Res 16(7): 1337−1342.
56. Augat P, Gordon CL, Lang TF, et al. 1998 Accuracy of cortical and trabecular bone measurements with peripheral quantitative computed tomography (pQCT). Phys Med Biol 43(10): 2873−2883.
57. Prevhal S, Engelke K, Kalender W. 1999 Accuracy limits for the determination of cortical width and density: the influence of object size and CT imaging parameters. Phys Med Biol 44: 751−764.
58. Rittweger J, Michaelis I, Giehl M, et al. 2004 Adjusting for the partial volume effect in cortical bone analyses of pQCT images. J Musculoskelet Neuronal Interact 4(4):436−441.
59. Ward KA, Adams JE, Hangartner TN. 2005 Recommendations for thresholds for cortical bone geometry and density measurement by peripheral quantitative computed tomography. Calcif Tissue Int 77(5):275−280.
60. Rauch F, Neu C, Manz F, et al. 2001 The development of metaphyseal cortex—implications for distal radius fractures during growth. J Bone Miner Res 16(8):1547−1555.
61. Schweizer R, Martin DD, Schwarze CP, et al. 2003 Cortical bone density is normal in prepubertal children with growth hormone (GH) deficiency, but initially decreases during GH replacement due to early bone remodeling. J Clin Endocrinol Metab 88(11):5266−5272.
62. Bechtold S, Ripperger P, Dalla Pozza R, et al. 2005 Musculoskeletal and functional muscle-bone analysis in children with rheumatic disease using peripheral quantitative computed tomography. Osteoporos Int 16(7):757−763.
63. Brennan BM, Mughal Z, Roberts SA, et al. 2005 Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. J Clin Endocrinol Metab 90(2):689−694.
64. Heap J, Murray MA, Miller SC, et al. 2004 Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr 144(1):56−62.
65. Lee DC, Gilsanz V, Wren TA. 2007 Limitations of peripheral quantitative computed tomography metaphyseal bone density measurements. J Clin Endocrinol Metab 92(11):4248−4253.
66. Rauch F, Tutlewski B, Fricke O, et al. 2001 Analysis of cancellous bone turnover by multiple slice analysis at distal radius: a study using peripheral quantitative computed tomography. J Clin Densitom 4(3):257−262.
67. Cameron N. 1999 The use and abuse of growth charts. Johnston F, Zemel B and Eveleth PB, eds. In Human Growth in Context. Smith-Gordon, London, 65−74.

68. Leonard MB, Shults J, Elliott DM, et al. 2004 Interpretation of whole body dual-energy X-ray absorptiometry measures in children: comparison with peripheral quantitative computed tomography. Bone 34(6):1044−1052.
69. Schoenau E, Neu CM, Mokov E, et al. 2000 Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. J Clin Endocrinol Metab 85(3):1095−1098.
70. Zemel B, Kalkwarf H, Leonard M, et al. 2005 Effects of skeletal and sexual maturation on trabecular and cortical density of the peripheral skeleton. J Bone Miner Res 20(Suppl 1):59.
71. Girschick HJ, Schneider P, Kruse K, et al. 1999 Bone metabolism and bone mineral density in childhood hypophosphatasia. Bone 25(3):361−367.
72. Dyson K, Blimkie CJ, Davison KS, et al. 1997 Gymnastic training and bone density in pre-adolescent females. Med Sci Sports Exerc 29(4):443−450.
73. Rauch F, Land C, Cornibert S, et al. 2005 High and low density in the same bone: a study on children and adolescents with mild osteogenesis imperfecta. Bone 37(5):634−641.
74. Schwahn B, Mokov E, Scheidhauer K, et al. 1998 Decreased trabecular bone mineral density in patients with phenylketonuria measured by peripheral quantitative computed tomography. Acta Paediatr 87(1):61−63.
75. Ward KA, Adams JE, Freemont TJ, et al. 2007 Can bisphosphonate treatment be stopped in a growing child with skeletal fragility? Osteoporos Int 18:1137−1140.
76. Quick JL, Ward KA, Adams JE, et al. 2006 Cortical bone geometry in asthmatic children. Arch Dis Child 91(4):346−348.
77. Matkovic V, Landoll JD, Badenhop-Stevens NE, et al. 2004 Nutrition influences skeletal development from childhood to adulthood: a study of hip, spine, and forearm in adolescent females. J Nutr 134(3):701S−705S.
78. Schonau E, Werhahn E, Schiedermaier U, et al. 1996 Influence of muscle strength on bone strength during childhood and adolescence. Horm Res 45(Suppl 1):63−66.
79. Schonau E. 1998 The development of the skeletal system in children and the influence of muscular strength. Horm Res 49(1): 27−31.
80. Remer T, Boye KR, Hartmann M, et al. 2003 Adrenarche and bone modeling and remodeling at the proximal radius: weak androgens make stronger cortical bone in healthy children. J Bone Miner Res 18(8):1539−1546.
81. Ruth EM, Weber LT, Schoenau E, et al. 2004 Analysis of the functional muscle-bone unit of the forearm in pediatric renal transplant recipients. Kidney Int 66(4):1694−1706.
82. Bechtold S, Rauch F, Noelle V, et al. 2001 Musculoskeletal analyses of the forearm in young women with Turner syndrome: a study using peripheral quantitative computed tomography. J Clin Endocrinol Metab 86(12):5819−5823.
83. Muller HL, Schneider P, Bueb K, et al. 2003 Volumetric bone mineral density in patients with childhood craniopharyngioma. Exp Clin Endocrinol Diabetes 111(3):168−173.
84. Lima EM, Goodman WG, Kuizon BD, et al. 2003 Bone density measurements in pediatric patients with renal osteodystrophy. Pediatr Nephrol 18(6):554−559.
85. Schneider P, Biko J, Schlamp D, et al. 1998 Comparison of total and regional body composition in adolescent patients with anorexia nervosa and pair-matched controls. Eat Weight Disord 3(4):179−187.
86. Zemel BS, Ittenbach R, Stallings V, et al. 2002 Patterns and pitfalls in pQCT measurements of the tibia in children. J Bone Miner Res 18(Suppl 1):178.
87. Stevenson DA, Moyer-Mileur LJ, Carey JC, et al. 2005 Case-control study of the muscular compartments and osseous strength in neurofibromatosis type 1 using peripheral quantitative computed tomography. J Musculoskelet Neuronal Interact 5(2):145−149.
88. Wahner HW, Looker A, Dunn WL, et al. 1994 Quality control of bone densitometry in a national health survey (NHANES III) using three mobile examination centers. J Bone Miner Res 9(6): 951−960.
89. Emaus N, Berntsen GK, Joakimsen R, et al. 2005 Bone mineral density measures in longitudinal studies: the choice of phantom is crucial for quality assessment. The Tromso study, a population-based study. Osteoporos Int 16(12):1597−1603.
90. Pearson J, Ruegsegger P, Dequeker J, et al. 1994 European semi-anthropomorphic phantom for the cross-calibration of peripheral bone densitometers: assessment of precision accuracy and stability. Bone Miner 27(2):109−120.
91. Cheng S, Lyytikainen A, Kroger H, et al. 2005 Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10-12-y-old girls: a 2-y randomized trial. Am J Clin Nutr 82(5):1115−1126. [quiz 1147−1148].
92. Cheng JC, Hung VW, Lee WT, et al. 2006 Persistent osteopenia in adolescent idiopathic scoliosis—longitudinal monitoring of bone mineral density until skeletal maturity. Stud Health Technol Inform 123:47−51.
93. Rauch F, Cornibert S, Cheung M, et al. 2007 Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. Bone 40:821−827.
94. Zemel BS, Paulhamus D, Dilzer C, et al. 2004 Precision of peripheral quantitative computed tomography measures of the tibia in children. J Bone Miner Res 19(Suppl 1):S232.
95. Rauch F, Schoenau E. 2005 Peripheral quantitative computed tomography of the distal radius in young subjects—new reference data and interpretation of results. J Musculoskelet Neuronal Interact 5(2):119−126.