

Age at Menarche and Cortical Bone Geometry in Premenopausal Women

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Previous studies have suggested that the timing of puberty might have an impact on the adult skeleton. What composite of bone structure could be affected by the timing of puberty is unknown at present. In this study, we evaluated the relationship between age at menarche and bone cortex geometry at the distal radius. Using peripheral quantitative computed tomography, we determined total area of the radial cross section, cortical bone area, periosteal cortical perimeter, endosteal cortical perimeter, and cortical width in 169 healthy premenopausal women aged 40–45 years. When stratified according to age at menarche (early, <12 years [$n = 22$]; intermediate, 12–14 years [$n = 118$]; late, >14 years [$n = 29$]), only endosteal cortical perimeter varied significantly between the groups ($p = 0.02$, by analysis of variance), the mean value being 10% higher in the late compared to the early menarche group. However, weight and body mass index also exhibited significant variations between groups. After adjustment for weight the differences in endosteal cortical perimeter remained significant ($p = 0.03$). In multiple regression analysis, endosteal cortical perimeter was the only parameter of cortex geometry, which was independently associated with age at menarche. In a model including height and weight, age at menarche explained about 2% of the variability in endosteal cortical perimeter ($p = 0.04$). These data suggest that the bone marrow cavity of the distal radius may be slightly larger when puberty occurs later. Whether this marginal effect influences fracture risk in later life appears questionable. (Bone 25:69–73; 1999) © 1999 by Elsevier Science Inc. All rights reserved.

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Introduction

Puberty is a critical event during skeletal development.²⁹ Bone size increases rapidly, clinically recognizable as the “pubertal growth spurt.” In vertebral bodies, the mass of mineralized tissue increases even more rapidly than bone size.^{8,11} At the same time, cortices of long bones increase in width.¹¹ These effects combine to increase skeletal mass dramatically. One third to one half of adult bone mass accumulates during puberty.²³

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The chronological age at which puberty occurs is quite variable in both genders.³⁴ As puberty is so evidently important for skeletal growth, it seems an obvious hypothesis to assume that variations in its timing affect the final outcome of pubertal bone development (i.e., the adult skeleton). In fact, this hypothesis has been investigated extensively in women, in whom age at menarche can serve as a retrospectively available “marker” of puberty. Studies have typically examined the relationship between the timing of puberty and areal bone mineral density (aBMD) (reviewed in ref. 24) in an effort to elucidate risk factors for osteoporosis. Several investigators found that later occurrence of menarche was associated with lower aBMD at various sites.²⁴

These results raised the possibility that the timing of puberty could influence adult bone structure. Which aspects of bone structure might be affected by the timing of puberty cannot be determined by aBMD analysis. This is because aBMD is a composite measure, which integrates many properties of the analyzed bone into a single numerical value. Structural elements of a bone determining its aBMD include external bone size and shape, cortical width, trabecular number, and trabecular thickness.²⁸

Quantitative computed tomography (QCT) yields a more detailed view of a bone. It allows separate assessment of bone size, shape, and cortical width, as well as the amount of mineral matter within the cancellous compartment. The most commonly reported parameter derived from these measures is apparent volumetric BMD—the mass of mineralized tissue in a slice of bone, averaged over the volume of the slice. Several QCT studies of lumbar vertebral bodies have reported a negative association between age at menarche and apparent volumetric BMD in adult women.^{2,14,25} These analyses were limited to cancellous bone.

It is currently not known, whether the timing of menarche has any influence on bone cortex geometry. As cortical bone provides about 75% of total skeletal mass, this question is of obvious relevance to judge the impact of the timing of puberty on the skeleton.²³ Indeed, the importance of cortex geometry for bone strength is becoming increasingly recognized.^{3,10,29}

Peripheral QCT (pQCT) at the distal radius allows precise determination of bone size and cortical geometry.^{12,19,26,27} Using this technique, we investigated the influence of age at menarche on cortical bone geometry in adult women. We limited this analysis to premenopausal women, as the variable rates of bone loss after menopause are likely to blur any effect that might be ascribed to the timing of puberty. To minimize the effects of age-related changes, we studied women who were of similar age (40–45 years).

Table 1. Clinical characteristics of the study population

	All (n = 169)	Age at menarche			p
		<12 years (n = 22)	12-14 years (n = 118)	>14 years (n = 29)	
Age at menarche (years)	13.1 ± 1.6	10.7 ± 0.6	13.0 ± 0.8	15.6 ± 1.2	<0.0001
Chronological age (years)	41.8 ± 1.8	42.0 ± 1.8	41.7 ± 1.7	42.0 ± 2.0	0.60
Height (cm)	164.3 ± 6.4	165.5 ± 6.2	164.0 ± 6.6	164.5 ± 5.3	0.59
Weight (kg)	64.1 ± 10.7	67.8 ± 12.6	64.4 ± 10.8	60.0 ± 6.9 ^a	0.03
Body mass index (kg/m ²)	23.7 ± 3.6	24.8 ± 4.3	23.9 ± 3.6	22.2 ± 2.5 ^a	0.02
Ever used oral contraceptives (n)	134 (79%)	19 (86%)	95 (81%)	20 (69%)	0.27
Total time of oral contraceptives use (years)	12.1 ± 6.6	11.2 ± 7.1	11.9 ± 6.6	13.6 ± 6.1	0.50
Oral contraceptives use started at: <20 years of age (n)	45 (27%)	7 (32%)	33 (28%)	5 (17%)	0.67
≥1 live births (n)	123 (73%)	16 (73%)	88 (75%)	19 (66%)	0.67
Live births (n)	1.61 ± 0.73	1.65 ± 0.71	1.61 ± 0.75	1.58 ± 0.72	0.71

Values given are mean ± SD or n (% of respective group). p values for differences between subgroups calculated by ANOVA or chi-square test, as appropriate.

^aSignificantly different from early menarche group.

Subjects and Methods

Subjects

The study population was a subgroup of a larger cohort, which has been described in detail previously.^{31,32} Women between 40 and 60 years of age were invited by their health insurance company to participate in this study (BKK Deutsche Bank, Düsseldorf, Germany). A questionnaire concerning health, use of drugs, and gynecological history was obtained from each subject. No attempt was undertaken to verify this information by an independent source. However, a similar questionnaire has been shown to yield reliable results on age at menarche even in women who were older than the participants of the present study.²² Height and weight were measured and body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). The study protocol was approved by the local ethics committee and all subjects gave their written informed consent.

The present analysis included all study participants with regular menstruations who were between 40 and 45 years of age, were free of a history of osteoporosis or recent fractures and did not take medications known to affect bone or mineral metabolism (hormone replacement therapy, corticosteroids, anticonvulsants, diuretics).

The study population was separated into three subgroups, according to age at menarche. Women in whom menarche had occurred at an age within 1 SD around the mean value for the whole group were classified as having an "intermediate" age at menarche. As age at menarche was given in 1 year steps by the study participants, this group finally comprised women who had experienced menarche at 12, 13, or 14 years of age (70% of the population). Women who had had menarche before the age of 12 years or after 14 years, constituted "early" (12%) or "late" (17%) menarche groups, respectively.

Peripheral Quantitative Computed Tomography

pQCT analysis was performed using Stratec XCT-900 equipment (Stratec, Pforzheim, Germany) installed on a mobile unit, as described previously.^{27,31,32} Measurements were taken at the nondominant forearm. Ulnar length was determined externally using a tape measure. The scanner was positioned on the distal

forearm and a scout view was carried out to position the scanner at the site on the radius whose distance to the radial facies articularis carpi corresponded to 4% of ulnar length. A single computed tomographic slice of 2.5 mm width was measured with a voxel size of 590 µm.

Image processing and the calculation of numerical values was done using the manufacturer's software package (version 5.10). To separate cortical from cancellous bone, a linear attenuation threshold value of 0.7 cm⁻¹ was used. Total cross-sectional area and cortical bone area represent the area of the whole radial cross section and the area attributed to cortical bone, respectively. Periosteal cortical perimeter, cortical width, and endosteal cortical perimeter were derived from these measurements assuming a circular ring model for the radial cross section. Use of derived rather than directly determined measures of cortical perimeters and width has the advantage that derived indices are less influenced by surface irregularities and differences in bone shape. The following formulas were used:

- Periosteal perimeter = 2 * [total area * π]^{1/2}.
- Endosteal perimeter = 2 * [(total area - cortical area) * π]^{1/2}.
- Cortical width = [total area/π]^{1/2} - [(total area - cortical area)/π]^{1/2}.

Statistical Analysis

Differences between subgroups were tested for significance using one-way analysis of variance (ANOVA). Differences in parameters of bone structure were reassessed by simple multifactorial ANOVA after adjusting for weight.

Pearson's correlation coefficients were used to express the associations in simple regression analyses. The relationship between bone cortex geometry, age at menarche, and other variables was evaluated by stepwise multiple regression analysis in the forward mode.

Throughout, p < 0.05 was considered significant. All statistical analyses were performed using the SPSS software package (version 6.0 for WINDOWS; SPSS, Chicago, IL).

Results

Table 1 shows clinical data in the whole study population and in the three subgroups defined according to age at menarche.

Table 2. Parameters of bone cortex geometry at the distal radius

	All (n = 169)	Age at menarche			p	p (adjusted for weight)
		<12 years (n = 22)	12-14 years (n = 118)	>14 years (n = 29)		
Total cross-sectional area (mm ²)	289 ± 47	286 ± 40	286 ± 46	301 ± 53	0.28	0.17
Cortical bone area (mm ²)	164 ± 32	170 ± 31	164 ± 32	158 ± 30	0.41	0.77
Periosteal cortical perimeter (mm)	60 ± 5	60 ± 4	60 ± 5	61 ± 5	0.31	0.20
Endosteal cortical perimeter (mm)	39 ± 6	37 ± 6	39 ± 6	41 ± 7 ^{a,b}	0.02	0.03
Cortical width (mm)	3.3 ± 0.7	3.5 ± 0.7	3.3 ± 0.7	3.1 ± 0.7	0.07	0.27

Values given are mean ± SD. p values for differences between subgroups calculated by ANOVA.

^aSignificantly different from early menarche group.

^bSignificantly different from intermediate menarche group.

Subgroups were similar in chronological age and height, but differed significantly in weight and BMI. There were no significant differences in indices of reproductive history.

Parameters of bone cortex geometry are given in **Table 2**. The total area of the radial cross section and the cortical bone area were not significantly different in the three menarcheal groups. However, the endosteal perimeter of the bone cortex was longer in the late than in the early menarche group. Differences in cortical width were of borderline significance.

As weight varied in the three menarcheal groups, differences in bone cortex parameters were reevaluated after adjustment for weight by simple multifactorial ANOVA (**Table 2**). Calculated in this manner, differences in endosteal cortical perimeter remained significant.

To further assess the relationship between age at menarche and cortical geometry, simple linear regression analyses were performed (**Table 3**). These revealed significant negative correlations between age at menarche and both cortical bone area and width. Endosteal cortical perimeter was positively associated with age at menarche. Age at menarche was negatively associated with weight ($r = -0.22$; $p = 0.002$) and BMI ($r = -0.21$; $p = 0.003$), but not with height or chronological age ($p > 0.2$).

To evaluate if age at menarche was independently associated with any of the parameters of cortex geometry, stepwise multiple regression analyses were performed. In addition to age at menarche, chronological age, height, and weight were used as independent variables. Age at menarche was independently associated only with endosteal cortical perimeter, with the following regression equation: endosteal cortical perimeter = 0.36 * height - 0.114 * weight + 0.57 * age at menarche - 5.6 ($p < 0.0001$; $r^2 = 0.15$). In this model, age at menarche explained about 2% of the variability in endosteal cortical perimeter ($p = 0.04$).

Discussion

This is the first study to examine the relationship between age at menarche and cortical bone geometry. We analyzed bone cortex at the distal radius, because this site allows measurement with high precision, combined with minimal body exposure to radiation.

Several studies have analyzed the association between age at menarche and aBMD at the distal radius.^{5,15,17,21,33} The effect of age at menarche on aBMD was either not detectable^{21,33} or, where present, was small.^{5,15,17} However, as mentioned earlier, these studies cannot be directly compared with the present data.

In the present study we found a small effect of age at menarche on cortical bone. When the whole study population was subgrouped according to menarcheal age, women with late menarche had a 10% longer endosteal cortical perimeter than women who had experienced early menarche. However, the total area of the radial cross section and, by consequence, the periosteal perimeter of the cortical bone were slightly (nonsignificantly) greater in the late menarche group. Therefore, differences in cortical bone area were not significant between the groups.

The statistical association between age at menarche and endocortical perimeter does not establish a cause-effect relationship, but might be due to a third factor. For instance, physical exercise or nutritional intake during adolescence could influence both the timing of menarche and bone development.⁴ The design of our study precluded the elucidation of most of these factors. However, our analyses suggest that the effect of age at menarche on cortical bone geometry is at least partly mediated by differences in body built. Despite similar height, women with later menarche weighed less. The inverse relationship between age at menarche and fat mass in later life is a well-documented phenomenon, for which a mechanism has not been clearly estab-

Table 3. Simple regression analyses: correlations between cortical bone geometry and clinical parameters

	Total cross-sectional area	Cortical bone area	Periosteal cortical perimeter	Endosteal cortical perimeter	Cortical width
Age at menarche	NS	-0.15 ^a	NS	0.18 ^a	-0.20 ^b
Age	NS	NS	NS	NS	NS
Height	0.35 ^c	0.17 ^a	0.34 ^c	0.28 ^c	NS
Weight	NS	0.24 ^c	NS	NS	0.24 ^c
Body mass index	NS	0.18 ^b	NS	-0.22 ^b	0.26 ^c
Time of oral contraceptive use	NS	NS	NS	NS	NS
Number of live births	NS	NS	NS	NS	NS

Data given are Pearson's correlation coefficients. ^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$. NS; not significant.

lished.^{9,16} Body weight in turn is known to be positively associated with bone mass.¹³ This was confirmed by the present study, as weight correlated positively with cortical bone area and width.

It is difficult to discriminate between the influences of menarcheal age and weight on bone cortex geometry simply by statistical means. We cannot exclude that the observed relationship between age at menarche and endosteal cortical perimeter is entirely mediated by differences in weight. However, both the analysis of group differences by ANOVA and multiple linear regression analysis in the entire study population showed that a small effect of age at menarche on endosteal cortical bone perimeter persisted after adjustment for weight. From these analyses it appears possible that the timing of menarche has an independent influence on endosteal cortical perimeter.

Endosteal cortical perimeter in premenopausal women is mainly determined by bone growth during childhood and adolescence.^{8,28} During growth, two successive movements occur on the endocortical surface: First, the endosteal cortex perimeter increases due to continuous endocortical resorption during prepuberty. Second, the endosteal cortical perimeter decreases due to net endocortical bone apposition during puberty.⁶ After that, changes are very slow until menopause.⁸

By what mechanism could the timing of menarche influence endocortical bone perimeter? In the late menarche group, more time was available for the process of prepubertal endocortical erosion, which might result in a larger marrow cavity. Also, endocortical apposition during pubertal development might be decreased in the late puberty group. Thus, the regulation of endocortical apposition during puberty might be analogous to that of longitudinal bone growth ("pubertal growth spurt"), which is less when puberty occurs later.¹⁸ Additionally, differences in growth patterns might have contributed to our findings, as body proportions are influenced by the timing of puberty.¹ Prepubertal growth favors lengthening of the extremities, whereas pubertal growth is more pronounced in the axial skeleton.¹ Thus, the timing of menarche could have an effect on some biomechanical aspects of the muscle-bone unit, such as muscle force or the length of lever arms. Such biomechanical factors might influence bone cortex development.⁷

It must be acknowledged that whatever direct or indirect effects the timing of menarche may have on the distal radius, it appears that late age at menarche is not a risk factor for radius fracture. This is suggested by two large case-control studies, which detected no influence of age at menarche on fracture risk at this site.^{20,30}

In conclusion, later age at menarche is associated with a slightly longer endosteal perimeter at the distal radius. This can be largely ascribed to the fact that weight is lower when menarche occurs later. However, the timing of menarche may also have a small independent influence on the size of the marrow cavity. Data presently available suggest that this small effect does not detectably influence the risk of fracture at the distal radius.

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