

Gender-specific Pubertal Changes in Volumetric Cortical Bone Mineral Density at the Proximal Radius

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It is well established that puberty affects the geometry of cortical bone differently in females and males. In the present study we investigated whether there are also gender differences in the volumetric bone mineral density of the cortical compartment (BMDcort). BMDcort was determined at the proximal radial diaphysis in 362 healthy children and adolescents (age 6–23 years; 185 females, 177 males) and in 107 adults (age 29–40 years; 88 women, 19 men) using peripheral quantitative computed tomography (pQCT). The densitometric result for BMDcort was similar in prepubertal girls and boys, but was significantly higher in females after pubertal stage 3. pQCT results for BMDcort are influenced by cortical thickness due to the partial volume effect. Therefore, these gender differences were reanalyzed in groups of subjects of the same developmental stage who were matched for cortical thickness. Thus calculated, no gender difference in BMDcort was detected in prepubertal children. However, adolescent females after pubertal stage 3 and adult women had a 3%–4% higher BMDcort than males at the same developmental stage. BMDcort is an integrated measure of both cortical porosity and mean material density of cortical bone. The metabolic activity of cortical bone (intracortical remodeling) increases cortical porosity and decreases the mean material density of cortical bone. Our results therefore suggest that intracortical remodeling is lower in postpubertal females than in males. (Bone 31:110–113; 2002) © 2002 by Elsevier Science Inc. All rights reserved.

Key Words: Bone cortex; Bone development; Bone mineral density (BMD); Children; Puberty; Remodeling.

Introduction

Skeletal development takes a gender-specific course during puberty. At many skeletal sites, pubertal girls add bone on endocortical surfaces, whereas boys do not.^{2,13} However, boys continue to add bone on periosteal surfaces long after girls have stopped periosteal apposition. The end result of these developmental differences is that men have larger external bone size and a relatively larger marrow cavity than women.^{2,6,13}

These observations refer to changes in cortical bone geometry and describe movements on endocortical and periosteal surfaces.

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It is less clear whether there are also gender-related differences in the bone tissue located between these two surfaces—within the cortical compartment of the bone. A densitometric parameter describing the cortical tissue compartment is BMDcort, which is defined as the mass of mineral contained between the periosteal and endocortical surfaces divided by the volume of this compartment (Figure 1).⁹ A measure of BMDcort can be obtained with densitometric methods such as peripheral quantitative computed tomography (pQCT).

In the present study we used pQCT to assess BMDcort in a well-characterized group of healthy children, adolescents, and adults. A 2-mm-thick cross-sectional slice of cortical bone was analyzed at the proximal radius. The aim was to evaluate the gender-related differences in pubertal development of BMDcort.

Subjects and Methods

Subjects

The study population comprised 371 healthy children and adolescents as well as those 107 parents who were <40 years of age (19 males, 88 females; age 29–40 years). Five children had to be excluded from the analysis because of motion artifacts during the measurement run. Results of four boys were excluded because a significant amount of trabeculized cortex interfered with analysis of the cortical bone. Thus, 362 children and adolescents (177 males and 185 females) were included in the following evaluation. The children were participants in the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) study, an ongoing observational study investigating the interrelations of nutrition, growth, and metabolism in healthy children.¹⁴ On an annual basis, all participants involved in this study undergo a full medical history and examination starting in infancy. Peripheral QCT was performed once in each participant on the occasion of a yearly check-up.

The stage of pubertal development was determined in all study participants by physical examination using the grading system defined by Tanner for breast development in girls and genital status in boys. Assessment of pubertal stage was refused by 26 boys and 26 girls. Forearm length was measured at the nondominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. Ulnar rather than radial length was determined, because the length of the radius cannot be determined exactly in the clinical setting.

Informed consent was obtained from the children's parents, or directly from the subjects aged who were aged >18 years. The study protocol was approved by the ethics committee of the University of Cologne and by the Bundesamt für Strahlenschutz

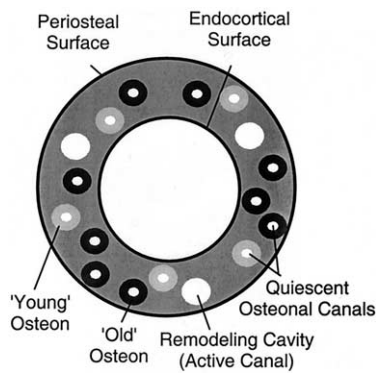


Figure 1. Schematic representation of a cross section through a long bone diaphysis. The cortical compartment is enclosed by the periosteal and endocortical surfaces. The different levels of gray represent different mineral densities. Light = low density; dark = high density. Osteonal canals do not contain mineral and are therefore shown in white. BMDcort is the average mineral density within the cortical compartment.

(Federal Agency for Protection from Radiation, Salzgitter, Germany).

Peripheral Quantitative Computed Tomography

Peripheral QCT analysis was performed at the nondominant forearm using a XCT-2000 device (Stratec, Inc., Pforzheim, Germany), as described in detail before.⁶ The rationale for choosing this location for pQCT measurements is that maximal muscle cross-sectional area of the forearm can be determined in the same run without additional radiation exposure to the patient. This allows for analysis of the interrelationship between bone and muscle development¹²; however, this was not the focus of the present study. The scanner was positioned at the site of the forearm whose distance to the ulnar styloid process corresponded to 65% of forearm length. A 2-mm-thick single tomographic slice was sampled at a voxel size of 0.4 mm × 0.4 mm × 2 mm. Image processing and the calculation of numerical values were done using the manufacturer's software package (version 5.40). Cortical bone was identified at a threshold of 710 mg/cm³.

When BMDcort is analyzed by pQCT, it is important to realize that the measured results may be influenced by the partial volume effect.^{1,8,11} Due to incompletely filled voxels at the periosteal and endocortical borders of the cortex, the actual BMDcort is underestimated (**Figure 2**). The extent of the underestimation will be greater in thinner cortices, because these have a higher surface-to-volume ratio than thicker cortices. As a result of this technical problem, pQCT results for BMDcort increase with cortical thickness, even if the mass of mineral per unit volume of the cortical compartment remains identical. Neglect of this methodological problem has led to erroneous conclusions about cortical bone development in the past, as pointed out by Augat et al.¹ Thus, cortical thickness must be taken into account when measuring BMDcort by pQCT. The mean cortical thickness of the bone's cross-section was calculated as:

$$\frac{(\text{total bone area}/\pi)^{0.5} - [(\text{total bone area} - \text{cortical bone area})/\pi]^{0.5}}$$

These cortical thickness values have been included in a recent report on pQCT reference data,⁶ but are presented here again because of the importance of cortical thickness in the interpretation of pQCT results for BMDcort.

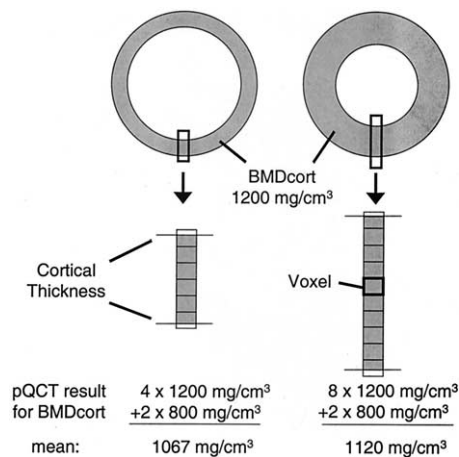


Figure 2. Illustration of the partial volume effect. The partially filled voxels at the edge of the cortex (it is assumed arbitrarily that these edge voxels are filled by two thirds) reduce the measured mean result for BMDcort. When cortical thickness is greater, the relative influence of these partially filled voxels becomes smaller.

Statistical Analyses

To eliminate the interfering effect of cortical thickness, female and male subjects of the same maturational stage were matched for cortical thickness. The number of matched pairs corresponded to the number of male or female subjects in each maturational group, whichever was smaller. For comparisons between two groups, *t*-tests were used. The significance of differences between more than two groups was calculated by the Kruskal–Wallis test. For these calculations, the SAS 6.12 software package (SAS Institute, Inc., Cary, NC) was used.

Results

pQCT results for BMDcort and cortical thickness are presented in **Table 1**. In the youngest age group, both parameters were slightly lower in girls than in boys. However, results for BMDcort increased faster with age in girls and, consequently, females had significantly higher values after the age of 11 years. Cortical thickness was higher in girls than in boys at 12–13 years of age, but was lower in girls after the age of 15 years.

The variation of the measured BMDcort and cortical thickness with pubertal stage is shown in **Table 2**. Before puberty, both parameters were similar in girls and boys. After pubertal stage 3, BMDcort was significantly higher in girls.

As pointed out in *Subjects and Methods*, pQCT-measured BMDcort is influenced by cortical thickness due to the partial volume effect. Therefore, the effects of gender on pQCT BMDcort might not only reflect differences in the actual BMDcort, but could be influenced by differences in cortical thickness. This problem was circumvented by reanalyzing the data taking cortical thickness into account. The individual results are shown in **Figure 3**. BMDcort was calculated for groups of female and male subjects who were matched for both maturational stage and cortical thickness. Thus matched, BMDcort was similar between genders in pubertal stages 1–3, although there was a trend for higher values in boys at pubertal stage 2 (*p* = 0.06). After pubertal stage 3, BMDcort was consistently higher in female than in male subjects (**Figure 4**). The difference amounted to 3.2% in pubertal stage 4, 3.5% in pubertal stage 5, and 4.2% in adults. By design, cortical thickness was similar between females and males

Table 1. Peripheral quantitative computed tomography (pQCT) results for proximal radius cortical bone mineral density (BMDcort) and cortical thickness in age- and gender-specific groups

Age (years)	Female			Male		
	n	BMDcort (mg/cm ³)	Cortical thickness (mm)	n	BMDcort (mg/cm ³)	Cortical thickness (mm)
6–7	28	942 ± 47 ^a	1.15 ± 0.39 ^b	27	975 ± 45	1.45 ± 0.31
8–9	26	1004 ± 50	1.68 ± 0.35	22	1008 ± 31	1.71 ± 0.21
10–11	30	1021 ± 37	1.84 ± 0.40	31	1025 ± 37	1.78 ± 0.26
12–13	31	1037 ± 47 ^a	2.14 ± 0.51 ^a	27	1018 ± 42	1.85 ± 0.28
14–15	25	1093 ± 27 ^c	2.38 ± 0.35	27	1031 ± 50	2.27 ± 0.46
16–17	23	1106 ± 26 ^c	2.42 ± 0.31 ^a	21	1072 ± 32	2.63 ± 0.35
18–23	22	1134 ± 27 ^c	2.42 ± 0.34 ^b	22	1102 ± 31	2.75 ± 0.41
Adults	88	1153 ± 30 ^c	2.48 ± 0.34 ^b	19	1116 ± 32	2.74 ± 0.44

Values are mean ± SD. The significance for the difference between females and males of the same age group is shown at:

^a*p* < 0.05; ^b*p* < 0.01; ^c*p* < 0.001. For all parameters, variation with age was highly significant for both genders (*p* < 0.0001 each, by Kruskal–Wallis test).

in these groups (*p* > 0.6 in each pubertal stage group and in adults).

Discussion

In this study we evaluated the gender-specific development of BMDcort at the “65% site” of the proximal radius. The main result of this study is that BMDcort at the proximal radius was higher in postpubertal, premenopausal females than in males, whereas there was no gender difference in BMDcort before puberty. These observations cannot be explained by the influence of the partial volume effect on pQCT results, because the effect of gender on BMDcort persisted when subjects were matched for cortical thickness.

Our findings are in close agreement with observations made by Meema et al., who used X-ray absorptiometry at the proximal radial shaft to estimate BMDcort.⁴ These investigators reported that BMDcort was 4.3% higher in premenopausal women than in men of the same age. Our results are also in line with those of Gilsanz et al., who found no gender difference in BMDcort in the femoral shaft of prepubertal children.³

What is the structural basis for the postpubertal gender difference in BMDcort? BMDcort is an integrated measure determined by two physical properties, cortical porosity and mean material density.⁹ The differences in BMDcort between males and females may therefore be due to differences in cortical porosity, mean material density, or both. Cortical porosity and mean material density of cortical bone are not independent from each other, but are both influenced by the metabolic activity of

cortical bone, that is, intracortical remodeling.⁹ Cortical porosity is higher when intracortical remodeling activity is high, because there are more incompletely refilled osteonal canals (Figure 1).⁷ At the same time, intracortical remodeling decreases the mean material density of cortical bone.⁷ This is because remodeling replaces “old” bone (which has a high material density) with “young” bone (which has a low material density).⁹ The observation that postpubertal girls and women have higher BMDcort than boys and men is therefore compatible with the hypothesis that intracortical remodeling is lower in females.

This study does not shed light on the causes of this possible gender difference in intracortical remodeling. Direct differential effects of sex hormones on bone cells are an obvious possibility, but there may also be a more mechanical explanation. Postpubertal females have more bone relative to their (lower) muscle mass than males.^{10,12} Consequently, muscle forces might lead to smaller mechanical stresses in females than in males. This could lead to fewer microcracks in the cortical bone tissue of postpubertal girls and women, which would result in less repair-directed intracortical remodeling.⁵ Indeed, microdamage density has been reported to be higher in men, at least in vertebral bodies.¹⁵ Obviously, more research on cortical bone in young subjects is required to substantiate this speculation.

In summary, BMDcort is higher in postpubertal girls and women than in males of the same developmental stage, possibly because intracortical remodeling is lower in females. Together with our previous results,^{6,12} and those of others,^{2,4} the present study suggests that female puberty leads to the acquisition of two types of calcium stores in cortical bone. The first is created by

Table 2. Variation of peripheral quantitative computed tomography (pQCT) results for cortical bone mineral density (BMDcort) and cortical thickness with pubertal stage (the “adult” group not included in pubertal stage 5)

Pubertal stage	Female			Male		
	n	BMDcort (mg/cm ³)	Cortical thickness (mm)	n	BMDcort (mg/cm ³)	Cortical thickness (mm)
1	59	981 ± 54	1.44 ± 0.41	49	998 ± 47	1.58 ± 0.31
2	17	1010 ± 33	1.81 ± 0.23	31	1024 ± 40	1.80 ± 0.27
3	16	1035 ± 48	2.02 ± 0.30	14	1027 ± 33	1.96 ± 0.42
4	11	1068 ± 24 ^a	2.34 ± 0.33 ^a	14	1020 ± 39	2.16 ± 0.31
5	56	1112 ± 30 ^b	2.50 ± 0.34	43	1077 ± 48	2.61 ± 0.47

Values are mean ± SD. The significance for the difference between females and males of the same age group is shown at:

^a*p* < 0.01; ^b*p* < 0.001. For all parameters the variation with pubertal stage was highly significant for both genders (*p* < 0.0001 each by Kruskal–Wallis test).

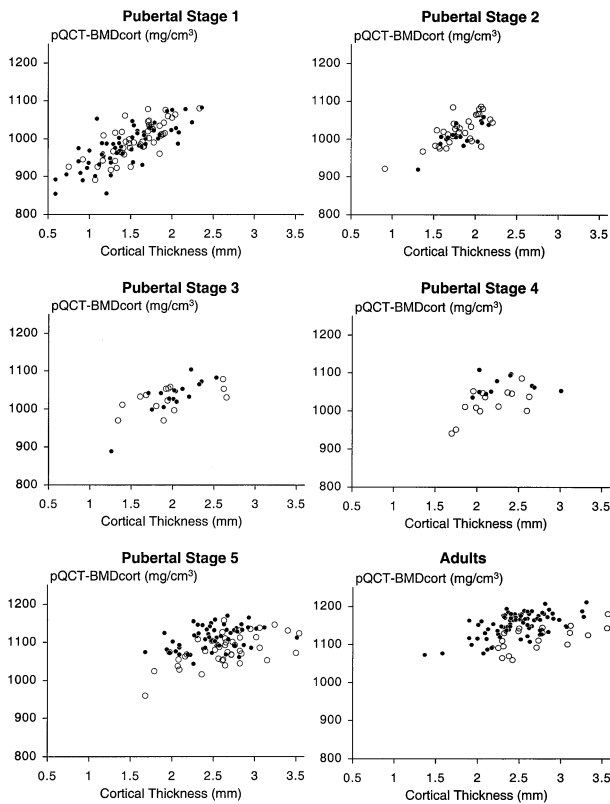


Figure 3. Relationship between cortical thickness and pQCT results for BMDcort in different maturational stages. Filled circles indicate results for females, open circles are results for males.

apposition of bone on endocortical surfaces, and the second is the result of increased mineral density in the cortical compartment.

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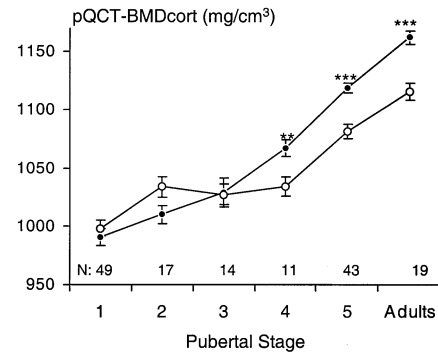


Figure 4. pQCT results for BMDcort in groups of female and male subjects who were matched for maturational stage and cortical thickness. N represents the number of matched pairs at each maturational stage. The significance of the difference between genders is indicated by asterisks: ***p* < 0.01; and ****p* < 0.001.

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