

BONE DENSITOMETRY IN PEDIATRIC POPULATIONS: DISCREPANCIES IN THE DIAGNOSIS OF OSTEOPOROSIS BY DXA AND CT

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Objectives To test the hypothesis that because of errors associated with growth and development, osteoporosis is frequently overdiagnosed in children when using dual-energy x-ray absorptiometry (DXA). This study compared bone density values obtained by DXA with those from computed tomography (CT), which is not influenced by body or skeletal size.

Study design Vertebral bone density was measured by using both DXA and CT in 400 children (100 each, healthy and sick boys and girls). Regression analysis was used to compare DXA and CT Z scores, and the agreement between DXA and CT classifications of Z scores below -2.0 was examined.

Results DXA and CT Z scores were moderately related ($r^2 = 0.55$ after accounting for age and anthropometric measures). DXA Z scores predicted CT Z scores below -2.0 with reasonable sensitivity (72%), specificity (85%), and negative predictive value (98%), but positive predictive value was low (24%). Many more subjects were classified as having bone density lower by DXA (76/400) than by CT (25/400), particularly subjects below the 5th percentile of height and/or weight for age.

Conclusions The inability of DXA to account for the large variability in skeletal size and body composition in growing children greatly diminishes the accuracy of this projection technique for assessing bone acquisition and diagnosing osteoporosis in pediatric populations. (*J Pediatr* 2005;146:776-9)

Dual-energy x-ray absorptiometry (DXA) is the most widely used technique for measuring bone acquisition in children because of its low cost, minimal radiation exposure, accessibility, and ease of use.¹ The availability of DXA has resulted in many large-scale studies of the genetic and environmental determinants of areal bone mineral density (aBMD) in healthy children.²⁻¹³ Although DXA studies in pediatrics have provided much information regarding changes in aBMD over time, there is still considerable confusion over the interpretation of DXA measures. Most growth-related increases in DXA aBMD values are due to increases in the size rather than the density of the bone, and sex differences in aBMD values are also largely the result of greater bone size in male subjects.¹⁴

The confounding effect of skeletal geometry on DXA measures is gaining much recognition. Recently, it has been suggested that major errors in interpretation occur when using this technique in pediatric populations, leading to the overdiagnosis of osteoporosis in growing subjects. Indeed, several investigators have proposed that osteoporosis should not be diagnosed on the basis of DXA densitometry criteria alone.^{15,16} In addition, whereas in adults, DXA aBMD is a powerful predictor of fracture and is used to define osteoporosis, there is insufficient pediatric evidence to determine aBMD standard deviation criteria for osteopenia and osteoporosis, as indicated by the World Health Organization. Hence, it is recommended that when reporting DXA results in subjects younger than 20 years of age, it is more appropriate to define a Z score of less than -2.0 as low bone density rather than using the World Health Organization classification for osteoporosis.¹⁵

In this study, we examined the relation between vertebral DXA measurements of aBMD and vertebral quantitative computed tomography (CT) values of volumetric bone density (vBD), which are not influenced by skeletal or body size, in a large cohort of healthy and sick children. We specifically examined the relation between DXA and CT Z scores, which are defined as the number of standard deviations the aBMD or vBD is above or below the mean for age-matched control subjects.

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p 764, and p 769.

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BMD	Bone mineral density	CT	Computed tomography
BMI	Body mass index	DXA	Dual-energy x-ray absorptiometry

METHODS

Study Subjects

During the past 5 years, many children and adolescents have had bone measurements through the use of both CT and DXA at Childrens Hospital Los Angeles. This retrospective review included the records from 100 healthy boys and 100 healthy girls who were participants in several studies on bone acquisition during growth and from 100 sick boys and 100 sick girls. For the purpose of this study, "sick" subjects were defined as patients being evaluated for bone mass deficiency. The protocol was approved by the institutional review board for clinical investigations at our institution. Written informed consent was obtained from all healthy subjects and their parents. Data from the sick subjects were reviewed retrospectively under a waiver of consent approved by the institutional review board.

All 400 subjects, ages 6 to 17 years, were enrolled in this study. Age, height, and weight were recorded for each. 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, Ill). Height, weight, and body mass index (BMI) percentiles-for-age were determined by using the references provided by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion.¹⁷

CT and DXA Assessments of Vertebral Bone

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, Milwaukee, WI). Identification of the sites to be scanned was performed with lateral scout views, and the density of cancellous bone in the vertebral body was obtained from the 10-mm midportion of the L1, L2, and L3 vertebral bodies. The average density of L1-L3 was calculated and compared with published normative data from our laboratory²⁰ to determine CT Z score (Z_{CT}). The coefficients of variation for repeated CT measurements of vertebral density are between 0.6% and 1.5%.^{21,22} The time required for the procedure was approximately 10 minutes. The radiation dose was approximately 100 to 200 mrem (1.5 mSv), localized to the midportions of the lumbar vertebrae; the effective radiation dose was approximately 8 mrem.^{23,24}

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-L4. The manufacturer's software calculated aBMD for each vertebral body as well as Z score for the average L1-L4 aBMD (Z_{DXA}). The time required for the procedure was approximately 5 minutes, and the radiation exposure was negligible.²³⁻²⁵

Statistical Analysis

Statistical analysis was carried out with the use of Statview (version 5.0.1; SAS Institute Inc, Cary, NC) and Stata (version 8.0; Stata Corp, College Station, TX). Linear regression was used to compare Z_{DXA} with Z_{CT} , both in simple regression and in multiple regression, including age, height, weight, BMI, height percentile, weight percentile, and BMI percentile as covariates. After the regression analysis, the ability of DXA Z scores to predict CT Z scores below -2.0 was examined. Sensitivity (proportion of subjects with CT Z scores below -2.0 who also had DXA Z scores below -2.0), specificity (proportion of subjects with CT Z scores above -2.0 who also had DXA Z scores above -2.0), positive predictive value (proportion of subjects with DXA Z scores below -2.0 who also had CT Z scores below -2.0), and negative predictive values (proportion of subjects with DXA Z scores above -2.0 who also had CT Z scores above -2.0) were calculated.

RESULTS

Table I summarizes the anthropometric measurements for all subjects.

A significant linear relation was observed between Z_{DXA} and Z_{CT} ($r^2 = 0.39$; $P < .0001$) (Figure). This relation was improved when age and anthropometric measures were included in the regression model ($r^2 = 0.55$). Results for subgroups divided by health status (healthy or sick) and sex were similar to the overall results (r^2 values of 0.27 to 0.48 for single regression, 0.51 to 0.65 for multiple regression).

When DXA Z scores were used to predict CT Z scores below -2.0 , sensitivity and specificity were reasonable and negative predictive value was extremely high. However, positive predictive value was low (Table II). This was true whether all subjects were analyzed together or sick and healthy subjects were analyzed separately. For the subjects who were classified differently by CT and DXA, many more were identified as having bone density lower by DXA (58/400) than by CT (7/400). Of the 58 subjects who were identified by DXA only, most were small for their age ($<5^{\text{th}}$ percentile) in terms of height (30/58, 52%), weight (22/58, 38%), or both height and weight (17/58, 29%).

DISCUSSION

Currently, DXA is routinely used worldwide in children to diagnose osteoporosis, assess response to therapy, and study the determinants of bone accretion during growth. The results of the current study indicate, however, that DXA measures of aBMD underestimate bone accretion in children and adolescents. On average, 3 times as many subjects were determined to have low bone density (Z score <-2.0 for chronological age) by DXA than by CT; this was true for both healthy (2% vs 7%) and sick (10.5% vs 31%) children.

We found that whereas DXA and CT Z scores are related, almost 50% of the variability remains even after age

Table I. Age and anthropometric measures for 400 children

	Healthy		Sick		All subjects (N = 400)
	Male (N = 100)	Female (N = 100)	Male (N = 100)	Female (N = 100)	
Age (y)	13.7 ± 3.2	13.1 ± 3.1	12.2 ± 3.2	12.0 ± 2.9	12.7 ± 3.2
Height (cm)	160.0 ± 20.1	152.2 ± 15.4	146.8 ± 20.4	141.6 ± 16.8	150.1 ± 19.4
Height percentile	48.3 ± 26.7	50.6 ± 27.6	36.1 ± 33.2	31.8 ± 32.3	41.7 ± 31.0
Weight (kg)	57.3 ± 21.5	49.7 ± 16.0	47.0 ± 21.1	44.6 ± 17.8	49.7 ± 19.8
Weight percentile	62.2 ± 26.9	60.9 ± 24.9	50.9 ± 39.0	51.8 ± 33.9	56.5 ± 32.0
BMI (kg/m ²)	21.5 ± 4.8	20.9 ± 4.5	20.7 ± 5.5	21.5 ± 5.6	21.2 ± 5.1
BMI percentile	63.1 ± 28.3	60.7 ± 26.9	60.6 ± 34.9	66.5 ± 27.7	62.7 ± 29.6

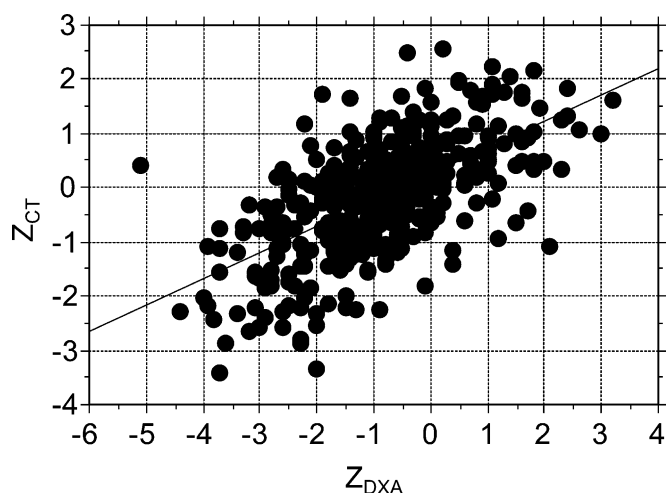


Figure. Linear regression comparing DXA with CT Z scores for 400 subjects ($r^2 = 0.39$).

and anthropometric measures are taken into account. When classifying low bone density based on a Z score cutoff value of -2.0 , DXA had a reasonable sensitivity and specificity in predicting CT classification, but positive predictive value was low. This is partly due to DXA underestimating bone density and overestimating osteoporosis in children who are small for their age ($<5^{\text{th}}$ percentile for height and/or weight), since bone size tends to increase with greater height and weight. The consequence is that DXA Z scores ≥ -2 have greater concordance with CT Z scores than do DXA Z scores < -2 , which require further screening to confirm osteoporosis.

Since this study involved two specific bone densitometers, the findings may differ with equipment of other manufactures. The systematic overreading of low bone mass by DXA may, in fact, be the result of the currently available Hologic reference data. When using values from the healthy children in the current study to calculate Z scores for the sick children, the tendency of DXA to yield lower Z scores than CT was greatly curtailed, although comparisons with this database did not strengthen the correlation between DXA and CT Z scores. Although many children were identified as having low bone density by one modality but not the other,

Table II. Classification of Z scores based on cutoff value of -2.0 and classification statistics for prediction of Z_{CT} by Z_{DXA}

	Healthy (N = 200)	Sick (N = 200)	Total (N = 400)
Z score < -2			
Neither CT/DXA	185	132	317
CT/DXA	3	15	18
CT only	1	6	7
DXA only	11	47	58
	Healthy (N = 200)	Sick (N = 200)	All subjects (N = 400)
Sensitivity	75% (3/4)	71% (15/21)	72% (18/25)
Specificity	94% (185/196)	74% (132/179)	85% (317/375)
Positive PV	21% (3/14)	24% (15/62)	24% (18/76)
Negative PV	99% (185/186)	96% (132/138)	98% (317/324)

PV, predictive value.

they were more evenly split with regard to which technique yielded the < -2 classification. Consequently, discrepancies probably will exist between DXA and CT assessments of low bone density regardless of the reference data used.

In addition, the discrepant results between DXA and CT classifications are, in part, due to the errors associated with the unknown composition of soft tissues adjacent to the axial skeleton. Because corrections for soft tissues are based on the assumption of a homogenous distribution of fat around the vertebrae, changes in DXA measurements are observed if fat is distributed inhomogeneously around the bone measured. It has been estimated that inhomogeneous fat distribution in soft tissues resulting in a difference of 2 cm of fat between the soft tissue and bone areas will influence DXA measurements by 10%.²⁶ This disadvantage especially limits the use of DXA in studies of children with eating disorders, such as obesity and anorexia nervosa.

Last, the lack of a definable association between pediatric bone density values and a clinical outcome measure obfuscates the significance of these measurements in children. The relation of bone measurements to pediatric fractures is, at

best, debatable, and their association to the risk of osteoporosis and fractures later in life has not yet been defined. However, previous studies have established the constancy of CT percentile measures for bone size and bone density throughout puberty, the time of life in which bone mass more than doubles.²⁷ Establishing the degree to which BMD values can be tracked throughout childhood and adolescence will help determine whether the identification of children at risk for low peak bone mass is also possible through the use of DXA.

CONCLUSIONS

The interpretation of DXA measurements is considerably more challenging in children and adolescents than in adults because of the dynamic changes in body and skeletal size and configuration associated with growth and sexual development. The results of this study support the contention that current DXA bone determinations frequently underestimate the amount of bone in children regardless of age, sex, or whether they are healthy or sick. The immediate challenge is to obtain valid interpretations of DXA bone measurements in pediatrics so that a subclinical deficiency in bone accrual can be identified accurately in "at risk" children. To this end, greater understanding of the DXA errors associated with variations in growth and development and the methods to correct for size bias and soft tissue distribution is needed.

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