Assessing Bone Mass in Children and Adolescents

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Growing awareness that osteoporosis may have its antecedents in childhood has led to increasing interest in assessing bone mass in children and adolescents. Several noninvasive imaging techniques are currently available to measure properties of the growing skeleton, including bone mass, density, cross-sectional area, and microarchitecture. Dual-energy x-ray absorptiometry (DXA) is the most widely used technique, but it has several major limitations associated with its dependence on two-dimensional projections. Quantitative CT and peripheral quantitative CT allow three-dimensional imaging but are more costly and have higher radiation exposure. Quantitative ultrasound is simple and inexpensive but can measure bone "quality" only at a single peripheral site. MRI techniques for measuring bone are still under development and not yet ready for clinical use. For all of these techniques, clinical interpretation of the bone measures obtained remains a significant challenge. Further research is needed to relate these measures to osteoporosis in the elderly and to short-term and long-term fracture risk.

Introduction

Growing awareness that osteoporosis may have its antecedents in childhood has led to increasing interest in assessing bone mass in children and adolescents. Several noninvasive imaging techniques to examine and measure properties of bone such as bone mass, bone density, cross-sectional area, and microarchitecture are currently available and have been adapted for use in children. These techniques include dual-energy x-ray absorptiometry (DXA), quantitative CT (QCT), peripheral QCT (pQCT), quantitative ultrasound (QUS), and MRI. For all of these measurement modalities, interpretation of the results is much more challenging in children and adolescents than in adults.

Dual-Energy X-ray Absorptiometry (DXA)

DXA is, by far, the most commonly used technique for assessing bone mass in persons of all ages, including children and adolescents. DXA is widely available and easy to use, with short scan times and very low radiation exposure. However, it has several major limitations, including dependence of the results on bone size and morphology, inability to account for soft tissue inhomogeneity, and inclusion of the posterior elements in anteroposterior (AP) imaging of the spine. These limitations are particularly problematic for bone measurements in growing children and adolescents, as discussed later in this section.

DXA evolved from single-photon and dual-photon absorptiometry (SPA and DPA), older projection techniques that used a radionuclide source, gadolinium-153. An x-ray tube is employed as the energy source to achieve a higher photon flux, better edge detection, and better precision. DXA measurements of bone derive from the difference in attenuation of high-energy and low-energy x-ray beams by soft tissue and bone. The low-energy beam is attenuated more than the high-energy beam in both soft tissue and bone, but to a much greater extent in bone. This difference enables estimation of the attenuation due to soft tissue overlying bone based on the measured attenuation of soft tissue adjacent to the bone. By accounting for this soft tissue attenuation, the attenuation due to bone can be calculated and converted to measurements of mass through phantom calibration.

The resulting measurements provide an estimate of bone mineral content (BMC, measured in grams) and bone mineral density (BMD, measured in g/cm^2). BMD is calculated by dividing BMC by the projected area of the bone in a plane perpendicular to the x-ray beam. This measure is often referred to as areal BMD (aBMD) to emphasize that it is not a true volumetric density. Common DXA measurement sites include the lumbar spine, hip, forearm, and whole body (usually minus the skull).

As mentioned previously, DXA has several major limitations, especially in children and adolescents. First, as a projection technique, DXA cannot account for the dimensions of the bone in the direction of the x-ray beam. Larger bones therefore produce higher BMC and aBMD measurements even if they do not have higher volumetric apparent density. This limitation has been recognized for many years, and correction factors have been proposed to adjust for this third dimension [1–5]. These correction factors work reasonably well in adults, but they have been less successful in children and adolescents, possibly because of changing bone morphology during growth [6].

The second major limitation of DXA is the use of soft tissue adjacent to the bone to estimate the effect of the soft tissue overlying bone. Because fat has attenuation properties different from those of most other soft tissues (loosely referred to as "lean" tissue), the assumption of homogeneous soft tissue composition breaks down when the soft tissue adjacent to the bone contains a proportion of fat different from that in the overlying soft tissue. The resulting errors have been reported to be up to 15% for adults [7,8]. We recently found errors of up to 25% (average 8%) in adolescents and young women aged 16 to 22 years. These errors may be particularly problematic in overweight or obese individuals and in those who undergo large changes in weight and body composition [9]. Compared with inaccuracies secondary to bone morphology, errors due to fat distribution have received relatively little attention, and correction factors are only now being developed.

The final major limitation of DXA is inclusion of the posterior elements in AP imaging of the lumbar spine. Since DXA is a projection technique, the bone measured by DXA includes all bone along the beam path. This includes both the cortical and cancellous compartments of the vertebral body, as well as the posterior elements. Because the posterior elements add a significant volume of cortical bone, they greatly increase the BMC and aBMD measured by DXA. This effect has received little attention and, to our knowledge, has not been rigorously studied.

Additional inaccuracies are due to variations in how manufacturers implement the basic DXA concepts. It is well known that different densitometers provide different BMC and aBMD values for the same bone. Conversions to a "universal" measure have therefore been developed [10,11], but they are seldom used in practice. Despite the inaccuracies, however, DXA is reasonably precise. The in vivo coefficient of variation of AP DXA measurements has been reported to range from 0.8% to 2.5% in children and from 1.5% to 2.5% in infants [12–16]. Longitudinal measures of the same subject on the same densitometer should therefore be clinically useful if bone morphology and body composition are stable. Unfortunately, although this appears to be the case for most adults, it is unlikely to be the case for growing children and adolescents.

Quantitative CT

QCT, an alternative to DXA for bone determinations, allows three-dimensional imaging. This volumetric imaging makes possible separate assessments of bone density, bone size, and bone geometry, as well as separation of cortical and trabecular bone compartments. These assessments have provided important insights into bone development. For example, changes in vertebral cancellous bone density occur primarily during puberty, whereas changes in vertebral size occur continuously throughout childhood and adolescence. In addition, boys and girls have similar cancellous bone density in the vertebrae, but vertebral cross-sectional area is approximately 15% to 20% smaller in girls than in boys, even after matching for height and weight.

QCT bone assessments are performed on a standard clinical CT scanner. X-rays are transmitted through the body in different directions, usually in a spiral or helical pattern, and attenuation is measured for each transmission. Since each voxel in the region of interest is traversed by multiple x-ray beams traveling in different directions, the data set can be resolved to determine an attenuation value (CT number) for each voxel. The attenuation values are converted into Hounsfield units using a bone mineral reference phantom. The Hounsfield scale is calibrated so that a value of 0 represents water. Bone has values in the 400 to 1000 range; fat and air, which are less dense than water, have negative values.

Because of the relatively small size of the trabeculae when compared to the pixel, QCT values for cancellous bone reflect not only the amount of mineralized bone and osteoid but also the amount of marrow per pixel [17]. QCT measurements of cancellous bone density are therefore analogous to the volumetric apparent density obtained by washing in vitro bone specimens, weighing them, and dividing the weight by the bulk volume of the specimen including the pores [18]. This measure primarily reflects the bone volume fraction or, conversely, the porosity of the bone.

In contrast, QCT measurements of cortical bone reflect the material density of the bone if the cortex is sufficiently thick (> 2 to 2.5 mm) to avoid volume-averaging errors [19]. Because of the high attenuation coefficient of mineral, the CT value of cortical bone depends primarily on the calcified bone fraction. This measure is analogous to the intrinsic mineral density of bone determined in vitro as the ash weight divided by the bone volume. On average, the CT values for cortical bone density are eight times higher than those for cancellous bone, reflecting the porous nature of cancellous bone rather than a difference in composition of the bone material.

In addition to measures of bone density, QCT can be used to obtain measures of three-dimensional bone geometry. Bone cross-sectional area and volume are often measured, along with cortical bone area for diaphyseal sites. The cross-sectional images can also be used to determine structural parameters such as principal and polar moments of inertia, section modulus, and stress-strain index. These structural parameters are theoretically related to bending and torsional stiffness and strength.

The most commonly mentioned disadvantage of CT is radiation exposure. Although CT uses ionizing radiation, the radiation exposure varies greatly depending on the technique employed. For CT measurements of bone, the radiation exposure can be as low as 100 to 200 mrem (1.5 mSv) localized to the region of interest. The total body equivalent dose is approximately 4 to 9 mrems (40–90 μSv), including the radiation associated with screening digital radiographs used to localize the site of measurement [20,21]. This dose is much lower than the radiation associated with other CT imaging procedures and is less than many other commonly used radiographic diagnostic tests. It is similar to the radiation exposure that occurs during a round-trip transcontinental airplane flight across North America [20,21].

Peripheral (pQCT) scanners have been specifically designed to perform bone imaging with low radiation doses. Compared with clinical QCT equipment, pQCT scanners have the additional advantages of smaller size, lower expense, and portability. A major limitation of pQCT scanners is that they can be used only for peripheral sites. The radius and tibia are the most common sites of measurement, although the femur and humerus can also be measured with most scanners. The measurements obtained are the same as for QCT: the density and cross-sectional area of trabecular and cortical bone and structural parameters.

Next-generation pQCT systems promise volumetric imaging capabilities. Imaging of multiple slices can be performed using current pQCT scanners, but this process will be automated in future scanners, already available in Europe. This process may allow for better characterization of bone at rapidly changing sites such as the long-bone metaphyses.

Quantitative Ultrasound

QUS is another available technique for assessing bone. It offers low cost, portability, ease of use, and lack of ionizing radiation. It is widely used in Europe, but has not been as readily adopted in the United States. The calcaneus is the most common measurement site, although QUS has also been used for the patella, tibia, and phalanges.

QUS measures the transmission properties of sound waves as they pass through the body. QUS machines generally have fixed transducers designed for a specific measurement site. Consequently, they do not readily accommodate patients of different sizes. Because commercial systems are usually configured for adults, they must be adapted with smaller transducers and special foot pads or calipers to study children. A coupling medium is also needed between the ultrasound transducers and the patient's body. Older systems generally used a water bath as the coupling medium, but most current systems use rubber pads and sonographic gel. The temperature of the coupling medium must be kept constant to avoid temperature-associated errors in the ultrasound measurements.

QUS does not directly measure bone mass. Rather, it measures bone "quality," which is thought to depend on bone density, bone size, and trabecular architecture [22–25]. In the calcaneus, for example, QUS measurements primarily reflect the number, thickness, mineral content, and three-dimensional arrangement of the trabeculae. QUS values may vary by as much as 50% depending on the principal orientation of the trabeculae [17] and are strongly influenced by bone size [26]. In addition to being influenced by properties of the bone, QUS measurements are also influenced by the amount and composition of marrow in the bone and by the soft tissue surrounding the bone [17,25].

The primary measures obtained using QUS are speed of sound (SOS, measured in meters per second) and broadband ultrasound attenuation (BUA, measured in dB/MHz). SOS is the sound-wave transmission velocity, which is obtained by dividing the distance between the transducers by the wave transit time. BUA is the slope of the attenuation-versus-frequency curve in the 200 to 600 kHz range, where the curve is linear. BUA and SOS are sometimes combined into a single parameter referred to as "stiffness" or quantitative ultrasound index (QUI) [27].

In children, SOS and BUA values generally increase with age and pubertal stage, but there is considerable variability [23,25,28–32], especially in the patterns of change between measurement sites [26]. The rate of increase differs between boys and girls during puberty [31] and a higher SOS has been reported in girls between the ages of 9 and 15 years [23–25,33].

Reported intraobserver coefficients of variation in children range from 0.5% to 1.2% for SOS [25,28,29,34,35] and from 2% to 5% for BUA [25,29,31]. Unfortunately, numerous studies in adults and children have found that QUS measurements of bone are not highly correlated with bone measures obtained using other methods [17,29,31,34,36,37]. Therefore, QUS cannot be used as a surrogate for other modalities, and the interpretation of QUS measurements remains unclear.

Magnetic Resonance Imaging (MRI)

Recent advances in MRI acquisition and processing techniques have made quantitative bone measurements possible. These assessments require high-resolution images and are therefore referred to as micro MR (μMR). μMR has been used primarily to analyze trabecular bone architecture at peripheral locations such as the distal radius, distal tibia, phalanges, and calcaneus [38,39]. Optimized pulse sequences and high-strength magnets have also made possible measurements at more proximal sites such as the proximal femur [39].

Analysis of μMR images involves the application of stereologic techniques and texture analysis tools such as fractal analysis. These analysis techniques can be used to calculate a number of microarchitectural parameters, including trabecular bone area, bone volume fraction, trabecular width, trabecular number, and trabecular spacing [38,40]. As might be expected, much more reliable results are obtained with higher-strength magnets because the signal-to-noise ratio may be improved up to 60% in a 3-T magnet compared with a 1.5-T magnet [39,41]. Even with higher-strength magnets, however, the results must be carefully interpreted because of susceptibility to technical artifacts. The coefficient of variation for apparent bone volume fraction and trabecular separation, thickness, and number in the proximal femur has been reported to be between 2% and 10% [39,42].

The use of MRI to obtain quantitative measures of bone is still very much under development and has not yet been standardized. The technique is technically challenging, requiring fast gradients, dedicated coils with a small field of view, and a high signal-to-noise ratio [38]. It is also costly and requires a relatively long acquisition time of 10 to 20 minutes, during which the patient must remain motionless [38]. There is some evidence that structural analysis parameters from μMR can differentiate adult patients with fractures from controls [43,44]. However, we are not aware of any studies using these techniques in children. Although this technique is of interest because of its lack of ionizing radiation, it is not yet ready for use in a clinical setting.

Interpretation of Bone Mass Measurements

Currently, our ability to obtain bone measurements far outpaces our ability to interpret these measurements in a clinical context. In adults, a clear relationship has been established between BMD values obtained using DXA and fracture risk through multiple large, prospective, controlled studies [45–50]. Unfortunately, a comparable evidence base does not exist for bone measures in children and adolescents. There are also significant differences in the assessment of bone status in children when using different measurement techniques. We have recently shown that many more children are classified as having low bone mass when the assessment is done using DXA, compared with CT [51•]. This discrepancy highlights the need to determine the clinical significance of pediatric bone measurements obtained through different techniques.

The primary clinical significance of bone measures in children and adolescents would be as a predictor of osteoporosis and fractures in old age. If such a link were established, it would allow early identification and possibly early intervention for children who are at risk of developing osteoporosis later in life. Longitudinal QCT measurements of cancellous bone density and cross-sectional area of the vertebrae and femurs have shown that measures in early puberty predict values at sexual maturity [52]. When baseline values were divided into quartiles, a linear relation across pubertal stages was observed for each quartile. The regression lines differed among quartiles, paralleled each other, and did not overlap, indicating that volumetric bone density and bone size "track" through the period of most rapid growth. Studies are currently under way to see if similar patterns hold for DXA values throughout childhood and adolescence. If longitudinal tracking can be established, not only before skeletal maturity but also through the entire lifespan, strong evidence would be provided that bone measures in children are useful indicators of the risk of developing osteoporosis and fractures later in life.

In addition to the possible association between bone measures during childhood and bone measures in later years, which are known to be predictive of fractures, bone measures in children may be useful as predictors of short-term fracture risk. A number of case-control studies have examined this topic but have yielded conflicting results [53–59]. A recent meta-analysis concluded that there is some evidence of an association between bone density and fractures in children [60•]. However, individual studies have found other factors, such as bone cross-sectional area or weight, to be more important in differentiating children with fractures from matched controls [53,56,57]. There are currently no prospective studies examining the relationship between pediatric fractures and bone measures in children and adolescents.

In adults, the relationship between bone mass and fractures is at least established, but the clinical significance of other bone measures such as bone "quality" and architectural parameters remains poorly understood. Further study is needed to determine the clinical significance of these measures in children and adolescents.

Conclusions

Several noninvasive imaging techniques are available for measuring bone properties in children and adolescents. DXA is the most widely used, but it has several major limitations associated with its dependence on two-dimensional projections. QCT and pQCT allow three-dimensional imaging but are more costly and involve higher radiation exposure. QUS is simple and inexpensive, but can measure bone "quality" only at a single peripheral site. MRI techniques for measuring bone are still under development and are not yet ready for clinical use. For all of these techniques, clinical interpretation of the bone measures obtained remains a significant challenge. Further research is needed to relate these measures to osteoporosis later in life and to short-term and long-term fracture risk.

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This study highlights the challenges of interpreting bone measurements in children and adolescents. DXA and CT were performed in the same subjects, and many more were classified as having low bone density by DXA than by CT.

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This meta-analysis summarizes the literature relating bone density measures in children to fractures. It concludes that there is some evidence for an association between bone density and fractures in children, but no large prospective studies have been conducted.