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Bone Acquisition in Healthy Children and Adolescents: Comparisons of Dual-Energy X-Ray Absorptiometry and Computed Tomography Measures

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The effect that growth has on dual-energy x-ray absorptiometry (DXA) bone measurements is yet to be fully defined. The purpose of this study was to determine the best method for optimizing pediatric bone measurements using DXA. Height, weight, body mass index, skeletal age, and Tanner stage of sexual development were determined for 64 healthy boys and 60 healthy girls ages 6–17 yr. DXA of the lumbar vertebrae was performed to measure bone mineral content (BMC, grams) and areal bone mineral density (aBMD, grams per square centimeter), and geometric corrections were used to calculate volumetric bone mineral densities (vBMD): vBMD1 = aBMD/$\surd$(DXA-area) and vBMD2 = aBMD/bone height. Computed tomography (CT) imaging was performed to measure volumetric bone density (vBD) and vertebral volume (Vol) and to calculate CT-BMC = vBD $*$ Vol. Linear regression was used to compare DXA-BMC *vs.* CT-BMC and CT vBD *vs.* DXA aBMD, vBMD1, and vBMD2. Multiple regression including the anthropometric and developmental parameters was also performed.

DXA and CT BMC were highly correlated ($r^2 = 0.94$). However, DXA aBMD correlated more strongly with CT Vol ($r^2 = 0.68$) than with CT density ($r^2 = 0.39$), and calculation of DXA volumetric densities only slightly improved the density correlations ($r^2 = 0.49$ for vBMD1; $r^2 = 0.55$ for BMD2). The correlations for density were particularly poor for subjects in Tanner stages 1–3 ($r^2 = 0.02$ for aBMD; $r^2 = 0.13$ for vBMD1; $r^2 = 0.27$ for vBMD2). In contrast, multiple regression accounting for the anthropometric and developmental parameters greatly improved the agreement between the DXA and CT densities ($r^2 = 0.91$).

These results suggest that DXA BMC is a more accurate and reliable measure than DXA BMD for assessing bone acquisition, particularly for prepubertal children and those in the early stages of sexual development. Use of DXA BMD would be reasonable if adjustments for body size, pubertal status, and skeletal maturity are made, but these additional assessments add significant complexity to the studies. (*J Clin Endocrinol Metab* 90: 1925–1928, 2005)

DUAL-ENERGY X-RAY absorptiometry (DXA) is, by far, the most widely used technique for measuring bone acquisition in children due to its low cost, accessibility, and ease of use (1). Because DXA bone determinations are based on a two-dimensional projection of a three-dimensional structure, values are a sum of cortical and trabecular bone mineral content (BMC) within the projected bone area. DXA provides an estimate of BMC expressed as grams per anatomical region (*e.g.* individual vertebrae, whole body, or hip). Dividing the BMC (grams) by the projected area of the bone (square centimeters) then derives areal bone mineral density (aBMD) (grams per square centimeter).

The availability of DXA has resulted in many large-scale studies of the genetic, behavioral, and nutritional determinants of aBMD in healthy children (2–13). Although DXA studies in pediatrics have provided much information regarding changes in BMC and BMD over time, there is still considerable confusion over the interpretation of DXA measures. Most of the growth-related increases observed in DXA BMD values are due to increases in bone size, and gender differences in BMD values are largely due to greater bone size in males (14). The confounding effect of skeletal geometry on DXA measures is gaining much recognition, and two main strategies have been proposed to decrease the influence of bone size on DXA bone measures. The first assumes that the vertebral body has a defined geometrical shape, such as an ellipse, and uses the dimensions of the projected anterioposterior bone area to estimate the total vertebral volume (15). The BMC is then divided by this estimate of volume to generate bone mineral density (BMD). The second strategy takes into account various anthropometric parameters to adjust for the influence of body and skeletal growth and development on BMD values (12). Whereas these approaches are likely to reduce the influence of skeletal size on DXA

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Abbreviations: aBMD, Areal bone mineral density; BMC, bone mineral content; BMI, body mass index; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; vBD, volumetric bone density; vBMD, volumetric bone mineral density.

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measurements, it is yet to be determined which provides the best correction for pediatric subjects.

In this study, we examined the relationships between vertebral DXA measurements of BMC and aBMD and vertebral computed tomography (CT) measurements of volumetric bone density (vBD), which are not affected by body or skeletal size. We also examined the usefulness of correction factors based on anthropometric parameters and on published geometric formulas on DXA measurements.

Subjects and Methods

Study subjects

Criteria for inclusion in the study consisted of white racial background; age between 6 and 17 yr; residency in the United States for at least 3 yr; a gestational age of at least 37 wk; a birth weight of at least 5 pounds; normal developmental milestones with school placement within 1 yr of expected chronological age; height, weight, and body mass index (BMI) between the 3rd and 97th percentiles for sex and age using current CDC reference values; and normal pubertal development. For girls, inclusion criteria consisted of breast development occurring between 8 and 13 yr, menarche between 10 and 15 yr, and no pubic hair before 7 yr of age. For boys, inclusion criteria consisted of testicular size of less than 4 cc by 9 yr and greater than 4 cc by 14 yr.

Candidates for the study were excluded based on the following criteria: a history of medical or surgical disorder resulting in a period of illness or recuperation that interrupted their usual physical activity and/or nutritional status for 1 month or more in the 2 yr before enrollment, or 1 wk or more of hospitalization or 2 wk or more of enforced bed rest in the 6 months before enrollment; current or previous chronic medical condition known to affect growth that required medical follow-up beyond the usual well-child care and/or affected or limited their activities; current or previous chronic medication that might affect growth, appetite, or bone mineral accrual, including glucocorticoids, testosterone or anabolic steroid treatment, medroxyprogesterone acetate, gonadrotropin inhibitors, GH treatment, anticonvulsants, isotretinoin, methylphenidate or other stimulants used for ADHD, and antidepressants; genetic or dysmorphic syndromes; scoliosis of more than 20 degrees or kyphosis of more than 40 degrees; previous surgery with metal pins, rods, screws, or staples; a nonremovable body piercing in the chest or abdomen; conditions, such as old fractures, associated with abnormal bone size or shape; a history of recurrent long bone fractures; secondary amenorrhea defined as no menses for at least 6 months during or after the third postmenarcheal year; and current or previous pregnancy.

One hundred twenty-four subjects were enrolled in this substudy (64 boys and 60 girls). These subjects were family members or companions of employees at Childrens Hospital Los Angeles or were recruited from schools of Los Angeles County. The investigational protocol was approved by the institutional review board for clinical investigations at Childrens Hospital Los Angeles, and informed consent was obtained from all subjects and/or their parents.

All potential candidates underwent a physical examination by a Pediatric Endocrinologist to determine their general health and stage of sexual development. Tanner stage of sexual maturity was assessed based on breast development in girls and testicular size in boys (16). Measurements of total height were obtained to the nearest 0.1 cm using the Harpenden stadiometer (Holtain Ltd., Crymmych, Wales), and measurements of weight were obtained to the nearest 0.1 kg using the Scale-Tronix (Scale-Tronix, Inc., Wheaton, IL). BMI was calculated as weight in kilograms divided by the square of height in meters.

Imaging assessments of skeletal maturity and vertebral bone

Skeletal maturation was assessed from an anteroposterior view of the left hand and wrist, using high-resolution extremity radiographs according to the method of Greulich and Pyle (17).

The technique for determining lumbar vertebral bone density by quantitative CT has been described in detail elsewhere (14, 18, 19). All CT studies were performed by the same radiology technologist using the same scanner (CT-T 9800; General Electric Co., Milwaukee, WI) and the same mineral reference phantom (CT-T bone densitometry package; General Electric Co.). Identification of the sites to be scanned was performed with lateral scout views, and the integral density of bone (including both cortical and cancellous bone) of the vertebral body were obtained from the 10-mm midportion of the L1, L2, and L3 vertebral bodies. Excluded for the determinations were the transverse process and the posterior elements. The cross-sectional area at the same sites was also determined. The volume of each vertebra was calculated by multiplying the cross-sectional area by vertebral height from the scout view. The average volumetric density (CT-vBD) and volume (Vol) of L1–L3 was calculated, and BMC was calculated as CT-BMC = CT-vBD $*$ Vol. The coefficients of variation for repeated CT measurements of vertebral cross-sectional area, vertebral volume, and vertebral bone density are between 0.6 and 1.5% (20, 21). The time required for the procedure was approximately 10 min. The radiation exposure was approximately 100–200 mrem (1.5 mSv) localized to the midportions of the lumbar vertebrae; the effective radiation dose was approximately 8 mrem (22, 23).

Subjects also underwent DXA scanning by the same radiology technologist using the same densitometer (Delphi W; Hologic, Inc., Waltham, MA). Anterior-posterior scans were obtained for L1–L3. The manufacturer's software calculated BMC, projected area (DXA-area), and aBMD for each vertebral body. These values were used to obtain the average BMC (DXA-BMC) and aBMD of L1–L3. Volumetric bone mineral densities (vBMD) were estimated from the DXA measurements using published geometric correction factors (vBMD1 = aBMD/$\sqrt{}$(DXA-area); vBMD2 = aBMD/bone height) (15). The coefficients of variation for repeated DXA measurements of vertebral BMC and aBMD have been reported to range from 0.7 to 1.7% (20, 21, 24). The time required for the procedure was approximately 5 min, and the radiation exposure was negligible (22–24).

Statistical analysis

Statistical analysis was carried out using Statview (version 5.0.1; SAS Institute Inc., Cary, NC). Linear regression was used to compare DXA-BMC *vs.* CT-BMC as well as CT-vBD *vs.* DXA aBMD, vBMD1, and vBMD2. Multiple regression including chronological age, height, weight, BMI, skeletal age, and Tanner stage of sexual development was also performed.

Results

Table 1 shows the results of the anthropometric measurements for all subjects. There was excellent agreement between DXA-BMC and CT-BMC ($r^2 = 0.94$; $P < 0.0001$) (Fig. 1). In contrast, there was only moderate agreement between DXA aBMD and CT vBD ($r^2 = 0.39$; $P < 0.0001$) (Fig. 2). In fact, DXA aBMD had a stronger correlation with vertebral volume ($r^2 = 0.68$; $P < 0.0001$) than with CT density. Geometric corrections to calculate DXA volumetric densities resulted in only slight improvement in the correlations with CT density ($r^2 = 0.49$, $P < 0.0001$ for vBMD1; $r^2 = 0.55$, $P < 0.0001$ for vBMD2) (Fig. 3). Accounting for chronological age, height, weight, BMI, skeletal age, and Tanner stage of sexual development improved the agreement between DXA aBMD and CT vBD ($r^2 = 0.91$), but this remained lower than the agreement for BMC. The most significant variables in the

TABLE 1. Age and developmental parameters of 124 children

	Male (n = 64)	Female (n = 60)	All subjects (n = 124)
Age (yr)	12.1 ± 3.4	11.2 ± 3.2	11.7 ± 3.3
Tanner stage	3.2 ± 1.8	3.0 ± 1.8	3.1 ± 1.8
Skeletal age (yr)	12.2 ± 4.1	11.8 ± 3.5	12.0 ± 3.8
Height (cm)	153.1 ± 22.9	144.5 ± 18.1	148.9 ± 21.1
Weight (kg)	48.4 ± 18.8	42.4 ± 15.9	45.5 ± 17.6
BMI	19.6 ± 3.1	19.5 ± 3.7	19.5 ± 3.4

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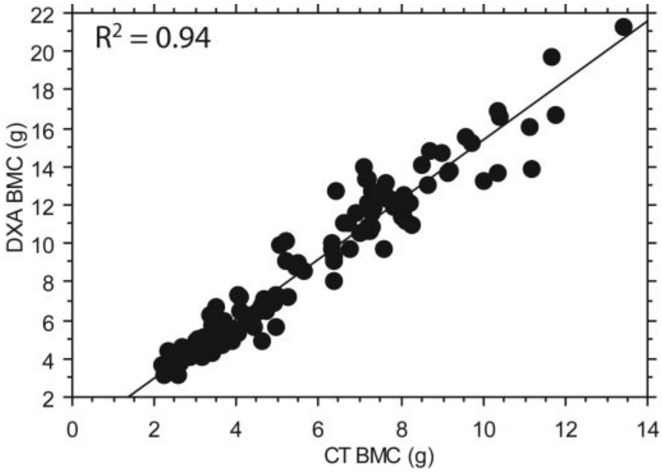

FIG. 1. Correlations between CT-BMC and DXA-BMC.

multiple regression were CT vBD ($P < 0.0001$), Tanner ($P = 0.04$), and weight ($P = 0.08$).

When subjects in Tanner stages 1–3 were considered separately from subjects in Tanner stages 4 and 5, correlations for the density were particularly poor for the less mature subjects even after correction with geometric formulas (Table 2). The correlations for BMC and the multiple regression were only slightly lower in the younger subjects. Results for boys and girls were similar to the overall results, with slightly lower correlations for the boys.

Discussion

Previous studies have suggested that the inability of DXA to accurately account for variations in body and skeletal size and to account for the posterior elements of the vertebrae are major limitations of its use in pediatrics. However, the results of the current study indicate that DXA measures of vertebral BMC in children are strongly associated with CT measures of vertebral BMC, supporting the notion that this projection technique provides accurate determinations of bone mass during growth. We found this to be true for all subjects when analyzed together and when males and females were assessed independently. These findings support the use of DXA BMC as an outcome measure in studies on the environmental and genetic determinants of bone acquisition during growth.

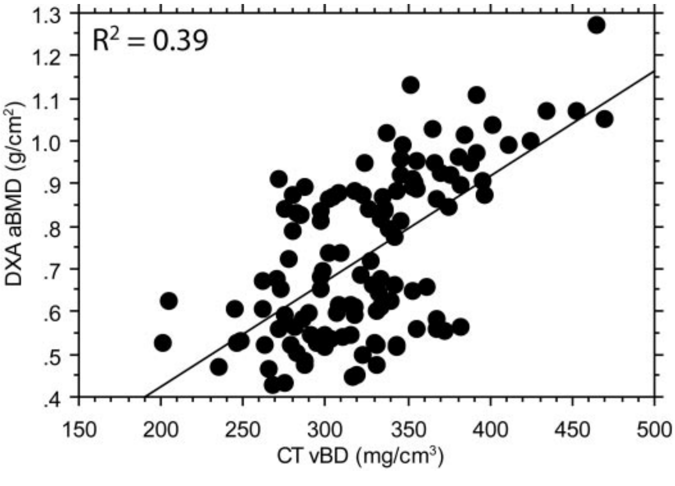

FIG. 2. Correlations between CT vBD and DXA aBMD.

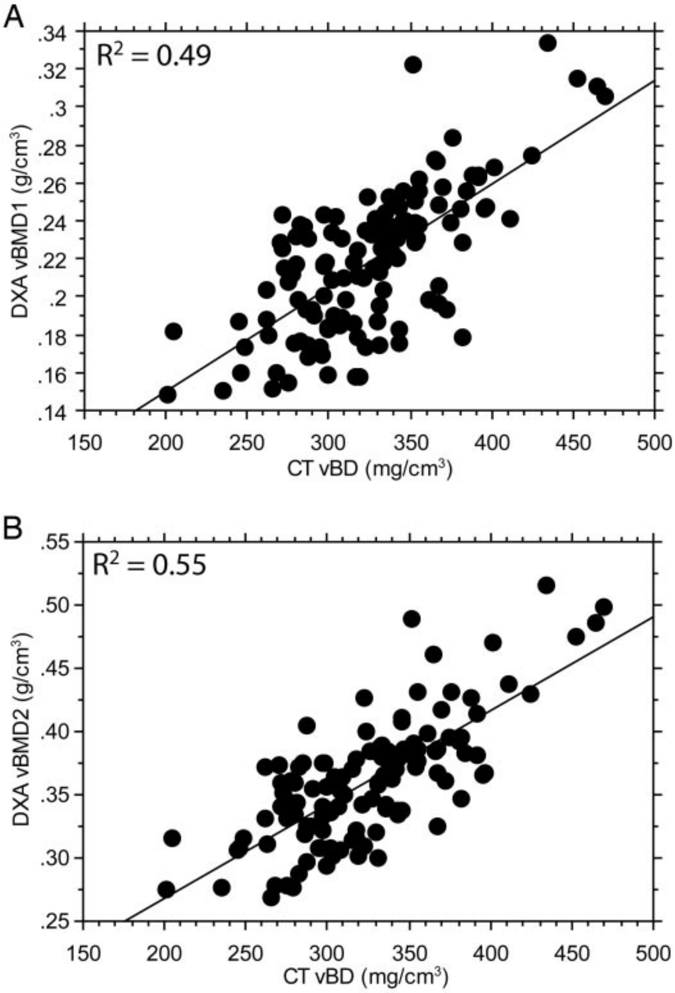

FIG. 3. Correlations between CT vBD and DXA vBMD1 (A) and DXA vBMD2 (B).

In contrast to the findings for BMC, correlations between values for bone density measured by DXA and CT were weak. Stronger associations were observed between DXA areal density measurements and CT values for vertebral volume than between DXA and CT values for bone density. It should be stressed that, in prepubertal children and those in the early stages of sexual development, there was no association between these two measures of bone density.

Two main strategies have been proposed to decrease the

TABLE 2. Regression results (r^2) for CT and DXA measurements in subjects grouped by Tanner stage of sexual development

	Tanner 1–3 (n = 61)	Tanner 4–5 (n = 63)
DXA-BMC *vs.* CT-BMC	0.80	0.84
DXA-aBMD *vs.* CT-vBD	0.02	0.51
DXA-vBMD1 *vs.* CT-vBD	0.13	0.60
DXA-vBMD2 *vs.* CT-vBD	0.27	0.56
Multiple regression for DXA-aBMD *vs.* CT-vBD, including developmental and anthropometric measures	0.76	0.79

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influence of growth on DXA bone measures; one primarily attempts to correct for variations in skeletal size and the second takes into account multiple measures of growth and development (1, 15). We found that using published correction factors to overcome the confounding effect of skeletal geometry on DXA aBMD only slightly improved the association with CT vBD, although adjusting for body size, pubertal status, and skeletal maturity greatly improved the association between aBMD and vBD values. Indeed, after accounting for chronological age, bone age, height, weight, BMI, and Tanner stage of sexual development, measures of aBMD predicted about 91% of the variance of true vBD. The need for additional examinations, such as skeletal age and Tanner stage of sexual development, to optimize aBMD values, however, adds a significant amount of complexity to these studies. Moreover, even after including these growth assessments, the agreement between aBMD and vBD remained weaker than the relation between DXA and CT BMC.

This study has several limitations. First, we examined healthy children from 6–16 yr of age with average height and weight, and it is likely that the strength of the associations differs in other populations, *i.e.* children who are younger, sick, overweight, short, *etc.* Second, our findings are only valid for the axial skeleton and cannot be extrapolated to the appendicular skeleton. Lastly, our results were obtained from comparisons between two specific bone densitometers and may not apply with equipment from other manufacturers.

In conclusion, the results of this study support the contention that areal bone density measurements in children are markedly influenced by growth-related changes in body and skeletal size. Only when the degrees of sexual and skeletal development, as assessed by Tanner stage and bone age, are taken into account do DXA values for bone density reflect true vBD. In contrast, our findings suggest that neither the inclusion of the posterior elements of the vertebrae nor the effects of soft tissue distribution influence spinal BMC measurements obtained with DXA, at least for healthy children within the 3rd to 97th percentiles for height, weight, and BMI. We suggest that when using this projection technique in growing subjects, BMC is a more accurate and reliable measure than aBMD for assessing bone acquisition.

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