

Limitations of Peripheral Quantitative Computed Tomography Metaphyseal Bone Density Measurements

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Context: Peripheral quantitative computed tomography (pQCT) measurements are frequently obtained to assess cancellous bone density in the appendicular skeleton. Large variations in bone morphology associated with skeletal development may limit the interpretation of pediatric pQCT studies based on a single slice.

Objective: The objective of the study was to characterize the variability in trabecular bone density values along the length of the metaphysis.

Design: The design was an analysis of pQCT bone density data.

Setting: The study was conducted at a hospital radiology department.

Patients: The study included 35 children with cerebral palsy aged 6–12 yr.

Main Outcome Measure: Variations in cancellous bone density along the length of the proximal tibial metaphysis were measured.

Results: The patterns of decay in metaphyseal trabecular bone density were different in all subjects, and the density changed from the physis to the shaft at a rate of $16.8 \pm 8.2\%$ per 1 mm (range 8.6–37.9% per 1 mm). The slopes of the density curve drastically changed in some children over a short period of 6 months. Even with a high correlation ($r^2 = 0.88$) between the density of a slice located a fixed distance from the growth plate and the overall mean metaphysis density, the respective changes in density over 6 months were only moderately correlated ($r^2 = 0.58$).

Conclusions: These results underscore the difficulty in interpreting metaphyseal pQCT bone density measurements from a single slice and highlight the need for developing pQCT acquisition techniques that provide more representative bone density determinations in the appendicular skeleton of children. (*J Clin Endocrinol Metab* 92: 4248–4253, 2007)

THE DEVELOPMENT OF precise noninvasive methods for measuring bone has significantly improved our ability to study the influence of genetic and environmental factors influencing the attainment of bone in children (1). Currently the most commonly used quantitative radiologic method to assess bone mass is dual-energy x-ray absorptiometry (2). However, dual-energy x-ray absorptiometry is limited by a two-dimensional interpretation of a three-dimensional structure. In contrast, peripheral quantitative computed tomography (pQCT) provides three-dimensional images, allowing for volumetric density measures, an evaluation of bone morphology, and an independent assessment of trabecular and cortical bone in the appendicular skeleton (3).

Because of its porosity and large surface area, trabecular bone has greater turnover and is a better indicator of bone remodeling than cortical bone. Trabecular bone density determinations by pQCT are commonly obtained by a single scan at a relative location, such as 4 or 8% length of the radius or tibia (4–8), or a fixed location, such as 10 mm from the end of the growth plate (9).

Whereas available data indicate that the short-term reproducibility of these measurements is excellent (10, 11), positioning is critical, and due to the variability of trabecular bone

density throughout the metaphysis, any offset in the location to be scanned would significantly influence the values obtained (12). Additionally, the large range of metaphyseal morphology among subjects, diseases, and ages limits comparative cross-sectional studies and interpretation of the same scan location in longitudinal examinations (13).

In this study, we characterized the variability in trabecular bone density values along the length of the proximal tibial metaphysis and the change in cancellous bone density over a 6-month period in a cohort of children with cerebral palsy who were participants in an ongoing study requiring longitudinal pQCT determinations.

Subjects and Methods

Subjects

This study examined existing pQCT data from 37 children with cerebral palsy. Two were excluded for motion artifacts, leaving 35 for analysis (five hemiplegic, 22 diplegic, two triplegic, six quadriplegic). The subjects were originally recruited for ongoing studies at Childrens Hospital Los Angeles, and informed consent was obtained for all subjects. All subjects were ambulatory either with or without assistive devices and were excluded if they had recently undergone any procedure or medication that could alter bone or muscle function. Of the 35 children, 19 returned for a 6-month follow-up measurement. Tanner stage was not evaluated at the time of the exams.

Data acquisition and processing

pQCT was performed on the proximal tibia of each subject using the same scanner (General Electric Hilite Advantage, Milwaukee, WI) and with the same K_2HPO_4 mineral reference phantom for simultaneous calibration (CT-T bone densitometry package; General Electric). The

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FIG. 1. pQCT data of the proximal tibia represented as a three-dimensional rendering (*top*) and sagittal cross-section (*bottom*) with area of interest in *dotted lines*.

thickness of each cross-section was 1.25 mm, and the field of view was 345 mm. Data sets of at least 70 contiguous slices per subject were taken to ensure coverage of the metaphysis region (Fig. 1). The same technician analyzed all images. Scans were evaluated and excluded if motion artifacts were found.

To isolate cancellous bone from within the metaphysis, a cylindrical core was built from the contiguous slices (Fig. 1). The circular cross-section of the core was determined by fitting the largest circle possible into the narrowest region of the proximal tibia, without coming into contact with the cortex.

The length of the core from the metaphysis was defined as the region containing cancellous bone, specifically between the growth plate and where density values drop less than 0 mg/cm^3 K_2HPO_4 . Density values below zero, as calibrated by the phantom, were considered mainly fat or nonbone elements, as found in the intermedullary canal. Care was

taken to ensure that the cylindrical core was placed in the same position relative to the growth plate in all subjects.

All image processing was performed with custom algorithms using MATLAB R2006a (MathWorks, Natick, MA).

Data analysis

The density data from the cylindrical core containing the metaphyseal cancellous bone can be depicted graphically (Fig. 2). For each cross-section along the length of the core, mean density and density variation are represented. Several parameters of interest can be extracted from the core data.

First, the mean rate of change in density or slope of the curve was calculated by averaging the difference of mean density from one transverse slice to the next and then dividing by the slice thickness. Similar calculations were performed to express the rate of change as a percentage. The resultant values describe the variation and potential error associated with a 1-mm offset in the location of a single cross-sectional density measurement.

Also, the length of the metaphysis can be found by observing the occurrence of cancellous bone, previously defined as between the growth plate and zero density values. The overall mean density of the metaphysis is the average of the mean densities from each cross-section. The area under the curve, which represents the total amount of cancellous bone in the metaphyseal core, is the product of the overall mean density and length of the metaphysis.

Additionally, the overall mean density was compared with density values along the length of the metaphysis by both relative and fixed distances. The percent length or fixed distance with the strongest correlation was then used to measure percent change in a period of 6 months and compared with the percent change using overall mean density.

Because the slice thickness used in this study (1.25 mm) differed from other pQCT studies (2.0–2.5 mm) (4–8, 14, 15), we also approximated a thicker slice (2.5 mm) by averaging two adjacent slices ($2 \times 1.25 \text{ mm}$) in an example subject. We compared the measurements using 1.25- and 2.5-mm slices.

Regression analysis was used to relate the metaphyseal bone measurements to the subject anthropometric measures. Regression was also used to compare the overall mean density and density from a single slice. Paired *t* tests were used to compare baseline and follow-up measurements. Wilcoxon sign rank tests were used to compare variables with skewness coefficients greater than 1. All statistical analysis was performed with Statistics Toolbox Version 5.2 (MathWorks).

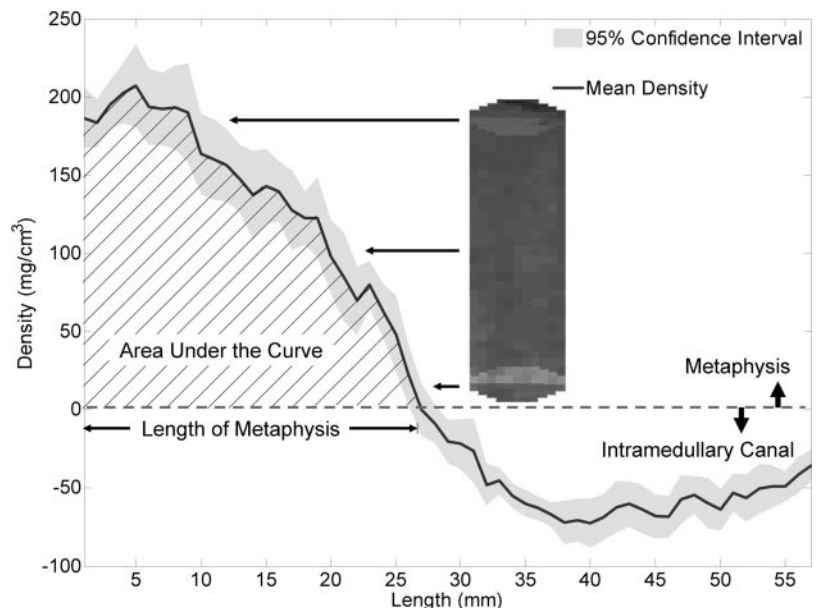


FIG. 2. Density gradient of cancellous core.

TABLE 1. Subject anthropometric data at baseline (n = 35)

	Mean ± SD	Range
Age (yr)	9.5 ± 1.5	6.0–12.4
Weight (kg)	30.5 ± 10.5	14.6–59.7
Weight (percentile)	37.5 ± 33.9	0.0–99.8
Height (cm)	127.8 ± 12.2	101.5–150.3
Height (percentile)	12.7 ± 17.0	0.0–88.8
Body mass index (kg/m ²)	18.3 ± 4.3	13.0–31.0
Body mass index (percentile)	56.6 ± 34.9	0.2–99.9

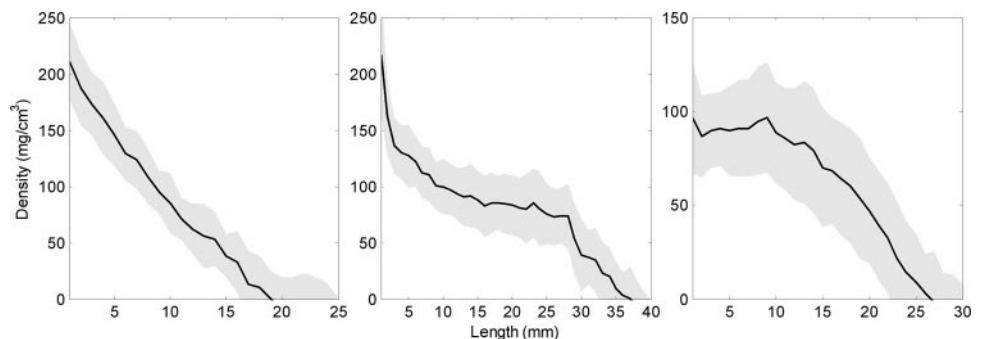
Results

A total of 35 subjects were included in this study. Seventeen of the subjects were independently ambulatory, and 18 used assistive devices. There were 18 females and 17 males at baseline (Table 1). Follow-up data were available for 19 of the subjects (eight females and 11 males) (Table 2).

The profiles or patterns of decay in metaphyseal trabecular bone density appeared to be unique in all subjects (Fig. 3). The length of the metaphysis, overall mean density of the entire metaphysis, and area under the curve (a measure of total bone in the metaphyseal core) all had wide ranges (Table 3). None of these measures from the metaphysis correlated strongly with anthropometric measures. The highest correlation was between metaphysis length and subject height ($r^2 < 0.14$). The mean change in density also varied greatly between subjects. Among all subjects the mean change in density was 6.9 ± 2.7 mg/cm³·mm, ranging from 4.2 to 14.7 mg/cm³·mm. As a percentage, the mean change in density per millimeter was $16.8 \pm 8.2\%$, ranging from 8.6 to 37.9% (Table 3). These results indicate that a 1-mm offset in positioning of a slice would result in errors averaging 6.9 mg/cm³ or 16.8%.

Significant differences between baseline and follow-up were found in age, weight, height, area under the curve, and overall mean density. Age, height, and weight increased (Table 2), and area under the curve and overall mean density decreased (Table 4).

The percent length of metaphysis that best reflected the mean metaphysis density was found to be at approximately 48% of metaphysis length from the proximal growth plate. Regression analysis showed high correlation ($r^2 = 0.89$, $P < 0.001$) between density measures at 48% length of the metaphysis and the overall mean density of the entire metaphysis. The fixed location that best reflected mean metaphysis density was the second slice from the growth plate (1.25–2.5 mm), which also had a strong correlation with mean density of the entire metaphysis ($r^2 = 0.88$, $P < 0.001$).

FIG. 3. Density gradient profiles from three different subjects.**TABLE 2.** Change in subject anthropometric data from baseline to follow-up (n = 19)

	Change from baseline to follow-up		
	Mean ± SD	Range	P value
Age (yr)	0.6 ± 0.05	0.47 ± 0.67	<0.001
Weight (kg)	1.7 ± 2.9	–5.4 to 6.8	0.019
Weight (percentile)	0.0 ± 12.3	–21.9 to 31.8	0.999
Height (cm)	3.8 ± 2.6	0–9	<0.001
Height (percentile)	2.5 ± 6.3	–5.3 to 18.2	0.106
Body mass index (kg/m ²)	–0.2 ± 1.6	–3.7 to 2.2	0.673
Body mass index (percentile)	–3.7 ± 22.1	–62.0 to 43.0	0.476

When the percent change over a 6-month period was examined, regression strength between density from the 48% slice and overall mean density was weak ($r^2 = 0.36$, $P = 0.013$). The range of percent change using a single slice at 48% length of metaphysis was wide, ranging from –50.2 to 31.3%, compared with a range of –32.8 to 11.9% for percent change using overall mean density (both ranges are without outliers, defined as points outside the fifth or 95th percentiles) (Fig. 4). The regression strength between the change in density over 6 months from the slice 1.25 away from the growth plate and overall mean density was stronger ($r^2 = 0.58$, $P < 0.001$), but the range was even wider at –45.1 to 50.9% (Fig. 4).

A case example demonstrating the difficulty of using density measurements from a single slice is illustrated in Fig. 5A. The shape of the cancellous bone density curve has changed in a 6-month period during which the subject grew 4.3 cm. At the cross-section at which the curves intersect, there is no change in density. At the same time, it is possible to select a slice in which the change is a 25.3% decrease in density. For comparison, the percent change using the overall mean density of the entire metaphysis was –25.4%. When using a thicker slice of 2.5 mm, approximated by combining two 1.25-mm slices, the density curve was smoother, although the general shape of the curve did not change (Fig. 5B). There was a 24.0% decrease in the same location in which a 25.3% decrease was found using the 1.25-mm thickness data. The mean density slope and area under the curve remained the same using the two thicknesses.

Discussion

To our knowledge, this is the first study to examine trabecular density along the entire length of the metaphysis using pQCT. Although informative, the data obtained in this study reflect a pediatric population with cerebral palsy and cannot be directly extrapolated to healthy subjects or other

TABLE 3. Metaphysis properties for baseline study (n = 35)

	Mean ± SD	Range
Length (mm)	25.6 ± 10.4	2.50–46.3
Mean density (mg/cm ³)	59.1 ± 25.8	9.0–118.6
Area under the curve (mg/cm ³ ·mm)	1360.6 ± 893.0	26.9–3202.5
Mean density slope (mg/cm ³ ·mm)	6.9 ± 2.7	4.2–14.7
Mean density slope (% change/mm)	16.8 ± 8.2	8.6–37.9

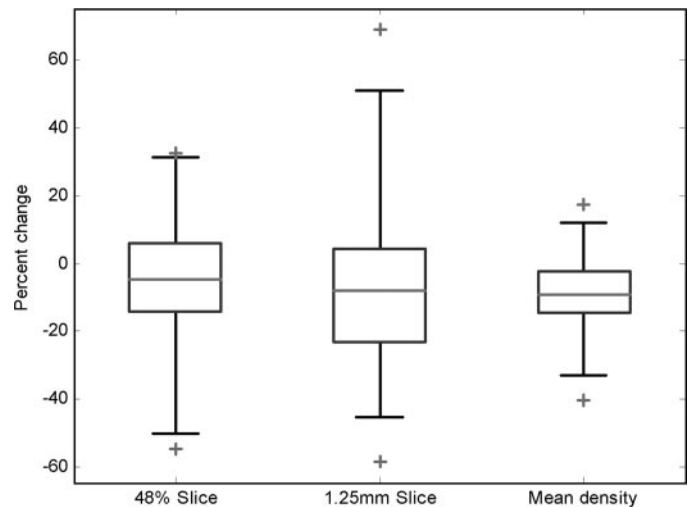
bones. Studies have shown that subjects with cerebral palsy have inhibited growth, compared with healthy children (16, 17). Decreases in bone density are not uncommon due to the disease process that leads to osteopenia and prevents normal weight-bearing activities. Future studies examining healthy subjects and other metaphyseal sites are needed to provide a more complete understanding of the variability in metaphyseal trabecular bone density.

Another significant limitation of this study is that tibia length was not measured, so assessments involving percentage of tibia length could not be done. We attempted to use percentage of metaphysis length as a surrogate for bone length. Whereas metaphysis length is theoretically useful, it would not be known by clinicians before a scan, and the relationship between metaphysis length and bone length is complex. Longitudinal growth of long bones occurs at the growth plate and is associated with extension of the metaphysis (18, 19). At the same time, the metaphysis gradually shortens as a proportion of bone length. This dynamic process is specific to each extremity of the long bone. The distal and proximal growth plates grow at disproportionate and varying rates (20), making exact locations difficult to track longitudinally. It is therefore likely that cross-sections based on a percentage of long bone length will not be measuring the same site over time.

In contrast, our results suggest that a scan location near the growth plate (1.25–2.5 mm) may be a promising measurement site. There was a strong correlation between trabecular density at this location and mean density of the entire metaphysis. Nevertheless, we observed tremendous variability in the percent change after 6 months at this location. At this site, some children showed a decrease of up to 45.1% in trabecular bone density, whereas others showed an increase of up to 50.9%. The unexpectedly large range suggests that even if we were able to choose the site that best reflects overall trabecular density in cross-sectional studies, longitudinal measures would still yield conflicting results. Additional studies are needed to determine whether mean density or a slice reflecting mean density is indeed superior to single

TABLE 4. Change in metaphysis properties from baseline to follow-up (n = 19)

n = 19	Change from baseline to follow-up		P value
	Mean ± SD	Range	
Length (mm)	-2.1 ± 6.5	-16.25 to 12.5	0.175
Mean density (mg/cm ³)	-5.1 ± 6.1	-16.0 to 7.3	0.002
Area under the curve (mg/cm ³ ·mm)	-282.2 ± 381.1	-1112.4 to 335.3	0.005
Mean density slope (mg/cm ³ ·mm)	-0.3 ± 2.4	-3.3 to 4.6	0.613
Mean density slope (% change/mm)	2.0 ± 9.1	-18.9 to 20.9	0.348

**FIG. 4.** Box plots showing percent change from baseline to 6-month follow-up using single-slice density at 48% length of metaphysis, single-slice density of 1.25-mm from growth plate, and mean density of entire metaphysis.

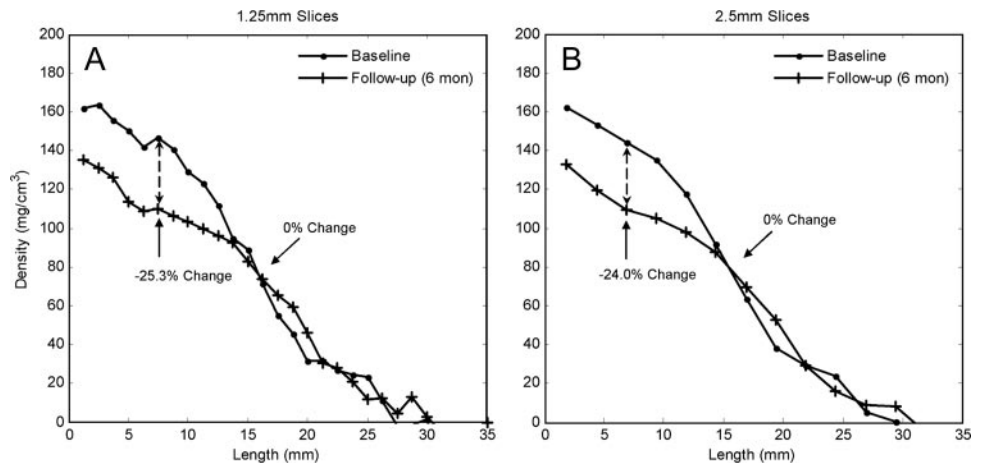
slice measurements at other locations. Additional studies are also needed to discern which slice, if any, is the best choice and whether a single slice can provide sufficient information to infer any relation to bone strength or fracture risk.

Previous studies using pQCT in children have investigated the effects of age or maturity related growth, gender differences, physical activity, disease, geometry, and strength (5–8, 14, 15, 21–23). These studies used a variety of methods, such as measurements at 4 or 10% length of the radius or tibia or at a fixed length 10 mm distal to the growth plate. More recent studies using high-resolution pQCT have scanned 9-mm-thick sections of long bones to assess trabecular microarchitecture (24–27). Although this relatively new technique is promising, further evaluation is necessary to determine how measures from a 9-mm-thick section should be interpreted, especially across a growing population.

The results of this study highlight the limitations of current pQCT methodology using single scans as outcome measures in cross-sectional and longitudinal studies assessing trabecular bone density. We found a large variability in metaphyseal morphology among subjects; the length of the metaphysis, overall trabecular mean density, and slope of the density curve all had wide ranges. In addition, longitudinal assessments showed that the slopes of the density curve drastically changed in some children, even over a short period of 6 months. These results emphasize the need for developing pQCT acquisition techniques that provide more accurate bone density determinations in the appendicular skeleton of children.

The findings of this study corroborate the presence of a considerable gradient in trabecular bone density from the physal plate, in which values are higher, to the shaft of the bone, in which no trabecular bone is present. The large intra- and intersubject variability in the bone density measures along the metaphysis highlights the limitations of assessments with a single scan. Subjects in this study showed a substantial range of variability from a 1-mm offset slice positioning with an average of 6.9 mg/cm³ or 16.8%.

FIG. 5. Variability of cancellous bone density changes at different positions along the length of the metaphysis using 1.25-mm slices (A) and 2.5-mm slices (B).



Single-slice studies are also prone to error from the metaphysis' changing morphology. In the case example (Fig. 5), the density slope or gradient changed over 6 months. Thus, any cross-section selected would yield a unique percent change.

Several issues regarding the design of this study need to be considered for the appropriate interpretation of the current results. First, because the image resolution of pQCT does not allow clear delineation between the inner margin of cortical bone and the outer margin of trabecular bone, especially near the growth plate, we chose to measure a defined cylindrical core of trabecular bone rather than sample all the trabecular bone in the metaphysis. Similar difficulties apply to histopathological studies because of the gradual transition from cortical to trabecular bone in the subcortical region along the endosteum. Second, the slice thickness (1.25 mm) used in this study differs from that typically used in other studies (2.3–2.5 mm) (4–6). The thinner slices enabled greater resolution in examining density variation, the main objective of this study. However, to better compare with other studies, we also simulated a 2.5-mm slice by averaging adjacent 1.25-mm slices. The thicker slice made the density curves slightly smoother but did not greatly reduce the effect of positioning errors. The slope of the density curve remained the same whether using 1.25- or 2.5-mm slices.

In summary, this study, which quantified the variability of trabecular bone density along the length of the metaphysis, underscores the difficulties in obtaining reproducible pQCT measures from a single scan in the appendicular skeleton of children. Future studies are needed to determine whether different acquisition methods could provide more representative measures of bone density.

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