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Differential Effect of Gender on the Sizes of the Bones in the Axial and Appendicular Skeletons*

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ABSTRACT

Recent observations suggest that throughout life the size of the vertebral bodies in females is smaller than that in males even after accounting for differences in body size. To confirm these reports and to determine whether similar differences exist in the appendicular skeleton, detailed measurements of the sizes of the vertebrae and the femur were obtained using computed tomography in 30 pairs of prepubertal boys and girls matched for age, height, and weight. Anthropometric parameters as well as gender influenced the cross-sectional area of the vertebrae. Heavier children had greater vertebral cross-sectional area than slender children regardless of gender, and the vertebral bodies were found to be significantly smaller in girls than in matched boys (~11%), both using Student's t test ($P < 0.0001$) and its multivariate analog, the Hotelling's T^2 test ($P < 0.0001$). In contrast to these findings in the axial skeleton, gender status did not influence the size of the bones in the appendicular skeleton, and neither the cross-sectional area (3.28 ± 0.84 *vs.* 3.10 ± 0.56 cm^2) nor the cortical bone area (1.80 ± 0.37 *vs.* 1.85 ± 0.36 cm^2) at the midshaft of the femur differed between boys and girls. These values, however, correlated strongly with all anthropometric indexes, and multiple regression analyses indicated that both measurements were primarily related to weight. The results suggest that although increases in mechanical loading associated with growth are the main determinant of the cross-sectional properties of the appendicular skeleton in children, factors other than body mass and related to gender have a significant role in the regulation of the sizes of the bones in the axial skeleton. (*J Clin Endocrinol Metab* **82:** 1603–1607, 1997)

BONE MASS is lower in women than in men, and this gender difference is considered to be an important determinant of the greater occurrence of osteoporosis and fractures in women (1). Because most data suggest that this disparity is present early in life, defining the factors that influence bone mass during growth and whether they regulate the size and/or the density of bone may help explain why girls are more at risk for osteoporosis than boys (2). Recent observations indicate that throughout childhood and adulthood females have smaller vertebral body size, but similar vertebral bone density, compared with males matched for age, degree of sexual development, height, and weight (3, 4). The smaller cross-sectional area of the vertebral bodies imparts a mechanical disadvantage that increases the stress within the spine and becomes an important determinant of vertebral fractures with age (5).

Variations in the dimensions of the appendicular skeleton in children and the degree to which gender influences the size of the femurs may also be an important determinant of the susceptibility to hip fractures in the elderly. However, little data are available regarding changes in femoral size during childhood, mainly due to the inability of commonly used techniques to measure the cross-sectional area of this bone (6). This study was undertaken to determine whether there are early differences in the sizes of the bones in the appendicular skeleton between boys and girls beyond those attributable to variations in body size.

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Subjects and Methods

Study subjects

The study subjects were healthy, Caucasian, prepubertal children who were either family members or companions seen regularly in the Childrens Hospital (Los Angeles, CA) or were recruited from schools of Los Angeles County. The investigational protocol was approved by the institutional review board for clinical investigation at this facility, and informed consent was obtained from all subjects or their parents. The subjects ranged in age from 8.3–12.8 yr.

The children and/or their parents were asked about their racial and ethnic backgrounds. Candidates were excluded if either of their parents or either set of grandparents were not of the same race. Candidates for the study were also excluded if they had been given a diagnosis of chronic illness, if they had been ill for longer than 2 weeks during the previous 6 months, if they had taken any medications, vitamin preparations, or calcium supplements regularly within the previous 6 months, or if they had been hospitalized at any time since birth. All subjects were appropriately physically active for their age.

Candidates underwent a physical examination performed by a pediatric endocrinologist to determine the stage of sexual development, and the grading system defined by Tanner was used for classification (7). Children who had entered puberty (Tanner stage II or more) were excluded from the study. Measurements of height and weight were also obtained, and children in whom either height or weight differed by more than 2 SD from the mean age-adjusted normal values for Caucasian children were excluded from further evaluation. Body surface area and body mass index were calculated as previously described (8). Skeletal maturation was assessed on the basis of roentgenograms of the left hand and wrist obtained on the same day as, but before, the measurements of bone density by computed tomography (CT). The radiographs were evaluated according to the method of Greulich and Pyle (9), and bone age was determined.

Subjects were matched by chronological age, height, and weight to control for these important anthropomorphic determinants of bone mass. Because of the smaller number of boys available for examination, girls were evaluated and enrolled in the study before their male counterparts. Thereafter, boys were recruited, evaluated, and matched with girls who had been studied. For this analysis, the ages of each pair of subjects differed by less than 6 months, and neither height nor weight differed by more than 5%. Using this approach, we studied 30 unique matched pairs of children.

CT bone measurements

All CT bone measurements in the spine and midshaft of the femur were performed with the same scanner (model CT-T 9800, General Electric Co., Milwaukee, WI) and the same mineral reference phantom for simultaneous calibration (CT-T bone densitometry package, General Electric). The techniques for these measurements have been described in detail previously (4, 10).

Briefly, for vertebral bone determinations, identification of the sites to be scanned was performed with lateral scout views. The heights of the anterior, middle, and posterior portions of the first, second, and third lumbar vertebral bodies were measured separately on lateral scout radiographs, and a mean value for the height of each vertebral body was calculated. CT measurements of cancellous bone density and the cross-sectional area of the vertebral bodies were obtained from the 10-mm midportion of the first through the third lumbar vertebrae at 80 kVp, 70 milliamperes, and 2 s. For bone determinations in the femur, the scanning site was located by physical examination, and measurements of cortical bone density, cortical bone area, and cross-sectional area of the femur were obtained from a single 1.5-mm thick imaging scan at the midportion of the distance between the knee and the hip using 120 kVp, 70 milliamperes, and 2 s. The outer and inner boundaries of the cortex were identified at the place of the maximum slope of the femoral profile through the bone. The area within the outer cortical shell represented the femoral cross-sectional area, and the area between the outer and inner cortical shells represented the bone area. The mean CT numbers of the pixels within the inner and outer cortical shells provided the average density (the amount of mineral and collagen per unit of area) of bone. Cortical bone mass was calculated as the product of bone density and cortical bone area.

In addition, to assess possible differences in physical activity, the area of thigh and paraspinous musculature at the levels of the midshaft of the femur and the third lumbar vertebra were determined from the same CT images (11). The coefficients of variation for repeated CT measurements of cancellous bone density, vertebral cross-sectional area, paraspinous musculature, femoral cross-sectional area, cortical bone area, cortical bone density, and thigh musculature were between 0.6–2.5%. The time required for the procedures was approximately 10 min, and the radiation exposure was 100–150 mrem (1–1.5 mSv) localized to the midportions of the first three lumbar vertebrae and the femurs; the effective radiation dose was approximately 4 mrem (12, 13).

Biochemical assessment

Blood was taken for routine serum chemistry (25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D_3, and osteocalcin). For each assay, results were analyzed simultaneously for purposes of comparison by Corning Nichols Institute (San Juan Capistrano, CA).

Statistical analysis

All results are expressed as the mean ± 1 SD. The data were analyzed by using Student's *t* test for paired samples, ANOVA, linear regression analysis, and Hotteling's T^2 (14, 15). A significance level of $P < 0.05$ was used for all comparisons.

Results

By design, there were no differences in the chronological age, height, weight, body surface area, or body mass index of the 30 matched pairs of prepubertal children (Table 1). Skeletal age, trunkal height, and the values for thigh and paraspinous musculature also did not differ between the boys and girls (Table 1).

Gender status did not influence cortical bone measurements and neither the area of cortical bone nor the cross-sectional area at the midshaft of the femur differed between boys and girls (Table 2). However, these dimensions correlated strongly with age, bone age, and all anthropometric indexes, including quantitative CT measurements of paraspinous and thigh musculature (Table 3). Multiple regression analyses indicated that the cross-sectional area and bone area in the midshaft of the femur were primarily related to weight.

In contrast to the findings in the appendicular skeleton, both anthropometric measurements and gender influenced vertebral cross-sectional area in these normal children, when the pooled data from all subjects were evaluated by ANOVA. The subjects with higher body mass had greater vertebral cross-sectional area than those with smaller body mass regardless of gender (Table 3), and there was a positive interaction between gender and body mass on vertebral cross-sectional area. Thus, the cross-sectional areas of L1, L2, and L3 were significantly smaller in girls than in boys, both using Student's *t* test ($P < 0.0001$) and its multivariate analog, the Hotelling's T^2 test ($P < 0.0001$). On the average, differences in cross-sectional area between girls and boys (11%) were greater than the variations that normally exist between adjacent vertebral levels (8%; Table 4). The heights of the lumbar vertebral bodies did not differ between sexes (Table 4).

Neither the density of cancellous bone in the lumbar vertebrae nor that of cortical bone in the femurs differed between boys and girls. This was true whether the mean values for the three lumbar vertebrae or for the two femurs were

TABLE 1. Chronological age, bone age, and anthropometric measurements for 30 boys and 30 girls matched for age, height, and weight

	Boys (n = 30)	Girls (n = 30)
Age (yr)	10.6 ± 1.5	10.3 ± 1.2
Bone age (yr)	10.3 ± 1.7	10.4 ± 1.3
Ht (cm)	139.0 ± 8.9	140.2 ± 8.9
Trunkal ht (cm)	73.2 ± 4.6	73.0 ± 5.2
Wt (kg)	37.2 ± 8.2	37.0 ± 7.8
Surface area (m^2)	1.2 ± 0.2	1.2 ± 0.2
Paraspinous muscle area (cm^3)	38.6 ± 8.6	37.4 ± 6.2
Thigh muscle area (cm^3)	73.0 ± 15	73.0 ± 14

TABLE 2. Cross-sectional area and cortical bone area at the midshaft of the femur in 30 boys and 30 girls matched for age, height, and weight

	Cross-sectional area (cm^2)			Cortical bone area (cm^2)		
	Boys	Girls	*P* value	Boys	Girls	*P* value
Right	3.25 ± 0.85	3.10 ± 0.55	NS	1.82 ± 0.38	1.85 ± 0.35	NS
Left	3.28 ± 0.83	3.10 ± 0.57	NS	1.78 ± 0.38	1.84 ± 0.37	NS
Mean	3.28 ± 0.84	3.10 ± 0.56	NS	1.80 ± 0.37	1.85 ± 0.36	NS

compared or whether the respective values for each vertebrae and femur were evaluated separately (Table 5). On the average, values for cortical bone density were 8 times higher than values for cancellous bone density. Values for cancellous and cortical bone densities were similar for all subjects and were not significantly influenced by age or any of the anthropometric measurements; correlations ranged between −0.21 and +0.13.

Overall, the values for vertebral cross-sectional area in all 60 children were positively correlated with the area of cortical bone ($r = 0.62$) and the cross-sectional area of the femurs ($r = 0.65$). Quantitative CT measurements of the area of paraspinous musculature also correlated moderately with muscle mass in the thigh ($r = 0.55$). However, no correlation was found between the density of cancellous bone in the vertebral body and that of cortical bone in the femur of all 60 subjects ($r = 0.00$).

Biochemical measurements were not influenced by gender status, and osteocalcin (boys, 14.8 ± 6.44; girls, 17.5 ± 8.13 ng/mL), 25-hydroxyvitamin D_3 (boys, 33.0 ± 10.98; girls, 29.3 ± 21.06 ng/mL), and 1,25-dihydroxyvitamin D_3 (boys, 54.2 ± 16.16; girls, 55.4 ± 21.94 pg/mL) levels did not differ between boys and girls.

Discussion

The results of this study indicate that gender has a differential effect on the sizes of the appendicular and axial skeletons. Although measurements of the cross-sectional area of the lumbar vertebral bodies were, on the average, 11% smaller in girls than in boys, there were no gender differences in the cross-sectional area of the femurs. As all subjects in this study were prepubertal Caucasian children, and groups were matched for chronological age, bone age, height, and weight, our findings cannot be attributed to differences in age, race, body size, or level of sexual or skeletal development. Similarly, because the amounts of musculature in the abdomen and the extremities were the same in boys and girls, it is unlikely that variations in physical activity influenced our results. Although the subjects were not recruited from the community at large, any bias introduced by the method of selection would apply equally to both groups.

TABLE 3. Correlations between age, bone age, and anthropometric measurements and the appendicular and axial skeletons in 60 children

	Femur		Vertebrae
	Cross-sectional area	Cortical bone area	cross-sectional area
Age	0.58	0.49	0.45
Bone age	0.59	0.53	0.47
Ht	0.78	0.72	0.69
Trunkal ht	0.72	0.70	0.65
Wt	0.80	0.77	0.57
Surface area	0.79	0.73	0.59
Paraspinous musculature	0.73	0.72	0.73
Thigh musculature	0.79	0.82	0.63

All correlations, $P < 0.001$.

Previous studies examining sex differences in bone growth have been limited by the inability of the techniques to measure the cross-sectional area of the bone and/or did not adequately control for body size. Numerous reports, including those of cadavers, have suggested a greater bone size and/or bone mass in the appendicular skeleton of boys than in that of girls (16, 17). Using skeletal radiogrametry, Garn *et al.* (18) found that boys have larger metacarpals than girls, and most studies using single photon absorptiometry also indicate that bone mass in the radius is greater in boys than in girls (19, 20). More recent studies assessing the axial skeleton of children using conventional radiography or dual x-ray or photon absorptiometry techniques have yielded conflicting results. Some studies found the vertebrae of girls to be smaller than those of boys (21), whereas others detected no gender differences in vertebral bone mass (22, 23), and still others reported that vertebral bone mass was greater in girls (24, 25).

In this study we used quantitative CT to separately assess the two components of skeletal mass, the size and density of bone, in both appendicular and axial skeletons. Our results indicate that in children, body weight is the primary determinant of the cross-sectional area and the area of cortical bone in the midshaft of the femur regardless of gender. Stronger correlations were consistently observed between these femoral measurements and body weight than with other developmental parameters. A multiple regression model accounting for chronological age, skeletal age, height, and muscle and fat areas in the abdomen and the lower extremities in addition to weight did not substantially improve the predictive power of a model accounting for weight alone. These results are consistent with analytical models proposing that long bone cross-sectional growth is strongly driven by mechanical load associated with increasing weight during growth (26, 27). On the other hand, both weight and gender influenced the cross-sectional area in the lumbar vertebrae when the pooled data were analyzed by ANOVA. Although vertebral cross-sectional area increased with weight in all children, the values were substantially greater in boys than in girls. The results of our use of quantitative CT bone measurements are in accord with previous observations that girls have smaller vertebral body size than boys even after accounting for differences in body size.

The reasons for the larger sizes of the bones in the axial, but not appendicular, skeleton of boys are unknown. Tes-

TABLE 4. Vertebral dimensions in 30 boys and 30 girls matched for age, height, and weight

	Cross-sectional area (cm^2)			Ht (cm)		
	Boys	Girls	*P* value	Boys	Girls	*P* value
L1	7.72 ± 1.24	6.69 ± 0.99	0.0001	1.83 ± 0.14	1.86 ± 0.18	NS
L2	8.33 ± 1.46	7.49 ± 0.99	0.0003	1.89 ± 0.14	1.93 ± 0.17	NS
L3	9.12 ± 1.46	8.12 ± 0.98	0.0001	1.94 ± 0.13	1.97 ± 0.16	NS
Mean	8.39 ± 1.35	7.50 ± 0.98	0.0001	1.89 ± 0.13	1.92 ± 0.17	NS

TABLE 5. Bone density in the axial and appendicular skeletons of 30 boys and 30 girls matched for age, height, and weight

	Vertebral cancellous density (g/cm^3)				Femoral cortical density (g/cm^3)		
	Boys	Girls	*P* value		Boys	Girls	*P* value
L1	0.25 ± 0.05	0.25 ± 0.09	NS	Right	1.89 ± 0.08	1.92 ± 0.07	NS
L2	0.24 ± 0.05	0.23 ± 0.04	NS	Left	1.89 ± 0.09	1.93 ± 0.08	NS
L3	0.22 ± 0.04	0.22 ± 0.04	NS	Mean	1.89 ± 0.09	1.93 ± 0.07	NS
Mean	0.24 ± 0.05	0.24 ± 0.04	NS				

tosterone has been implied to have a preferential effect on the growth of the axial skeleton. Observations on the treatment of children with hypopituitarism suggest that growth in the upper body segment, indicated by sitting height, is relatively more dependent on testosterone, whereas growth in the lower body segment, indicated by the difference between standing and sitting heights, is primarily under the control of GH (28, 29). However, by design, only prepubertal children were studied, and our results cannot be attributed to gender differences in the heights of upper skeletal segments, as sitting heights and the heights of the lumbar vertebrae were similar in boys and girls. Serum testosterone levels are, nevertheless, substantially higher in infant boys than girls, and serum levels in male infants during the first 6 months of life reach levels similar to those in adolescent males (30, 31). Although the precise function of this temporary neonatal surge in testosterone secretion is not understood, further evaluation is needed to determine whether androgens enhance growth in the axial skeleton during very early stages of development in boys.

Regardless of the mechanism by which gender influences skeletal growth, the cross-sectional growth of the femur and that of the vertebra result from two different processes, which are probably regulated by different means (27). Bone growth at the midshaft of the femur is achieved by subperiosteal formation of new bone, a process that begins before birth and continues throughout life. Simultaneous to the age-specific subperiosteal bone apposition, a complex activity characterized by resorption and apposition occurs at the endosteal surface of the bone. Whereas subperiosteal activity determines the width of the bone, endosteal activity determines the width of the medullary canal. The combination of the relative activities at the two modeling surfaces over a period of time determines the thickness of the cortex. On the other hand, endochondral ossification determines the cross-sectional area of the vertebrae. Endochondral ossification commences in the central area of the cartilage anlage in the vertebrae and, from this region, expands and progresses toward the periphery in all directions. It is generally assumed that normal development and growth of the diaphysis of the femur is mainly dependent upon mechanical loading, whereas endochondral growth and ossification may occur without mechanical stress (27).

The findings of this study corroborate previous studies indicating that females and males have identical cancellous and cortical bone density, emphasizing that gender differences in bone mass in children are related to variations in bone size (3, 4, 32, 33). Values for cancellous bone were, however, 8 times lower than those for cortical bone, reflecting its greater porosity (34). Because of the relatively small size of the spicules of cancellous bone compared to that of the voxel (CT unit of measurement), some degree of area averaging is always incorporated, and values for cancellous bone density reflect the amount of bone and marrow per unit of tissue (35). In contrast, the femoral cortex is sufficiently thick to circumvent area-averaging errors, and CT measurements reflect the true density of the bone (36). In the present study, the values for cancellous and cortical bone densities remained unchanged, whereas, simultaneously, the cross-sectional areas of the vertebrae and femur increased with age and body size, underscoring the importance of bone size to meet increasing loads.

The discrepant effect of gender in the appendicular and axial skeleton may account for the sex difference in the incidence of fractures in elderly subjects with osteoporosis. Because variations in the dimensions of the vertebrae and femurs in adults reflect differences in bone growth that evolve during early skeletal development, changes in bone size during childhood have important biomechanical implications with respect to the loading capacity of the skeleton in adulthood (2, 37). Recent studies have shown that vertebral size is a major determinant of vertebral fractures, and theoretically, the smaller cross-sectional area in women could explain their 4- to 8-fold higher incidence of vertebral fractures compared to that in men (38). In contrast, the lack of gender differences in the size of the femur between girls and boys may partially account for the less discrepant 2:1 ratio of hip fractures between women and men (39). Nevertheless, future studies are needed to establish whether the differential effect of gender on the size of the bones in the appendicular and axial skeletons during childhood is related to the disparity in fracture incidence in elderly women and men.

In conclusion, the cross-sectional dimensions of the appendicular and axial skeletons are influenced by separate determinants during childhood. Changes in cortical bone area and cross-sectional area in the midshaft of the femur correspond to a number of anthropometric indexes of body size and body mass, findings consistent with the view that weight-bearing or mechanical stresses applied to the skeleton are important regulators of appendicular bone mass. Changes in the cross-sectional area of the vertebral body during growth are not only associated with increases in body size, but they are also strongly influenced by gender. The results suggest that although increases in mechanical loading are the main determinant of cross-sectional properties in the appendicular skeleton, other factors related to gender play an important role in the regulation of the size of the axial skeleton.

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