

Bone Densities and Bone Size at the Distal Radius in Healthy Children and Adolescents: A Study Using Peripheral Quantitative Computed Tomography

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Peripheral quantitative computed tomography (pQCT) has the ability to improve the diagnostic utility of densitometry in children and adolescents, because bone size and volumetric bone mineral density (vBMD) can be measured independently. Nevertheless, detailed reference data are lacking. We therefore performed pQCT (XCT-2000 scanner, Stratec, Inc., Pforzheim, Germany) at the distal radius in 371 healthy children, adolescents, and young adults (185 males and 186 females, ages 6–23 years) and in 107 of their parents (19 men and 88 women, ages 29–40 years). Total vBMD, trabecular, and “cortical + subcortical” vBMD as well as cross-sectional area (CSA) were determined at the “4% site” of the distal radius. This location was defined as the site whose distance to the most distal portion of the growth plate or to the radial articular surface corresponded to 4% of the forearm length. In both genders, total vBMD remained stable between 6 and 15 years of age and then increased by 30% in girls and by 46% in boys. Regarding pubertal development, total vBMD remained almost constant throughout pubertal stages 1–4 and thereafter increased in both genders. Trabecular vBMD did not change with age in girls, whereas in boys an increase with age of about 10% was noted after 15 years of age. Males had higher trabecular vBMD than females. This gender difference increased from 6% in prepubertal children to 23% in adults. The variation with age and pubertal stage in “cortical + subcortical” vBMD-cort was similar to that of total vBMD. CSA roughly doubled between 6 and 15 years of age in both genders. In conclusion, the availability of this reference material will provide a basis for the use of pQCT in the assessment of pediatric bone diseases. (Bone 28:227–232; 2001) © 2001 by Elsevier Science Inc. All rights reserved.

Key Words: Bone mineral density (BMD); Children; Peripheral quantitative computed tomography (pQCT); Radius; Reference data; Trabecular bone.

Introduction

Metabolic bone diseases are relatively rare in children, but may have devastating consequences.¹⁸ In addition, many chronic

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disorders and/or their treatments are associated with secondary bone disease in children.¹⁸ It is also becoming increasingly appreciated that postmenopausal osteoporosis is likely influenced by events taking place during bone development.^{2,3,20} Therefore, evaluation of the growing skeleton is the focus of increasing interest in both pediatric and adult medicine.

Bone densitometry is a widely used tool for the quantitative assessment of the skeleton. Perhaps the most frequently assessed densitometric parameter at present is areal bone mineral density (aBMD; the mineral mass of bone per unit area of the two-dimensional projection image). This parameter can be measured by dual-energy X-ray absorptiometry (DXA) and is expressed as grams per square centimeter. However, the main drawback of aBMD in pediatric use is that it is a bone-size-dependent measure. For this reason, aBMD is often difficult to interpret in children, because short children will have a lower aBMD than their age-matched peers, even if their smaller bones are otherwise completely normal.

In contrast, peripheral quantitative computed tomography (pQCT) allows for unambiguous distinction between the effects of bone size and changes in bone mass per unit volume (volumetric bone mineral density [vBMD], expressed as grams per cubic centimeter). Therefore, pQCT has the potential to improve the diagnostic utility of densitometry in the growing skeleton. To make use of this potential it is essential to establish a detailed reference database. Thus, we performed pQCT at the distal radius in a large and well-characterized group of healthy children and young adults.

Subjects and Methods

Subjects

The study population comprised 371 healthy children, adolescents, and young adults (185 males and 186 females, ages 6–23 years) and 107 of their parents who were ≤ 40 years of age (19 men and 88 women, ages 29–40 years). All subjects were white. The children were participants in the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study, an ongoing observational study investigating the interrelationships between nutrition, growth, and metabolism in healthy children. Informed consent was obtained from the children's parents or from the subjects aged >18 years. The study protocol was approved by the ethics committee of the University of Cologne and by the Bundesamt für Strahlenschutz (a federal agency that provides protection from radiation, located in Salzgitter, Germa-

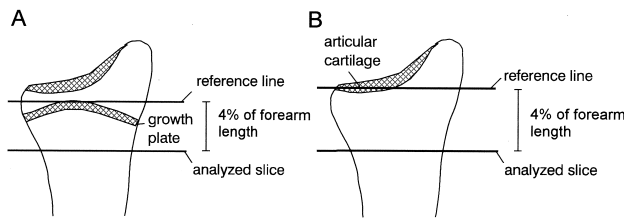


Figure 1. Schematic representation of the distal radius. pQCT was performed at a site having a distance from the “reference line” that corresponded to 4% of forearm length. The reference line was selected as follows: (A) when the growth plate was still open, the reference line was drawn through the most distal portion of the growth plate; (B) when the growth plate was no longer visible, the reference line was drawn through the middle of the ulnar border of the articular cartilage.

ny). On an annual basis, all participants involved in the DONALD study undergo a full medical history and examination starting in infancy. pQCT was performed once in each participant on the occasion of a yearly check-up. The present analysis included only subjects currently found to be healthy; not taking drugs known to affect bone metabolism; and with no history of disorders concerning nutrition, metabolism, or bone development. From the original population of 379 children and adolescents, 8 had to be removed due to the exclusion criteria. In five children, analysis of pQCT measurements was not possible due to movement artifacts, one had to be excluded because of lactose intolerance, one for Perthes disease at the age of 5 years, and one for Hirschsprung’s disease diagnosed at the age of 16 months.

The stage of pubertal development was determined by physical examination using the grading system defined by Tanner for pubic hair.²⁵ Examination for pubertal stage was refused by 25 boys and by 23 girls. Height was determined to the next succeeding 1 mm using a Harpenden stadiometer. Weight was measured to the nearest 0.1 kg using digital electronic scales with the children clothed in underwear. Forearm length was measured as the distance between the ulnar styloid process and the olecranon using a caliper at the nondominant forearm to the nearest millimeter.

Peripheral Quantitative Computed Tomography

pQCT was performed at the ultradistal radius using Stratec XCT-2000 equipment (Stratec, Inc., Pforzheim, Germany). The scanner was equipped with a low-energy (38 keV) X-ray tube. Radiation dose for a single scan was 0.3 mSv, with the effective dose for the forearm about 0.1 mSv from a radiation source of 45 kV at 150 μ A. The machine was calibrated once every 3 days (single slice) or once per month (multiple slice – cone phantom), respectively, with phantoms provided by the manufacturer.

Measurements were performed at the nondominant 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 mm. The speed of the translational scan movement was set at 15 mm/sec. The resulting time for a measurement run was about 2–3 min in the smaller children and 4–5 minutes in adults, depending on the cross-sectional size of the forearm.

Image processing and the calculation of numerical values were performed using the manufacturer’s software package (version 5.40). The cross-sectional area (CSA) of the radius was determined after detecting the outer bone contour at a threshold of 280 mg/cm³. Total vBMD (vBMD-tot) was defined as the

mean density of the total cross section. Trabecular vBMD (vBMD-trab) was determined as the mean density of the 45% central area of the bone’s cross section. The pQCT system also yields a parameter called “cortical + subcortical” vBMD (vBMD-cort). This represents the mean density in the 55% peripheral bone area.

Reproducibility was determined in a group of nine healthy adult volunteers (all women, age 34–56 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 duplicate measurements, as proposed by Glüer et al.¹⁰ Reproducibility was 1.40% for CSA, 1.49% for vBMD-tot, 0.82% for vBMD-trab, and 1.10% for vBMD-cort. Data for accuracy are not available for the XCT-2000 scanner. The accuracy of the previous version of this device (XCT-960) was determined using the European forearm phantom.¹ Average accuracy values of 10.0%, 2.6%, 1.9%, and 14.0% were reported for CSA, vBMD-tot, vBMD-trab, and vBMD-cort, respectively.

Statistical Analyses

For comparisons between two groups the Mann–Whitney *U*-test was used. The significance of differences between more than two groups was calculated by the Kruskal–Wallis test. For analysis of the significance of pubertal effects, the adult group was not included. Associations between two parameters were tested using Pearson’s correlation coefficient. Stepwise multiple regression analyses were performed in the forward mode. For all calculations, the SAS 6.12 software package (SAS Institute, Inc., Cary, NC) was used.

Results

The anthropometric characteristics of the study population are given in **Table 1**. Age-dependent results for basic pQCT parameters are shown in **Figures 2, 3, 4, and 5** and **Table 2**. The relationship between pQCT results and pubertal stages is shown in **Tables 3 and 4**.

In both genders, vBMD-tot remained stable between 6 and 15 years of age, and then increased by 30% in girls and by 46% in boys (**Figure 2** and **Table 2**). Boys tended to have higher vBMD-tot than girls from 6 to 11 years of age and after the age of 18 years. As suggested by the pattern of age-dependency, vBMD-tot remained almost constant throughout pubertal stages 1–4, and thereafter increased in both genders (**Tables 3 and 4**). The gender difference between pubertal stages was significant only in the prepubertal group.

Volumetric BMD-trab did not show a significant variation with age in the female group (**Figure 3** and **Table 2**; $p = 0.72$ by Kruskal–Wallis test). In the male subjects, the variation in vBMD-trab between age groups was significant ($p = 0.01$) because of a slight increase after 15 years of age. Males >15 years of age had a 10% greater vBMD-trab than those <15 years of age (217 ± 37 mg/cm³ vs. 198 ± 34 mg/cm³; $p = 0.002$). Volumetric BMD-trab tended to be higher in males than in females in most age groups, but the differences was significantly only from the age of 14 years to adulthood. Volumetric BMD-trab did not change between pubertal stages in girls (**Table 3**; $p = 0.77$) and increased slightly after Tanner stage 3 in boys (**Table 4**; $p = 0.01$). Prepubertal boys had a 6% higher vBMD-trab than girls. The gender difference in vBMD-trab increased to 13% in adolescents with Tanner stage 5 and was 23% in the adult group (**Tables 2 and 4**).

Table 1. Anthropometric characteristics of the study population (data expressed as mean ± SD)

Age (years)	Females				Males			
	n	Height (cm)	Weight (kg)	BMI (kg/m ²)	n	Height (cm)	Weight (kg)	BMI (kg/m ²)
6–7	28	122.4 ± 4.9	23.8 ± 3.6	15.8 ± 1.4	28	122.6 ± 5.8	24.0 ± 4.3	15.9 ± 1.8
8–9	27	133.8 ± 5.4	29.7 ± 5.5	16.5 ± 2.3	24	135.6 ± 6.6	29.9 ± 4.3	16.2 ± 1.6
10–11	30	148.9 ± 8.1	40.5 ± 9.8	18.0 ± 3.3	32	147.5 ± 8.2	40.7 ± 8.9	18.5 ± 2.9
12–13	31	157.6 ± 8.3	50.8 ± 13.9	20.2 ± 4.2	27	156.9 ± 8.9	47.6 ± 10.4	19.2 ± 3.1
14–15	25	166.7 ± 7.2 ^b	57.0 ± 11.8	20.4 ± 3.1	29	172.8 ± 7.7	60.3 ± 10.6	20.1 ± 2.4
16–17	23	169.4 ± 7.8 ^b	60.1 ± 7.9 ^a	20.9 ± 2.4	22	176.9 ± 8.7	68.6 ± 11.3	21.8 ± 2.5
18–23	22	169.6 ± 7.3 ^c	60.5 ± 11.0 ^c	21.0 ± 2.9 ^b	23	181.2 ± 6.2	78.0 ± 15.9	23.6 ± 3.6
Adults	88	167.9 ± 6.1 ^c	68.5 ± 12.2 ^c	24.3 ± 4.3	19	182.8 ± 5.4	83.3 ± 7.8	24.9 ± 2.3

BMI, body mass index. Significance levels for difference between females and males of the same age group are as follows: ^a*p* < 0.05; ^b*p* < 0.01; ^c*p* < 0.001.

The variation with age and pubertal stage in vBMD-cort was similar to that of vBMD-tot (Figure 4 and Tables 2–4). CSA roughly doubled between 6 and 15 years of age in both genders (Figure 5 and Table 2). Thereafter, CSA appeared to level off in females, but showed a small further increase in males. CSA was significantly higher for males in most age groups.

Table 5 shows the interrelationship between clinical characteristics and pQCT results in children and adolescents. Volumetric BMD-tot, vBMD-cort, and CSA were highly significantly correlated with all of these clinical parameters. In contrast, vBMD-trab in girls was related only to BMI. In boys but not in girls, vBMD-trab was associated with pubertal stage. To evaluate which of these parameters were independently associated with which of these parameters were independently associated with pQCT results, analyses of covariance were performed with models including age, pubertal stage, height, weight, and BMI as independent variables. These calculations revealed that only age (*p* < 0.001 each) and height (*p* = 0.02 in girls, *p* < 0.001 in boys) had an independent effect on vBMD-tot in both genders. The only variable that had a significant predictive power on vBMD-trab was BMI in girls (*p* = 0.002) and pubertal stage in boys (*p* = 0.04). Only height was an independent predictor of CSA in both genders (*p* < 0.001).

Discussion

In this study we performed pQCT at the distal radius in a group of 478 subjects aged 6–40 years. Following literature reports and our own experience with this method in adults,¹⁹ bone was analyzed at the so-called “4% site.” The advantage of this location is that it contains metaphyseal spongiosa,²¹ which allows for determination of vBMD-trab. However, in children, it is often not possible to use the same definition of the “4% site” as in adults (site whose distance to the articular cartilage corresponds to 4% of forearm length), because this site can be located very close to or even within the mineralized portion of the growth plate, which results in grossly elevated values for vBMD-trab. For this reason we used a different definition of the “4% site” when the growth plate was still open (site whose distance to the most distal part of the growth plate corresponds to 4% of forearm length). It is unlikely that this change in definition of the measurement site had a major impact on our results, because the difference amounts to only 2–3 mm. Nevertheless, for clarity, it might be preferable to perform pQCT at a site where the same definition could be used for both children and adults. It might be

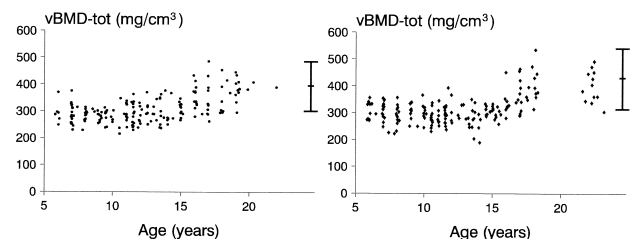


Figure 2. Age-dependency of vBMD-tot in girls (left) and boys (right). Results in adults from 29 to 40 years of age are shown as bars (mean ± 2 SD).

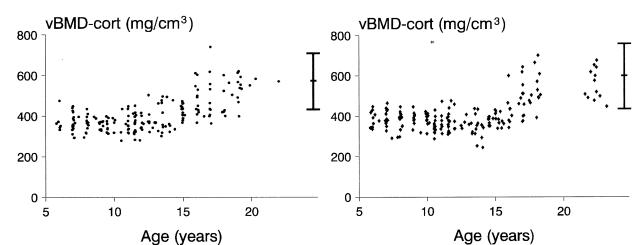


Figure 4. Age-dependency of vBMD-cort in girls (left) and boys (right). Results in adults from 29 to 40 years of age are shown as bars (mean ± 2 SD).

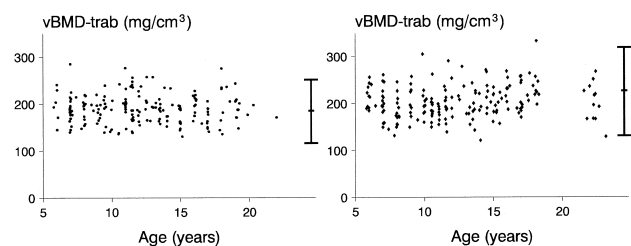


Figure 3. Age-dependency of vBMD-trab in girls (left) and boys (right). Results in adults from 29 to 40 years of age are shown as bars (mean ± 2 SD).

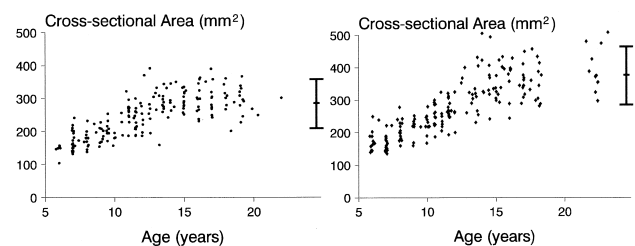


Figure 5. Age-dependency of cross-sectional area in girls (left) and boys (right). Results in adults from 29 to 40 years of age are shown as bars (mean ± 2 SD).

Table 2. Age-dependency of peripheral quantitative computed tomography (pQCT) results at the distal radius (mean ± SD)

Age (years)	Females				Males			
	vBMD-tot (g/cm ³)	vBMD-trab (g/cm ³)	vBMD-cort (g/cm ³)	CSA (mm ²)	vBMD-tot (g/cm ³)	vBMD-trab (g/cm ³)	vBMD-cort (g/cm ³)	CSA (mm ²)
6–7	290 ± 36 ^a	191 ± 31	370 ± 45	164 ± 30	306 ± 34	206 ± 32	388 ± 42	174 ± 31
8–9	283 ± 22	186 ± 23	362 ± 32	185 ± 25 ^b	294 ± 34	189 ± 34	380 ± 41	211 ± 31
10–11	281 ± 36	191 ± 36	355 ± 44	237 ± 39	290 ± 33	194 ± 32	368 ± 41	245 ± 37
12–13	295 ± 39	197 ± 32	376 ± 54	260 ± 55 ^a	292 ± 38	201 ± 36	366 ± 47	289 ± 47
14–15	303 ± 37	179 ± 25 ^a	407 ± 53 ^a	297 ± 32 ^b	293 ± 35	201 ± 33	369 ± 47	351 ± 70
16–17	350 ± 57	186 ± 26 ^b	483 ± 95	300 ± 45 ^c	349 ± 56	217 ± 30	458 ± 86	358 ± 49
18–23	371 ± 50	195 ± 35 ^a	516 ± 74	295 ± 42 ^c	401 ± 60	220 ± 42	549 ± 83	377 ± 64
Adults	395 ± 46 ^a	182 ± 34 ^c	569 ± 69	281 ± 37 ^c	428 ± 56	224 ± 46	594 ± 81	374 ± 45

Refer to *Subjects and Methods* for abbreviations. Significance levels for difference between females and males of the same age group are as follows: ^a*p* < 0.05; ^b*p* < 0.01; ^c*p* < 0.001.

advantageous to use a fixed distance from the distal articular cartilage.

We analyzed the four basic pQCT parameters that the system provides to the user (i.e., vBMD-tot, vBMD-trab, vBMD-cort, and CSA). Children <6 years of age were not included in the study, because they are usually unable to keep their arm in a fixed position for the duration of measurement. In this study the most recent version of the manufacturer’s pQCT system (Stratec XCT-2000) was used. Although this equipment uses the same basic technology as previous versions (XCT-900 and XCT-960), it differs from these in a variety of settings. These differences include a thinner slice thickness of the measured bone (2 mm for XCT-2000, 2.5 mm for XCT-900 and XCT-960) and a smaller voxel size (400 μm for XCT-2000, 590 μm for XCT-900 and XCT-960). In addition, it is important to note that the XCT-900 scanner was calibrated to read a density of 0 mg/cm³ at the linear attenuation of water, whereas XCT-960 and XCT-2000 read a density of 0 mg/cm³ at the linear attenuation of fat.¹² For this reason, the density readings of the XCT-960 or XCT-2000 equipment are about 40–50 mg/cm³ higher than those of the XCT-900 device.^{12,16}

Previous densitometric studies in children have reported relatively large increases with age in aBMD at the distal radius.^{7,26}

For example, a large Argentinean study using DXA found that at between 6 and 20 years of age, aBMD increased by 70% in females and 105% in males.²⁶ Our data suggest that at least half of this increase in aBMD is due to increases in bone size, as in our study vBMD-tot increased only by 34% in girls and by 39% in boys in the same age range. This re-emphasizes the fact that the term “bone density” should not be used without qualification (“areal” or “volumetric”), as otherwise basically different measurements can be confounded.^{2,22,24}

One of the advantages of pQCT is that trabecular bone can be analyzed without interference from cortical structures. The parameter describing trabecular bone, vBMD-trab, is an integrated measure of trabecular number, trabecular thickness, and mean material density of the trabeculae. In addition, vBMD-trab might also be influenced by changes in marrow composition,¹¹ but to our knowledge this has not been tested at the distal radius. Possibly, the most surprising result of our analyses was that vBMD-trab did not increase with age in girls and increased only very slightly in boys. This is in accordance with the results from smaller pQCT studies of the distal forearm,^{4,6,23} but contrasts with results obtained at the lumbar spine and in the ileum. Lumbar spine vBMD-trab increases by 15%–20% during puberty.⁸ Cancellous bone volume per tissue volume of ileal bone—

Table 3. Peripheral quantitative computed tomography (pQCT) results at the distal radius as a function of pubertal stage in girls (mean ± SD)

Tanner stages	n	Age (years)	vBMD-tot (g/cm ³)	vBMD-trab (g/cm ³)	vBMD-cort (g/cm ³)	CSA (mm ²)
1	65	8.5 ± 1.6	284 ± 30 ^b	187 ± 29 ^a	363 ± 39 ^b	188 ± 38 ^b
2	13	11.1 ± 1.0	277 ± 34	190 ± 37	348 ± 37	239 ± 57 ^a
3	14	11.7 ± 1.0 ^a	288 ± 44	204 ± 44	356 ± 50	250 ± 47
4	9	13.2 ± 1.4	291 ± 43	197 ± 32	375 ± 56	282 ± 30
5	62	16.3 ± 2.4 ^b	347 ± 54	190 ± 28 ^c	476 ± 87	295 ± 43 ^c

Refer to *Subjects and Methods* for abbreviations. Significance levels for difference between females and males of the same age group are as follows: ^a*p* < 0.05; ^b*p* < 0.01; ^c*p* < 0.001.

Table 4. Peripheral quantitative computed tomography (pQCT) results at the distal radius as a function of pubertal stage in boys (mean ± SD)

Tanner stages	n	Age (years)	vBMD-tot (g/cm ³)	vBMD-trab (g/cm ³)	vBMD-cort (g/cm ³)	CSA (mm ²)
1	74	8.8 ± 1.9	299 ± 32	198 ± 31	381 ± 41	212 ± 47
2	14	11.5 ± 1.3	288 ± 40	186 ± 31	372 ± 52	269 ± 43
3	10	12.5 ± 1.0	286 ± 33	197 ± 36	359 ± 37	293 ± 44
4	14	14.0 ± 1.2	296 ± 42	210 ± 35	367 ± 50	334 ± 65
5	48	18.0 ± 2.8	361 ± 72	215 ± 40	481 ± 109	377 ± 59

Refer to *Subjects and Methods* for abbreviations.

Table 5. Pearson's correlation coefficients in children and adolescents

	vBMD-tot		vBMD-trab		vBMD-cort		CSA	
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
Age	0.55 ^c	0.51 ^c	-0.02	0.16 ^a	0.63 ^c	0.56 ^c	0.76 ^c	0.81 ^c
Pubertal stage	0.54 ^c	0.44 ^c	0.04	0.22 ^b	0.60 ^c	0.46 ^c	0.75 ^c	0.81 ^c
Height	0.38 ^c	0.35 ^c	-0.03	0.13	0.44 ^c	0.38 ^c	0.86 ^c	0.89 ^c
Weight	0.47 ^c	0.44 ^c	0.12	0.16 ^a	0.50 ^c	0.48 ^c	0.80 ^c	0.85 ^c
Body mass index	0.46 ^c	0.40 ^c	0.29 ^c	0.15 ^a	0.44 ^c	0.43 ^c	0.58 ^c	0.67 ^c

Refer to *Subjects and Methods* for abbreviations.

^a*p* < 0.05; ^b*p* < 0.01; ^c*p* < 0.0001.

the histomorphometric equivalent to vBMD-trab—increases by about 25% between 7 and 20 years of age.⁹

The discrepant behavior of vBMD-trab at these sites might be related to developmental differences between radial and axial trabecular bone. Metaphyseal spongiosa of the distal radius is a transient structure during the growth period. Trabeculae are produced continuously at the interface between the growth plate and metaphysis and are resorbed at the diaphyseal end of the metaphysis. In contrast, mature trabeculae are not removed in vertebral bodies and the ileum, as these bones do not have a diaphysis. Therefore, trabeculae in vertebral bodies and in the ileum are, on average, “older” than trabeculae at the distal radius, and might have more time to thicken by remodeling with a positive balance.¹⁷

One of the limitations of the pQCT system used in this study is that the spatial resolution is not sufficient to identify precisely a thin cortical rim of bone, such as at the distal radius.^{1,13} Therefore, the system uses a geometric definition to separate two bone compartments. The outer 55% of the radial cross section is considered to represent “cortical + subcortical” bone, whereas the remainder is defined as trabecular bone. As shown by direct measurement and high-resolution pQCT, the thickness of the cortical rim at the “4% site” is in the order of 1 mm in adults.^{14,21} Therefore, the actual percentage of CSA consisting of cortical bone is much lower than 55%. Thus, the bone included in the analysis of vBMD-cort at the 4% site is a poorly defined mixture of trabecular and cortical bone. This explains why results for vBMD-cort are far below the typical vBMD of human cortical bone, which is close to 1200 mg/cm³.¹⁵ In our view, the utility of vBMD-cort as a parameter of cortical bone is questionable at this site. Determining cortical vBMD at the radial diaphysis can be expected to yield more useful results.

Our analyses of covariance revealed that body height is an important predictor of vBMD-tot and CSA. This is not unexpected, as with increasing length a bone is exposed to greater mechanical forces due to increasing lever arms. The positive association between height and vBMD-tot and CSA can be regarded as a consequence of an adaptive mechanism, which adjusts bone mass and geometry to mechanical requirements (Wolff's law).⁵ Interestingly, height was not associated with vBMD-trab, suggesting that adaptation to mechanical forces during growth affects cortical bone and bone geometry more than trabecular thickness and number.

In conclusion, our study presents the first detailed reference database for pQCT at the distal radius in children and adolescents. Important issues in many primary and secondary pediatric bone disorders, such as the development of trabecular bone and of bone size, await exploration. The availability of pQCT reference material will facilitate such studies.

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