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Assessment of Bone Acquisition in Childhood and Adolescence

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ABSTRACT

Availability, ease of use, relative low cost, and minimal radiation exposure have made dual-energy x-ray absorptiometry the most widely used technique worldwide to obtain bone measurements for both research and clinical purposes in pediatric populations. However, errors related to growth and maturity significantly diminish the accuracy of dual-energy x-ray absorptiometry bone measurements. Several investigators have found that dual-energy x-ray absorptiometry in children frequently leads to a misdiagnosis of osteoporosis and an underestimation of the amount of bone. In this regard, a recent official position paper by the International Society for Clinical Densitometry states that subjects <20 years of age should not be given a diagnosis of osteoporosis on the basis of dual-energy x-ray absorptiometry criteria. Nevertheless, the increased awareness that osteoporosis has its antecedents in childhood and the demand for examinations of bone acquisition and response to therapy stress the urgent need to improve the value of dual-energy x-ray absorptiometry measurements for children.

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Key Words

dual-energy x-ray absorptiometry, DXA, osteoporosis, pediatrics, QCT

Abbreviations

BMC—bone mineral content
DXA—dual-energy x-ray absorptiometry
BMD—bone mineral density
aBMD—areal bone mineral density
CT—computed tomography
QCT—quantitative computed tomography

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THERE ARE 2 main reasons for measuring bone mineral content (BMC) in children: to quantify the deficits in bone mineral associated with the various disorders that cause osteopenia in children and to improve our understanding of the childhood antecedents of osteoporosis, a condition that happens to manifest itself in elderly subjects. Available data suggest that the genetic susceptibility to osteoporosis may be detectable in early childhood.¹ This notion is supported by studies that have shown that there is a strong resemblance between mother-daughter bone traits and that this resemblance is present even before the daughters have begun puberty.^{1,2} Additional support comes from the evidence that some genes associated with the normal variations in bone mass in elderly women may also be related to variations in bone density in children.³⁻⁵ If bone loss were the exclusive determinant of late-life bone mass, one would not expect such a strong resemblance in bone traits between girls and their mothers or in the association between candidate genes and bone mass in childhood. Peak bone mass, a major determinant of the risk for osteoporosis and fractures in the elderly population, is largely achieved at the end of sexual development in the lumbar spine and the femur.⁶⁻⁸ By the age of 16 years, most children have completed sexual maturity, and studies have shown that bone-mass values in girls by this age are equal to or greater than that of their premenopausal mothers.^{9,10}

Currently, the most commonly used quantitative radiologic method for assessing bone mass in elderly patients is dual-energy x-ray absorptiometry (DXA).¹¹ This technique is also increasingly used in children because of the growing awareness that osteoporosis has its antecedents in childhood. This has increased the demand for examinations of bone acquisition and response to therapy in pediatric populations. Early bone health is key to the achievement of high peak bone mass in young adulthood and serves as the "bone bank" for the remainder of adult life. Support for this concept comes from data that indicate a strong resemblance in bone mass between mothers and prepubertal daughters and that candidate genes associated with osteoporosis and fractures in elderly patients are also associated with low bone mass in childhood.¹⁻⁵ Peak bone mass may be compromised by chronic malnutrition, inactivity, teenage pregnancy, hypogonadism, chronic steroid exposure, and a multitude of pediatric diseases.¹²

The need for accurate measurements of bone density in children is underscored by an online search for "bone mineral density children" on the National Library of Medicine's PubMed Web site, which results in 1784 hits from 1990 to 2004. During this same period of time, a search for "bone density children" revealed 496 awarded grants on the National Institutes of Health CRISP (Computer Retrieval of Information on Scientific Projects) Web site (available at <http://crisp.cit.nih.gov>). In the

year 2004 alone, 43 grants were funded by the National Institutes of Health to study bone accrual in pediatric cohorts with DXA values as major outcome measures; 15 clinical pediatric trials using DXA to monitor response are currently listed at www.ClinicalTrials.gov. Until 1997, clinical trials generally included only adults. However, the Food and Drug Administration is now encouraging therapeutic interventions to be tested in children, and many more trials involving children are under way. Accurate outcome measures are needed for pediatric interventions that are aimed at enhancing bone acquisition during growth.

At present, however, the interpretation of DXA bone studies is considerably more challenging in children than it has been in adults. Several investigators have found that osteoporosis in children is frequently misdiagnosed with DXA measures.¹³⁻¹⁵ Indeed, the American College of Radiology and the International Society for Clinical Densitometry have advised against the use of World Health Organization criteria for the classification of osteopenia and osteoporosis in adults to diagnose osteoporosis in children.¹² Specifically, the official position of the International Society for Clinical Densitometry on the diagnosis of osteoporosis in children (males and females <20 years old) is: "The [World Health Organization] classification should not be applied to children. T-scores should not be used in the interpretation of DXA measures in children; Z-scores should be used instead. The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone. Terminology such as low bone density for chronological age may be used if the Z-score is below -2.0. Z-scores must be interpreted in the light of the best available pediatric databases of age- and gender-matched controls. The reference database should be cited in the report. Spine and total body are the preferred skeletal sites for measurement. The value of BMD [bone mineral density] to predict fractures in children is not clearly determined. There is no agreement on standards for adjusting BMD or [BMC] for factors such as bone size, pubertal stage, skeletal maturity, and body composition. If adjustments are made, they should be clearly stated in the report."¹²

The 3 main limitations of DXA measurements in children are (1) the current lack of a standardized pediatric normative database, (2) the lack of a meaningful clinical outcome measure related to DXA values in children, and (3) inaccuracies resulting from growth-related variations in bone and body size and composition.^{16,17} The first 2 limitations are being addressed by the Bone Mineral Density in Childhood Study, which is sponsored by the National Institute of Child Health and Human Development. This study involves 5 clinical centers that have recruited 1530 boys and girls aged 6 to 16 years for longitudinal bone studies. Subjects undergo a baseline and 3 consecutive annual evaluations that include DXA measurements, a bone-age radiograph of the hand, a

physical examination to determine the stage of sexual maturation, and stadiometer-measured height and weight. The longitudinal measurements will determine the degree of tracking of BMC and areal BMD (aBMD) throughout growth and help to establish the constancy of a child's expected measures relative to population percentiles. Previous studies using quantitative computed tomography (QCT) have shown strong correlations between prepubertal and postpubertal bone-mass measurements, which suggests that bone traits can be tracked throughout adolescence.¹⁸ Establishing whether DXA values also retain their rank order across time will help in the identification of those children who are prone to develop low values for peak bone mass and may be at greater risk for osteoporosis later in life.

The third major limitation of pediatric DXA bone determinations, inaccuracies resulting from growth-related variations in bone and body size and composition, has not yet been addressed. Bone-mass measurements using DXA are based on a two-dimensional projection of a three-dimensional structure. The results are influenced by many skeletal and extraskeletal parameters including the size of the bone, the volume (tissue density) of the bone, and the material density of the bone being examined, as well as the amount and distribution of soft tissues around the bone.¹⁹ The inability of DXA to account for the influence of variations in these anatomic measures markedly hinders the accuracy and reproducibility of bone determinations in the growing skeleton. Multiple correction factors have been suggested in an attempt to overcome the influence of vertebral size on DXA measurements of the axial skeleton. Carter et al¹⁶ introduced a general approach for estimating a volumetric density that reduces the influence of bone size. Their approach was based on the concept of geometric similarity, which assumes that the skeleton scales proportionately in all directions. This implies that all lengths are proportional to each other and that areas are proportional to lengths squared. Bone thickness, therefore, should be proportional to other lengths or to the square root of an area. Convenient measures that have been used to estimate bone thickness include the square root of a bone's projected area, bone width, and subject height.^{16,20} Similar approaches used by other investigators have assumed that the vertebrae have specific shapes such as a cube,^{16,21} a cylinder with a circular base,²² or a cylinder with an elliptic base.^{23,24} Although all of these approaches are likely to reduce the effects of bone size on DXA measurements, it is not known which ones provide the best correction for a particular pediatric population. Moreover, because the shape of the vertebrae changes with age, corrections should be growth and maturity specific.

DXA values are also influenced by the unknown composition of soft tissues in the beam path of the region of interest.^{19,25,26} Corrections for the soft tissues are based

on the assumption that the proportion of lean tissue and fat is the same for the beam paths beside the bone and those through the bone. If the fat and lean-tissue proportion is the same for beam paths that contain no bone as for beam paths that traverse the bone, the calculated amount of bone is accurate.²⁷ Unfortunately, marked changes in DXA measurements are observed if fat is distributed inhomogeneously around the bone measured.¹⁹ It has been estimated that inhomogeneous fat distribution in soft tissues resulting in a difference of a 2-cm fat layer between the soft-tissue and bone areas will influence DXA measurements by 10%.¹⁹ Soft-tissue-related errors especially limit comparative studies on the effects of obesity, malnutrition, anorexia nervosa, lactation, puberty, etc, on aBMD values. In addition, longitudinal studies using DXA are subject to considerable error, because aBMD measurements may reflect changes in body size and composition more than true changes in bone density.²⁷ It should be noted that although the precision of spinal DXA aBMD measurements has been reported to be 0.7% to 1.7%, the long-term reproducibility of these measures in children is difficult to determine, because we do not know which anatomic variable most influences the measure.²⁸

To assess the influence of growth and development on DXA bone-mass measurements, comparative studies were performed by using QCT, which measures volumetric BMD and is not influenced by bone size.²⁹ Among healthy children, measurements of spine BMC using DXA and QCT were highly correlated (Fig 1), but there was a far weaker relationship between aBMD (g/cm^2) and volumetric BMD (g/cm^3) using QCT. In fact, DXA aBMD had a stronger correlation with QCT measurements of vertebral volume ($r^2 = 0.68$) than with density. When subjects in Tanner stages 1 to 3 were considered separately from subjects in Tanner stages 4 to 5, correlations for the density were particularly poor for the less mature subjects even after correction with geometric formulas. It should be stressed that, in prepubertal children and those in the early stages of sexual development, there was no association between DXA aBMD and QCT volumetric BMD measures.

The relation between DXA and QCT z scores (defined as the number of SDs the aBMD or volumetric bone density is above or below the mean for age-matched controls) was also compared in 400 children and adolescents (100 each of healthy and sick boys and girls).³⁰ A significant linear relationship was observed between z_{DXA} and z_{QCT} ($r^2 = 0.39$; $P < .0001$) (Fig 2). Results for the subgroups divided by health status (healthy or sick) and gender (boys or girls) were similar to the overall results (r^2 values of 0.27–0.48). When DXA z scores were used to predict QCT z scores below -2.0 , sensitivity and specificity were reasonable, and the negative predictive value was extremely high. However, the positive predictive value was low. This was true regardless of

FIGURE 1
Relation between DXA and CT bone measurements in the lumbar vertebrae of 124 children. vBD indicates volumetric bone density.

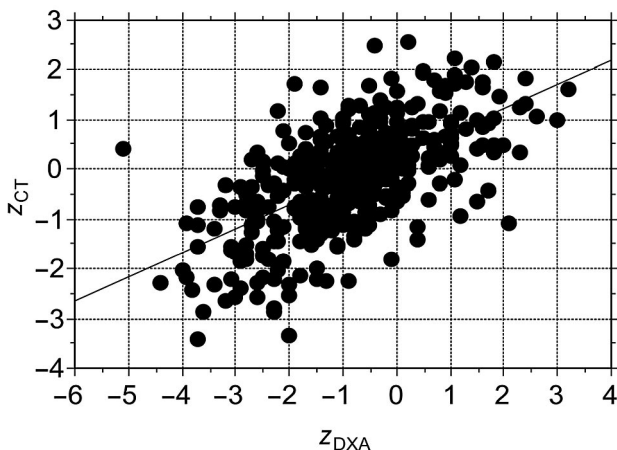
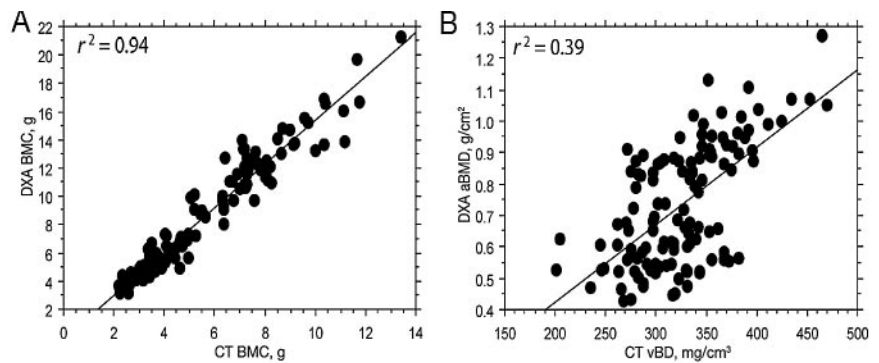


FIGURE 2
Linear regression comparing DXA and CT z scores in 400 subjects ($r^2 = 0.39$).

whether all subjects were analyzed together or sick and healthy subjects were analyzed separately.

For the subjects who were classified differently by QCT and DXA, many more were identified as having low bone density by DXA (58 of 400) than by computed tomography (CT) (7 of 400). Of the 58 subjects who were identified by DXA only, most were small for their age (<5th percentile) in terms of height (30 of 58 [52%]), weight (22 of 58 [38%]), or both height and weight (17 of 58 [29%]). The results of the current study, however, indicate that DXA measures of aBMD underestimate bone accretion as assessed by QCT in children and adolescents.

On average, 3 times as many subjects were determined to have low bone density (z score less than -2.0 for chronological age) by DXA than by QCT; this was true for both healthy and sick children. We found that although DXA and QCT z scores are related, almost 50% of the variability remains even after age and anthropometric measures are taken into account.

A critical question is whether DXA or QCT is a better surrogate measure of bone fragility in childhood. This issue remains unresolved because there are too few data linking either densitometry measure to fracture risk in children. Bone strength is determined not only by bone

mass (such as BMD) but also by the size, geometry, turnover, and microarchitecture of bone. For this reason, it is possible that the influence of bone size (captured better by BMD) is more highly correlated with bone fragility. The choice of an appropriate surrogate measure for fracture is a key area of controversy that must be resolved when planning bone-health-intervention studies in pediatric populations.

In conclusion, skeletal mass is accrued throughout childhood and adolescence and is largely determined by genetic and/or familial factors. Gonadal steroids, physical activity, and dietary intake are key to bone acquisition throughout growth. Bone mass measurements using DXA, although currently limited in some respects for pediatric applications, should be optimized for the assessment of health strategies to improve a child's skeletal status and growth.

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