Original Article

Peripheral quantitative computed tomography of the distal radius in young subjects – new reference data and interpretation of results

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Abstract

Application of bone densitometry to clinical use requires the availability of accessible reference data and is helped by an interpretative framework that is based on bone physiology. The aim of this contribution is to provide both reference data and help in the interpretation of results for peripheral quantitative computed tomography (Stratec XCT2000®) performed at the distal radius of young subjects. Data from a previous reference data study on 478 subjects between 6 and 40 years were re-analyzed and smooth curves were fitted. The corresponding equations allow for calculation of age- and sex-specific z-scores of bone mineral content, volumetric bone mineral density (vBMD) of the trabecular compartment, vBMD of the entire radial cross-section, total cross-sectional area and cortical thickness. These data should facilitate the clinical use of peripheral quantitative computed tomography in young subjects.

Keywords: Bone Geometry, Bone Mineral Density, Bone Size, Children, Peripheral Quantitative Computed Tomography

Introduction

Bone densitometric techniques are becoming increasingly popular in pediatrics. Among these, dual energy X-ray absorptiometry (DXA) is by far the most widely used method. Unfortunately, there are a number of problems with this technique, which limit its practical utility in children and adolescents. Notably, DXA is based on the analysis of the shadow image of a bone, which makes it difficult to determine mineral density independently from bone size and shape.

Peripheral quantitative computed tomography (pQCT) analyzes cross-sectional images of long bones. Bone size, shape and mineral density can be evaluated independently from each other with this technique. It is also possible to assess the so-called volumetric bone mineral density (vBMD) in different compartments of the bone, such as the trabecular or the cortical compartment. Thus, pQCT is a potentially useful tool in the diagnosis and follow-up of pediatric bone disorders. In order to make use of this potential it is essential to establish a detailed reference database.

We have previously published results of pQCT analyses at the distal radius in healthy children, adolescents and young adults[1,2]. Results were given as mean and standard deviations of two-year age groups. Although this is a simple way of showing such data, this method of presentation is not ideal for clinical use. The mean and standard deviations may change considerably between successive age groups. When a patient's test results are compared to such reference data, the interpretation of the result as 'normal' or 'low' can differ markedly, depending on whether the patient is slightly younger or slightly older than the cut-off age between two age groups. It is preferable to present reference data in a way that avoids discontinuities. We have therefore re-analyzed the results of the studies in healthy subjects. using a statistical method that allows for fitting of smooth curves.

Whatever method of bone densitometry is used, it is important to interpret the results in light of the underlying physiologic or pathophysiologic mechanisms that they reflect. However, as lamented by Parfitt, "bone densitometry

Age (years)	Girls	Boys
6-7	1006	1020
8-9	1033	1035
10-11	1041	1045
12-13	1038	1036
14-15	1077	1019
16-17	1088	1035
18-23	1116	1056
Adults	1131	1071

The unit of the values is mg/cm^3

Table 1. Age- and sex-specific mean values for cortical vBMD, as used for the calculation of cortical thickness. Source: Schönau et al. (7).

... has encouraged physicians to make diagnostic and therapeutic decisions on the basis of an abstract set of numbers that are completely divorced from the underlying structural reality which the numbers purport to represent"[3]. The present contribution therefore has a two-fold aim: first, to present new and easily usable reference material for pQCT at the distal radius of young subjects; and second, to provide a framework for the interpretation of results.

Subjects and methods

Subjects. As described previously in detail, the study population comprised 478 healthy children, adolescents and young adults[1]. The children and adolescent group (defined as an age below 21 years) included 173 males and 185 females. The young adult group (21.0 to 39.9 years of age) was comprised of 31 men and 89 women. All subjects of the present analysis were either participants of the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) Study or parents of participants. The DONALD Study is an ongoing observational study investigating the interrelations of nutrition, growth and metabolism in healthy children. This study is performed at the Research Institute for Child Nutrition in Dortmund, Germany. The cohort was initially recruited for an anthropometric study in a representative sample of school children of Dortmund and later through personal recommendation of parents whose children were already participating. Overall, the study population mostly comprised middle class families and all participants were of Caucasian origin. On an annual basis, all participants undergo a full medical history and examination starting in infancy.

Forearm length was measured at the non-dominant forearm as the distance between the ulnar styloid process and the olecranon.

Peripheral quantitative computed tomography. Peripheral QCT was performed at the ultradistal radius using the Stratec XCT2000® equipment (Stratec Inc., Pforzheim, Germany). Measurements were performed at the non-dominant forearm. The scanner was positioned on the distal forearm and a coronal computed radiograph (scout view) was carried out. The scout view was used to position the scanner at the measurement site as indicated in Figure 1. A single tomographic slice of 2.0 mm thickness was taken at a voxel size of 0.4 x 0.4 x 2 mm. The speed of the translational scan movement was set at 15 mm/s.

Image acquisition, processing and the calculation of numerical values were performed using the manufacturer's software package (XCT 5.40). The cross-sectional area of the radius (total CSA) was determined after detecting the outer bone contour at the default threshold of 280 mg/cm^3. Total vBMD was defined as the mean density of the entire cross-section. Trabecular vBMD was determined as the mean density of the 45% central area of the bone's cross-section. Total CSA, total vBMD and trabecular vBMD were calculated using the software's CALCBD routine. Bone mineral content (BMC) was calculated as the product of total CSA and total vBMD.

Derivation of cortical thickness at the distal radius. As the cortex at the distal radius is very thin, it can not be directly determined with the pQCT system used in this study due to the partial volume effect[4-6]. To avoid this problem, an algorithm was developed which allows the calculation of cortical thickness at the distal radius from results which are less influenced by the partial volume effect[2]. This algorithm is based on three simplifying assumptions. First, the analyzed section through the distal radius was postulated to be composed of two homogeneous compartments, trabecular and cortical bone. Second, the radial cross-section was assumed to be circular. Third, cortical vBMD was assumed to be identical at the distal and proximal sites. In mathematical terms, the first of these assumptions can be translated into the following formula:

Total vBMD =
Relative cortical area x Cortical vBMD + (1 - Relative cortical area) x Trabecular vBMD, (1)

where relative cortical area is the fraction of the entire bone's cross-section consisting of cortical bone. Equation 1 can be reformulated to:

$$\text{Relative cortical area} = \frac{\text{total vBMD} - \text{trabecular vBMD}}{\text{cortical vBMD} - \text{trabecular vBMD}} \quad (2)$$

Following the second assumption, the distance of the periosteal (outer) bone surface and of the endocortical (inner) bone surface from the center of the bone correspond to:

$$\text{Periosteal radius} = (\text{Cross-sectional area} / \pi)^{1/2} \quad (3)$$
$$\text{Endocortical radius} = (\text{Trabecular bone area} / \pi)^{1/2} \quad (4)$$
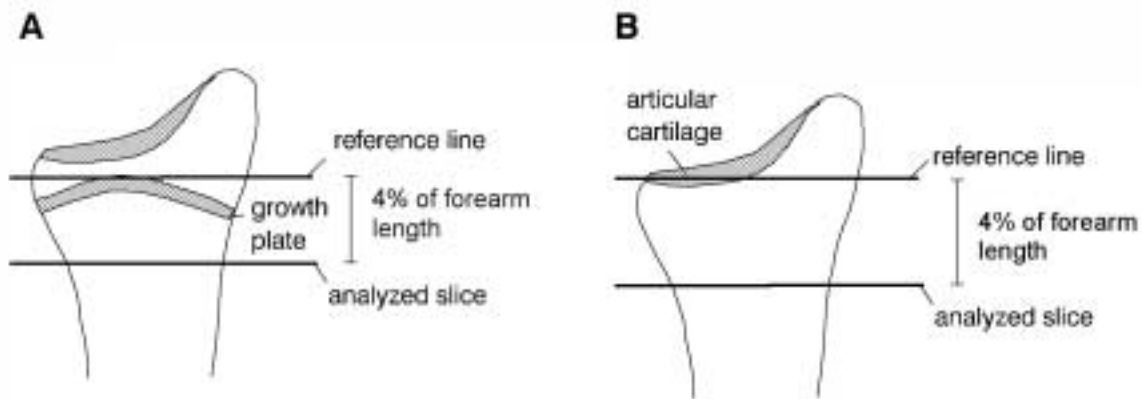
Figure 1. Schematic representation of the distal radius. Peripheral QCT is performed at a site whose distance to the 'reference line' corresponds to 4% of forearm length. The reference line is selected as follows. A. When the growth plate is still open, the reference line is drawn through the most distal portion of the growth plate. B. When the growth plate is no longer visible, the reference line is drawn through the middle of the ulnar border of the articular cartilage.

The area of the bone's cross-section occupied by trabecular bone is:

Trabecular bone area = (1 – Relative cortical area) x Cross-sectional area   (5)

Substituting equation 4 for trabecular bone area, the endocortical radius can be calculated as

Endocortical radius = [(1 – Relative cortical area) x Cross-sectional area / π)]$^{1/2}$ (6)

Cortical thickness is the difference between periosteal and endocortical radius. Substituting equation 2 for relative cortical area, cortical thickness can be calculated from equations 3 and 6 as follows:

Cortical thickness = (Cross-sectional area / π)$^{1/2}$ – {[1 - (total vBMD – trabecular vBMD) / (cortical vBMD – trabecular vBMD)] x Cross-sectional area / π}$^{1/2}$ (7)

Total CSA, total vBMD, trabecular BMD are measured results, cortical vBMD is assumed to be identical to the age- and gender-specific mean values for cortical vBMD at the proximal radius (Table 1). For example, to calculate distal radius cortical thickness in an 11-year-old girl, the adjusted mean value of proximal radius cortical vBMD in the female 10-11 year age group was used[7].

The reproducibilities of primary and derived pQCT parameters were determined in a group of 9 healthy adult volunteers (all women; age 34 to 56 years) by performing the measurement twice, with repositioning of the forearm. Reproducibility was not tested in children, because it was judged unethical to perform repeated analyses involving ionizing radiation in children solely for methodological purposes. The precision error was calculated as root-mean-square standard deviations of the duplicate measurements, as proposed by Glüer et al.[8]. Reproducibility was 1.40% for cross-sectional area, 0.91% for BMC, 1.49% for total vBMD, 0.82% for trabecular vBMD and 2.70% for cortical thickness.

Statistical analyses. Cole's LMS method was used to derive age- and sex-dependent reference data[9]. This method assumes that the data can be transformed to a normal distribution by a suitable power transformation (L). The distribution is then summarized by the median (M) and the co-efficient of variation (S). The present data were skewed towards higher values, but were normally distributed after logarithmic transformation, which in the LMS system corresponds to an L of 0 (ref. 9). Therefore, the value of L was fixed to 0 for all analyses, and only median and co-efficient of variation needed to be modeled to derive reference ranges.

Age-dependent regression curves for M and S were independently fitted for girls (from 6.0 to 18.5 years) and boys (from 6.0 to 17.5 years). The different age ranges for the sexes were due to the difference in availability of data. Linear, exponential, logarithmic and hyperbolic simple regression models, as well as polynomials of second, third and fourth order were tested. The relationship with age was assumed to be linear, unless one of the other models yielded an adjusted co-efficient of determination (r^2) which was higher by at least 0.03. In this case, the model with the maximum co-efficient of determination was chosen. For the adult age range from 21 to 40 years, none of the pQCT parameters showed significant changes with age. Therefore, M and S were calculated as constant values. Very few data were available between 18.5 and 21 years in females (N=13) and between 17.5 and 21 years in males (N=11). For this age range, reference ranges were therefore obtained by linear interpolation between the end points of the regression curves (values at 18.5 years for females, at 17.5 years for males) and the 'adult' result.

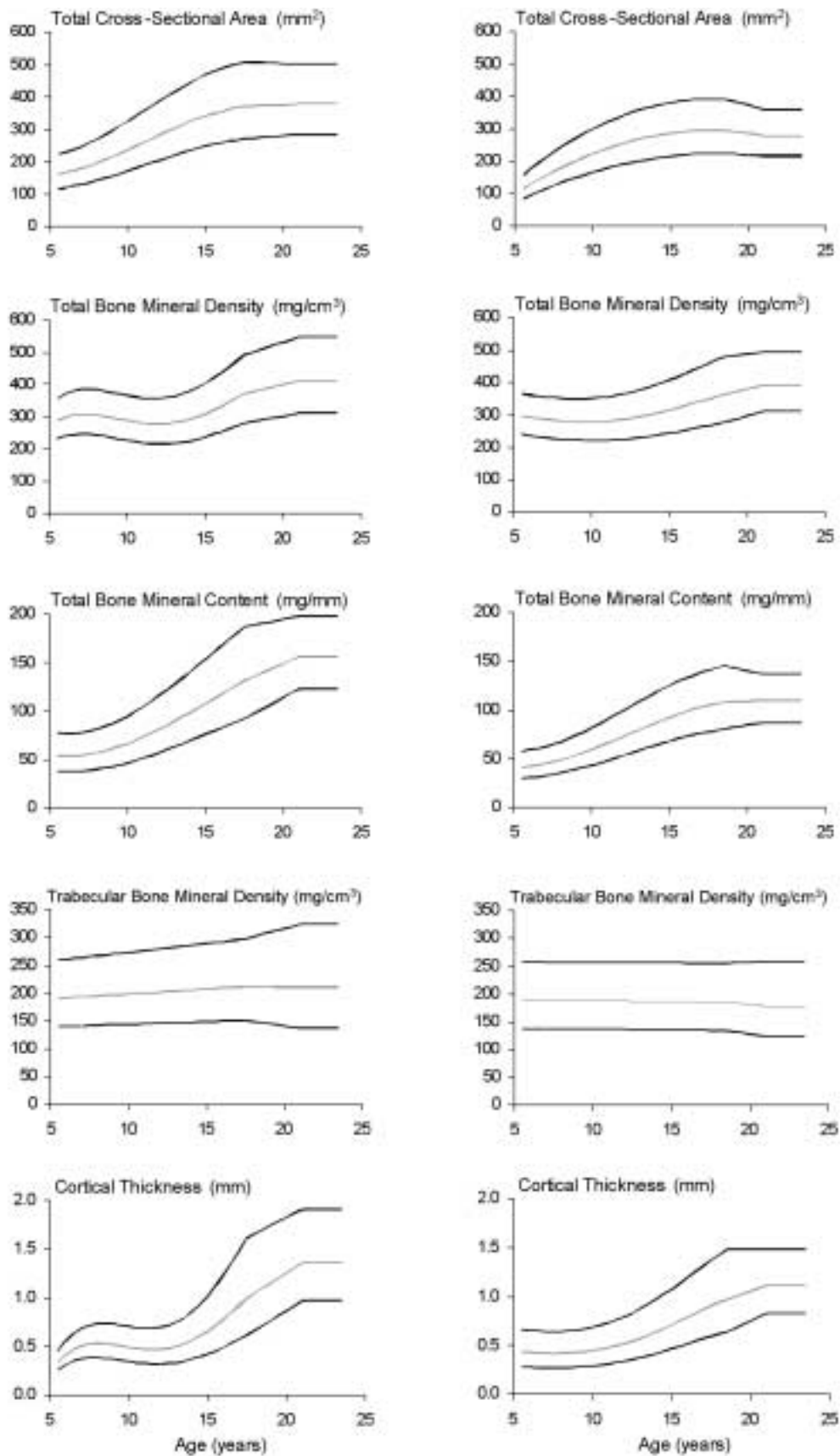The use of z-scores implies that data are normally distrib-

Figure 2. Reference ranges for pQCT results at the distal radius in males (left) and females (right). Shown are the mean (grey middle line) and the range of 2 standard deviations around the mean (black lines).

	S	M
6 to 18.5 years		
BMC (mg/mm)	$0.1703-0.001246 \times age$	$67.47-11.56 \times age+1.474 \times age^2-0.03948 \times age^3$
Trabecular vBMD (mg/cm^3)	$0.1563+0.00019168 \times age$	$189.9-0.2504 \times age$
Total CSA (mm^2)	$1/(6.284+0.04612 \times age)$	$-78.49+41.90 \times age-1.169 \times age^2$
Total vBMD (mg/cm^3)	$0.09171+0.002507 \times age$	$320.8+3.581 \times age-2.646 \times age^2+0.2423 \times age^3-0.005554 \times age^4$
Cortical Thickness (mm)	$0.2146-0.0003348 \times age$	$0.3475+0.07192 \times age-0.01706 \times age^2+0.001414 \times age^3-0.00003256 \times age^4$
21 to 40 years		
BMC (mg/mm)	0.1110	109.5
Trabecular vBMD (mg/cm^3)	0.1847	178.9
Total CSA (mm^2)	0.1276	279.0
Total vBMD (mg/cm^3)	0.1155	392.4
Cortical Thickness (mm)	0.1449	1.11

Age represents chronological age in years

Table 2. Reference data for pQCT analysis at the distal radius (4% site) in females. Given are values for the age-dependent co-efficients of variation (S) and mean values (M).

uted, a condition which is often neglected when reference data for a method are presented. As the present data were normally distributed only after logarithmic transformation, it is necessary to calculate z-scores on the basis of the logarithmically transformed data. After back-transformation this results in asymmetrical reference ranges, as the lower end of the reference range (corresponding to a z-score of -2) is closer to the mean value than the upper end of the reference range (corresponding to a z-score of +2). This reflects the fact that the original data were skewed towards higher values. In this situation, the use of symmetrical reference ranges (based on mean ± 2 SD of the untransformed data) would decrease the lower limit of the reference range, which would make the diagnostic procedure less sensitive for detecting low values.

Results

Age- and sex-specific reference ranges for pQCT results at the distal radius are shown graphically in Figure 2. The equations for M and S that describe these curves are given in Tables 2 and 3. As indicated by Cole, a given test result can be converted into the age- and sex-specific z-score using the formula[9]:

$$\text{Z-score} = [\text{Ln(patient's test result/M)}]/S$$

where Ln is the natural logarithm, M corresponds to the age- and sex-specific mean value as derived from the equations in Tables 2 and 3, and S is the age- and sex-specific co-efficient of variation as derived from the same Tables.

An example of how to use these data: assume that a 12.4 year-old girl has a total BMC of 40 mg/mm. As shown in Table 2, S can be calculated as $0.1703 - 0.001246 \times 12.4 = 0.1549$ and M is $67.47 - 11.56 \times 12.4 + 1.474 \times 12.4^2 - 0.03948 \times 12.4^3 = 75.50$. The z-score of this girl therefore is

$\text{Ln}(40/75.50)/0.1549 = -4.10$. These calculations may appear complicated, but once the equations from Tables 2 and 3 have been entered into a spreadsheet program, z-scores can be computed automatically.

Discussion

In this study we derived smoothed reference ranges for pQCT results at the distal radial metaphysis. Cole's LMS method was chosen to establish reference data because it is easy to implement and is widely used in the field of pediatric bone research[10-12]. We had previously presented results from the same study as mean and standard deviations in discrete age groups. Although mathematically very simple, this approach is not practical for clinical use, because of the discontinuities that arise when a patient crosses the cut-off age between two age intervals. The differences between the two types of reference ranges are shown in Figure 3.

Figure 3 also shows a practical example to highlight the utility of the new reference data. Three sequential BMC results of an adolescent patient are shown. According to the new reference data, all three results correspond to a z-score of -2.6. The clinician might conclude that this patient's BMC is low for age, but is showing an increase that is appropriate for age. Based on the older reference data, his BMC results at time points 1, 2 and 3 correspond to z-scores of -1.6, -2.2 and -1.9, respectively, which is certainly more difficult to interpret.

To evaluate pQCT results at the distal radial metaphysis in children and adolescents, it is useful to remember the physiology of bone growth at that location. As long as bone length increases, new bone is continuously added at the junction between the growth plate and metaphysis. At the opposite end of the metaphysis, all trabeculae are removed and

	S	M
6 to 17.5 years		
BMC (mg/mm)	0.1787-0.0001154 x age	$102.9–17.30 \times age+1.750 \times age^2–0.03816 \times age^3$
Trabecular vBMD (mg/cm^3)	0.1473-0.001256 x age	$181.0+1.782 \times age$
Total CSA (mm^2)	0.1633-0.000332 x age	$207.1–29.93 \times age+4.709 \times age^2–0.1408 \times age^3$
Total vBMD (mg/cm^3)	0.09289+0.002707 x age	$-430.6+285.3 \times age–38.67 \times age^2+2.138 \times age^3–0.0406 \times age^4$
Cortical Thickness (mm)	0.09470+0.008307 x age	$-3.609+1.502 \times age–0.1938 \times age^2+0.01038 \times age^3–0.0001915 \times age^4$
21 to 40 years		
BMC (mg/mm)	0.1190	156.2
Trabecular vBMD (mg/cm^3)	0.2154	211.3
Total CSA (mm^2)	0.1416	378.5
Total vBMD (mg/cm^3)	0.1409	412.6
Cortical Thickness (mm)	0.1704	1.363

Table 3. Reference data for pQCT analysis at the distal radius (4% site) in males. Given are values for the age-dependent co-efficients of variation (S) and mean values (M).

the cortex is integrated into the diaphysis. As the growth plate proceeds in a distal direction at a speed of approximately 1 cm/year, a section of newly created metaphyseal bone continues to decrease its diameter by periosteal resorption until it has reached the cross-sectional size of the diaphysis (metaphyseal inwaisting). A detailed analysis of these processes has been presented in an earlier publication[2].

Interpretation of individual pQCT parameters

Total Cross-Sectional Area: Due to metaphyseal inwaisting, the cross-sectional area of the radial metaphysis decreases with increasing distance from the growth plate. Although the periosteum of the 4% site is continuously undergoing resorption during growth, cross-sectional area increases. This is because metaphyseal inwaisting starts at the growth plate, which expands laterally with growth. Thus, the two determinants of total CSA at the 4% site are the cross-sectional area of the growth plate and the activity of metaphyseal inwaisting.

A low CSA can reflect generalized small bone size (i.e., short stature), or − where bone length is normal – slender bones. Exaggerated metaphyseal inwaisting, as is often seen in osteogenesis imperfecta, can also be a cause of a low total CSA. A falsely low total CSA reading can arise if the measurement has been obtained too far away from the growth plate. The user of the above reference data must therefore be sure to position the reference line in the same manner as was done in the present study (Figure 1).

A high total CSA can be due to the opposite of the above (tall stature; sturdy bones; decreased metaphyseal inwaisting; the measurement was done too far distal). Decreased metaphyseal inwaisting is observed in a number of bone dysplasias (e.g. osteopetrosis) and occasionally during bisphosphonate treatment of growing children[13].

Total vBMD: All densities measured by pQCT follow Archimedes' definition of density (density=mass/volume). Nevertheless, it may be appropriate to stress this point by using the label 'volumetric', because the term density is used for a variety of different measures in the current literature. Total vBMD is determined by trabecular and cortical vBMD and by the relative sizes of the trabecular and cortical compartments (Figure 4)[14]. The processes determining the relative volume of the cortical compartment are periosteal expansion and endocortical resorption or apposition. The size of the trabecular compartment is determined by the movements of the endocortical surface. During growth, these periosteal and endocortical processes are a function of bone modeling[15].

A total vBMD result below the reference range may reflect low trabecular vBMD. This possibility can be easily verified, as trabecular vBMD is usually quantified in the same measurement run. A low total vBMD reading in the presence of a normal trabecular vBMD points to a problem within the cortical compartment (usually reduced cortical thickness, see below).

Total BMC: BMC in the setting of pQCT analyses represents the mass of mineral per unit of axial bone length. It is therefore given in units such as mg/mm. Thus, a BMC result of 80mg/mm means that a bone slice of 1mm thickness contains 80mg of mineral. BMC is the product of total CSA and total vBMD. The factors influencing these two components of BMC have been discussed above.

Trabecular vBMD: Trabecular vBMD is the mass of mineral in the trabecular compartment divided by the volume of this compartment. In pQCT measurements, trabecular vBMD is usually measured as the mean mineral density of the 45% central area of the bone's cross-section. This geometric definition of trabecular bone includes some margin of safety to exclude admixture of cortical bone to the trabecular region of interest. The actual relative cross-sectional area of the tra-
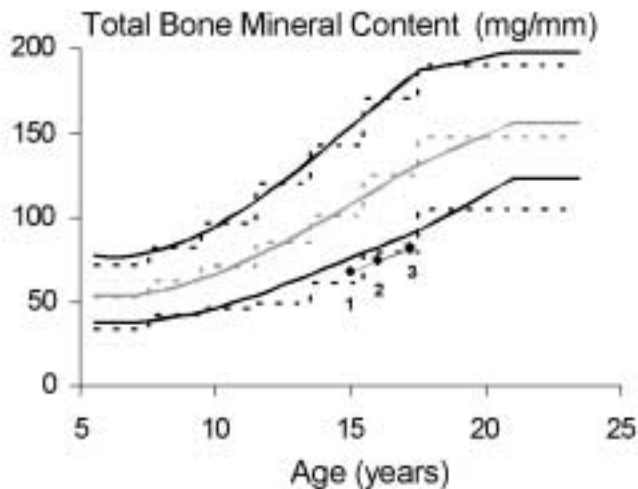
Figure 3. Comparison of reference ranges for BMC at the distal radius in boys. New reference ranges obtained with the LMS method are shown as drawn lines, reference ranges based on mean value and standard deviations in discrete age groups are shown as dotted lines. Grey lines show the results corresponding to a BMC z-score of 0, black lines represent z-scores of -2 and +2, respectively.

Figure 4. Relationship between total vBMD, relative cortical area and trabecular and cortical vBMD in a cross-sectional slice of a bone.

becular compartment is considerably larger than 45% (4), but the resolution of the pQCT system is not sufficient to exactly trace the border between trabecular and cortical bone.

Trabecular vBMD depends on trabecular number (this is the number of trabeculae which an imaginary line through the bone would hit per mm of its length), mean trabecular thickness and the average material density of the trabeculae (i.e., the mineral density excluding all 'holes' in the bone, such as bone marrow and osteocyte lacunae)[14]. The mechanisms determining trabecular number during growth have not been well characterized. Trabecular thickness depends on remodeling activity (through variations in remodeling space) and on remodeling balance[16].

A number of disease processes can lead to low trabecular vBMD in children. These include insufficient production or increased resorption of trabeculae at the junction between the growth plate and metaphysis. An example for this is osteogenesis imperfecta[17]. Trabeculae may be too thin, which is also observed in osteogenesis imperfecta. Low trabecular vBMD can also be due to a low material density, when a mineralization defect is present (e.g., osteomalacia). In this case the total vBMD should also be low. Finally, trabecular vBMD decreases in a distal to proximal direction[18]. Therefore, falsely low trabecular vBMD results will occur, if the site of analysis is selected too far proximal.

Cortical thickness: It is difficult to evaluate cortical bone at the distal radius, because the cortex is very thin at that location. The XCT software of Stratec scanners yields a number called 'cortical + subcortical BMD'. This number reflects an ill-defined mix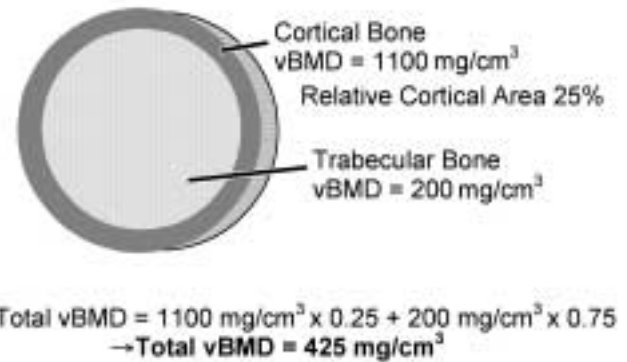ture of cortical and trabecular bone in the outer 55% of the total CSA and is therefore difficult to interpret. In our view it is more appropriate to express the amount of bone within the cortical compartment as cortical thickness. This approach helps to understand the structural properties of the analyzed bone.

When results are analyzed in this way, it becomes apparent that cortical thickness at the distal radius does not increase much during the growth phase (Figure 2). This may be surprising at first sight, but is an inevitable consequence of the growth process. In growing children a pQCT measurement at the 4% site looks at newly formed bone. The 'age' of the bone at the 4% location depends directly on the growth rate of the radius, which is fairly constant before puberty[2]. Thus, no matter whether the child is 6 or 12 years old, the analyzed bone section will usually be less than one year old. Conceivably this makes it difficult for the bone to adapt its strength to the increasing mechanical needs during this period of life, which may explain the high rate of distal radius fractures in older children[2]. Once longitudinal growth has stopped, bone strength can catch up with requirements and cortical thickness increases rapidly.

Conclusion

In this study we provide reference data for pQCT analyses at the distal radius and give some hints for the interpretation of results in children and adolescents. These data should facilitate the use of this technique in the paediatric setting.

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