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Methods for measurement of pediatric bone

Teresa L. Binkley · Ryan Berry · Bonny L. Specker

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Abstract Many experts believe that optimizing bone mineral accrual early in life may prevent childhood fractures and possibly delay the development of osteoporosis later in life. Adequate nutrition and physical activity are environmental factors important in determining whether or not children acquire an appropriate amount of bone for their body size. Pediatric diseases, or therapeutic interventions used in their treatment, may interfere with normal bone development. Although there are specific methods available for assessing pediatric bone, there is no one method that can adequately assess bone health and identify the specific bone deficits that may be occurring. Understanding the biological basis for bone deficits and the ability of various bone assessment methods to discriminate or measure these deficits is important in understanding normal bone development and how to prevent and treat pediatric bone disease. The purpose of this review is to briefly describe changes in bone with growth, to define "bone density" in biological terms, to discuss some of the issues with pediatric bone measurements, and to review the three main methods for assessing bone parameters in pediatric populations. These methods, including dual energy X-ray absorptiometry (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomography (pQCT) will be described, the advantages and disadvantages discussed, and the relationship between bone parameters and fracture risk presented for each of the methods.

Keywords Pediatrics · pQCT · DXA · Ultrasound · Bone density · Bone geometry

T. L. Binkley · R. Berry · B. L. Specker (✉)
EA Martin Program, South Dakota State University, Brookings, SD, USA
e-mail: Bonny.Specker@sdstate.edu

T. L. Binkley
e-mail: Teresa.Binkley@sdstate.edu

R. Berry
e-mail: rmberry@jacks.sdstate.edu

1 Introduction

Approximately 90% of adult bone mass is gained in the first two decades of life, and many experts believe that optimizing bone mineral accrual early in life may prevent childhood fractures and possibly delay the development of osteoporosis later in life. Environmental factors important in determining whether or not children reach their genetic potential in achieving peak bone mass include adequate nutrition and physical activity. Pediatric diseases, or even the therapeutic interventions used in their treatment, may prevent children from reaching their genetic potential. Diseases or conditions known to adversely affect bone include gastrointestinal illnesses (i.e., inflammatory bowel disease, Crohn's disease), cystic fibrosis, juvenile rheumatoid arthritis, and growth hormone deficiency. Chronic use of steroids and history of previous fracture also are risk factors for decreased areal bone mineral density (aBMD). It is even possible that the epidemic of childhood obesity may in part directly or indirectly explain the increase in childhood fracture incidence that has recently been reported [1]. Obese and less active children have been shown to have decreased aBMD or bone mass compared to non-obese children of similar weight [2, 3]. Whether this decreased aBMD among obese children is due to decreased muscle mass, reduced activity levels, or a direct effect of fat on bone is not clear.

Pharmaceutical agents to treat osteopenia and osteoporosis in children are now available and the appropriate use of these agents requires an understanding of the bone deficit an individual child may have. In this regard, the concept of optimizing "peak bone density" may oversimplify the dynamics involved in growth and adaptation. Identifying the specific bone deficit will be important in determining not only therapeutic options, but also preventative measures, in order to optimize bone accrual and consequently bone strength.

The purpose of this review is to briefly describe changes in bone with growth, to define "bone density" in biological terms, to discuss some of the issues with pediatric bone measurements, and to review the three main methods for assessing bone parameters in pediatric populations. These methods, including dual energy X-ray absorptiometry (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomography (pQCT) will be described, the advantages and disadvantages discussed, and the relationship between bone parameters and fracture risk presented for each of the methods.

2 Changes in bone with growth

Childhood is a period of rapid growth. During longitudinal growth, prechondrocytes in the growth plates at the proximal and distal ends of bones differentiate into columns of proliferative and then hypertrophic chondrocytes, and cartilage is eventually replaced with bone in the adjacent metaphyses. In addition, an increase in bone size occurs through bone modeling and remodeling. The differences between bone modeling and remodeling are shown in Fig. 1. Modeling during childhood allows individual bones to grow in width by the formation of new bone on the outer or periosteal surface, while resorption occurs on the inside, or endosteal surface, of the bone. The degree of modeling is determined in part by genetics, but also by the response to loading that occurs with strains on bone from physical activity and gains in body weight during growth. According to Wolff's law, bones will ultimately achieve a shape and size that best fits their function [4]. Remodeling occurs throughout life and although it does not change the shape of bone it is important for bone maintenance and repairing bone damage. It also prevents the accumulation of too much old bone that can become brittle. Resorption of the surface of trabecular bone is important for supplying needed calcium and phosphorus during periods of acute mineral need.

The different processes involved in bone growth will have different influences on the skeleton. Some of these effects are measurable with certain imaging devices, while others are not. For example, increases in the total cross-sectional area of bone (i.e., periosteal circumference) and cortical thickness are both functions of increased modeling, whereas cortical volumetric BMD (vBMD) is a function of remodeling. The increase in bone size and the bone modeling and remodeling that is occurring during rapid growth will lead to larger bones and the higher remodeling rates may lead to lower cortical vBMD. These changes may influence fracture risk during this period.

Fractures actually constitute 10–25% of all pediatric trauma cases [5]. Although there is little sex difference in distal forearm fracture incidence prior to 5 years of age, fracture rates rise rapidly and peak among girls between 8 and 11 years and among boys between 11 and 14 years [1]. This increase in fracture risk around the time of the pubertal growth spurt, or peak height velocity, is thought in part to be explained by the rapid growth and possible concurrent decrease in vBMD [6]. Increases in body weight also occur, yet the increase in weight and areal BMD (aBMD) around the time of puberty do not occur simultaneously; rather, weight gain precedes the gain in

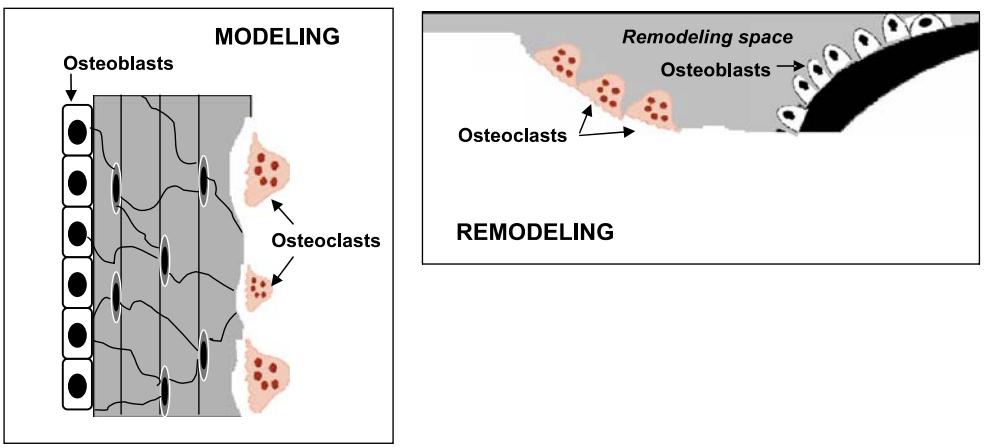


Fig. 1 Modeling occurs on both sides of bone. New bone is formed by osteoblasts on the periosteal surface and old bone is removed by osteoclasts on the endosteal surface. Remodeling occurs on the same bone surface, with bone being removed from either the surface of trabeculae or from the inner cortex by osteoclasts and replaced along the same surface by osteoblasts

bone mineral. This lag in bone accrual following peak height velocity or weight gain also has been speculated to be the reason for the increased fracture rates that occur during this period [7].

Animal models have provided other information on what may be happening at the structural level during growth. Architectural properties of trabecular bone in sheep change as the skeleton matures [8]. Tanck and coworkers [9] showed a time lag between increases in trabecular density and adaptation of trabecular architecture in rapidly growing pigs. During periods of rapid growth, body weight increases faster than bone cross-sectional area causing increased mechanical loads on bones. Trabecular bone responds to these loads with increased trabecular deposition causing increased trabecular density. Once growth slows, the trabeculae align to become more efficient in distributing mechanical loads and trabecular density decreases.

3 What is "bone density"?

Density, in terms of physical science, is defined as mass per unit volume. The ratio of the amount of matter in an object compared to its volume seems straightforward, but "bone density" brings considerable challenges to this simple definition. Bone is a composite tissue made up of an organic collagen protein and inorganic mineral hydroxyapatite. The arrangement of these composites determine two types of bone tissue; trabecular bone tissue found mainly in the vertebrae and ends of the long bones and cortical bone tissue found mainly in the shafts of the long bones. When defining or measuring bone density it is not only important to consider what type of bone tissue is being measured, but also what mass and what volume are being used in the calculation. Rauch and Schoenau [10] suggest considering three levels when interpreting bone density depending on the biological organization of bone: material bone density ($BMD_{material}$), compartment bone density ($BMD_{compartment}$) and total bone density (BMD_{total}). In each level of analysis (Fig. 2), the mass and volume of bone tissue used is defined and gives a more complete meaning to the definition and interpretation of the bone density measurement.

The analysis of $BMD_{material}$ considers the mass of the extracellular bone matrix whether it is mineralized or not and the volume of the bone matrix not including marrow spaces, osteonal canals, lacunae and canaliculi (Fig. 2). During remodeling, bone matrix is mineralized over time with recently deposited matrix having a lower material density than existing matrix. Lower $BMD_{material}$ could be an indication of increased bone remodeling in existing bone. During growth, new bone gained on the periosteal surface has a higher $BMD_{material}$ than existing bone, even though it is younger.

Trabecular and cortical compartments are defined by the endocortical surface of the bone. The space within the endocortical surface is considered the trabecular compartment and the space between the endocortical and periosteal surface is considered the cortical compartment (Fig. 2). Both compartments contain bone matrix and non-bone tissues, however,

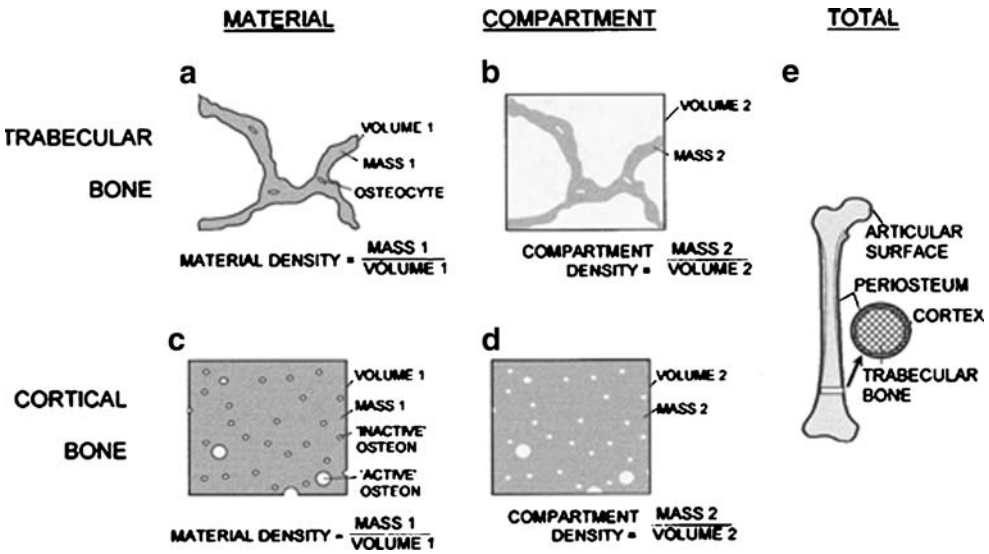


Fig. 2 Definitions of the various types of mineral density. $BMD_{material}$ and $BMD_{compartment}$ (**a** and **b**) in trabecular and (C and D) in cortical bone. The mass of mineral (in *grey*) determining $BMD_{material}$ and $BMD_{compartment}$ is identical (mass 1=mass 2), but the volume (*encircled by black lines*) differs (volume 2>volume 1). Therefore, $BMD_{material}$ is higher than $BMD_{compartment}$. (E) BMD_{total} is defined as the mass of mineral divided by the volume enclosed by the periosteal envelope. This definition can be applied to the entire bone, part of the bone (e.g., the distal or proximal end), or a section through the bone, as shown. Reproduced from *J Bone Miner Res* 2001;16:597-604 [10] with permission of the American Society for Bone and Mineral Research

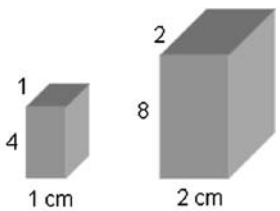
the trabecular compartment has more non-bone tissue than the cortical compartment. The analysis of $BMD_{compartment}$ uses the same mass as $BMD_{material}$ but the volume used is greater since the compartment volume includes all the spaces that are excluded in material density analysis. $BMD_{compartment}$ of trabecular bone would increase as the number and thickness of the trabeculae increase. During remodeling, osteonal canals increase in size and the compartment density of cortical bone decreases. $BMD_{compartment}$ is sometimes referred to as apparent density in the bone literature and is always lower than the material density.

BMD_{total} is determined using both trabecular and cortical compartments and their relative volumes. Changes in BMD_{total} are noted during growth because the relative volumes of each compartment change as the bone grows. This is especially noted in the newborn when at birth cortical bone in the femoral shaft represents 92% of the total cross-sectional bone area, which changes to 30% at age 6 months [11].

Interpretation of bone density measures in children must be based on these definitions with an understanding of how they differ in relation to bone physiology, modeling, remodeling and growth.

4 Bone measurement issues specific to pediatrics

It is difficult to interpret BMD changes during childhood since the majority of studies use dual energy X-ray absorptiometry (DXA) technology which measures bone in two-, rather than three-dimensions. It is important to consider bone size when assessing bone measures in only two dimensions. A larger bone size may artificially inflate aBMD measurements as shown in Fig. 3. This is illustrated in studies that show that aBMD increases with age, but



Volumetric BMD (g/cm³)	1.0	1.0
Projected Area (cm²)	4.0	16.0
Volume (cm³)	4.0	32.0
BMC (g)	4.0	32.0
BMD (g/cm²)	1.0	2.0

Fig. 3 Areal BMD measurements are influenced by bone size, with larger bones of similar volumetric BMC having higher areal BMD values. Reproduced from *J Bone Miner Res* 1992:7:137–45 with permission of the American Society for Bone and Mineral Research

vBMD measured in girls by computed tomography is relatively constant during childhood until the time of puberty when there is a large increase between Tanner stages 2 and 3 [12].

Mathematical methods have been proposed to adjust this two-dimensional "areal BMD" (aBMD) to more closely reflect vBMD [13, 14]. These methods include the calculation of bone mineral apparent density (BMAD) for the spine or femoral neck, which divides BMC by the projected bone area to the power of 1.5 for spine [15] and 2.0 for the femoral neck [16], or by applying formulas for the femoral neck measurements that assume a cylinder shape [17]. Inclusion of bone and body size parameters in a regression approach (size-adjusted bone mineral content (SA-BMC)), or expressing BMC-for-bone area or BMC-for-height also have been suggested for correcting for the influence of size on aBMD measures [14]. It is important to address these bone size-related problems, and to understand the differences and appropriate use of bone size, bone mass, and bone density measurements.

5 Dual energy X-ray absorptiometry (DXA)

5.1 Method

DXA was introduced in the late 1980s for use in postmenopausal women. Improvements in algorithms for detecting bone edges in children opened the door for pediatric software to be used in the 1990s. Regional measurements at the spine and hip are often obtained for bone density testing. As discussed above, since DXA images are two-dimensional, a true measure of volumetric BMD cannot be obtained. BMD obtained from DXA is referred to as areal BMD (aBMD) and is obtained by dividing the bone mineral content [BMC (g)] by the projected bone area (cm^2) and is reported in grams/cm^2. Total body scans should be used for body composition measurements, including total body BMC. Whether or not BMC or BMD of the head should be included has been an issue in pediatric bone measurements due to the large contribution of the head to total bone mass in this age group [18]. However, there is a possibility that bone is redistributed during loading and unloading: head BMD has been found to be lower in young gymnasts compared to controls [19] and to increase in astronauts during space flight [20].

aBMD results are often presented as *T* and *Z* scores. The WHO criterion for diagnosing osteoporosis in adults is based on BMD *T* scores. A *T* score is defined as the standard deviation (SD) score of the observed aBMD compared with that of a normal young adult. A *T* score of less than −1 SD in adults indicates osteopenia and a *T* score

of less than −2.5 SD indicates osteoporosis [21]. Because *T* scores compare the observed aBMD with that of young adults they are not appropriate for growing children and should *never* be used. A more appropriate method of comparison of aBMD in pediatrics is the use of the *Z* score, defined as the SD score based on age-specific and sex-specific norms. The International Society of Clinical Densitometry (ISCD) currently recommends that the pediatric bone density be evaluated based on *Z* scores, with low-for-chronological-age being defined as a *Z* score less than −2.0 [22].

Numerous studies have included normative DXA data, although the populations are typically small or highly selected based on specific population characteristics. Normative pediatric reference ranges are now appearing in some of the manufacturer's software. Recently, pediatric bone mineral reference values for DXA measurements obtained on 1,554 US children in five centers across the USA have been published [23]. These data indicate that BMD measures are not necessarily normally distributed and the use of the standard *Z* scores may not be appropriate. The LMS modeling approach, which was used in this recent paper, does not require normally distributed data and can provide greater accuracy in defining the upper and lower ends of the population distributions. Normative data for several bone sites were provided since disease processes and medications may influence trabecular and cortical bone differently.

In situations where a child's growth is stunted or maturation is delayed, which is particularly true in children with chronic diseases, it may be more appropriate to determine whether aBMD or BMC result is appropriate for his or her body size by comparing the measurements with those of children of similar height or weight. However, these reference databases are not available on the DXA software and must be obtained from the pediatric literature on published normative values. It also is important to realize that there are significant differences among published pediatric norms, in part due to differences in the machines that are used or due to varying population sample sizes.

5.2 Advantages and disadvantages

The advantages and disadvantages of DXA are summarized in Table 1. DXA is the most commonly used densitometric

Table 1 Comparison of dual energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT) and QUS

	DXA	pQCT	QUS
Bone Site	Total body	Tibia	Calcaneus
	Spine	Radius	Tibia
	Total hip, femoral neck and other hip regions		Radius
	Forearm		Phalanx
Parameters	Bone area	Bone geometry (periosteal and endosteal circumferences, cortical thickness)	SOS
	BMC	BMC (total and cortical)	BUA
	Areal BMD	Volumetric BMD (cortical and trabecular)	
	Derived bone mineral apparent density (BMAD)	Estimates of bone strength (CSMI, BSI, pSSI)	
Effective Radiation Dose	1.4 to 13 μSv depending upon the scan	Usually <1.5 μSv (varies with scan speed, voxel size and number of image slices)	None
Scan Time	<3 min (varies depending on type of scan)	<3 min for scout view and one slice (varies depending on scan speed, voxel size)	<1 min (varies depending on machine and site)
Advantages	Low cost	Measures true vBMD	Low cost
	Minimal radiation exposure	Differentiates bone tissue (cortical vs trabecular)	Portable scanning devices
	Relatively fast	Measures bone size and geometric properties	No radiation exposure
		Minimal radiation exposure	
Disadvantages	Cannot separate cortical & trabecular bone	Underestimates cortical vBMD when cortical shell thickness is small (<2 mm)	Bone size (cortical thickness in particular) will influence SOS
	No measures of bone geometry	Longitudinal measurements difficult	
	Bone size will influence aBMD		

BMC Bone mineral content, *BMD* bone mineral density, *CSMI* cross-sectional moment of inertia; *BSI* bone strength index, *pSSI* polar strength strain index, *SOS* speed of sound, *BUA* broadband ultrasound attenuation

method for assessing bone health in adults and children, in part because of its relatively low cost and accessibility. The speed of a DXA scan and the minimal radiation exposure also allow it to be easily used in pediatric populations. Effective doses of radiation exposure for the different regional scans and the total body scan are all less than 13 μSv. Annual radiation exposure limits recommended by the National Council for Radiation Protection [24] for public infrequent exposures and limits recommended by the Federal Drug Administration Regulation for exposures from medical research procedures in children are both 5000 μSv. DXA measurements also have high reproducibility and may be useful for longitudinal assessment of BMC. Care should be taken in interpreting longitudinal measures of aBMD due to potential size effects on this measure.

The major disadvantages of DXA are the inability to obtain separate measurements on cortical and trabecular bone and the influence of bone size on aBMD measurements as described above.

5.3 Bone measures and fracture

Although bone density in adults has been shown to be associated with fracture risk, the association between bone measures and fracture risk in children has only recently been confirmed in longitudinal studies. Several older case control studies were completed that have shown decreased aBMD in children with a fracture [25, 26]. A population-based case-control study also found reductions ranging from 1.25–4.5% in BMAD at several bone sites in children with wrist and forearm fractures compared to controls [27]. However, the problem with these studies is that the BMD measurement often takes place a significant time after the fracture when BMD could be decreased due to immobilization or decreased activity levels. The choice of controls in these studies also is difficult. Children who are more physically active are more likely to be at risk for injuries resulting in a fracture, but the higher activity levels theoretically should lead to increased BMD. These previous findings from case-control studies on associations between fracture risk and low BMC or BMD also has been confirmed in a more recent longitudinal study. Clark and coworkers recently reported the results of a two year longitudinal study of 6,213 children who had total body DXA measurements completed at a mean age of 9.9 years [28]. There were 550 children who reported a fracture over the 2-year period following the DXA measurement and 45% of the fractures were in the forearm. Adjusting for body size, these investigators found an 89% increased risk of fracture per SD decrease in total body (less head) BMC and a 51% increased risk of fracture per SD decrease in total body (less head) bone area.

6 Quantitative ultrasound (QUS)

6.1 Method

The first QUS device was developed for the assessment of calcaneal bone status in adults in 1984 [29]. The velocity and attenuation of the ultrasound waves are measured and expressed as speed of sound (SOS) and broadband attenuation (BUA). SOS through bone is defined by the ratio of the traversed distance to the transit time (m/s) and is dependent on the density, the micro- and macrostructure, and the elastic modulus, which reflects the stiffness of a material. Energy is lost when the ultrasound wave travels through the material and this phenomenon is known as attenuation. In the range of frequencies used, total attenuation is linearly proportional to frequency. The slope of attenuation as a function of frequency in dB/MHz/cm has become known in clinical practice as broadband ultrasound attenuation (BUA).

A variety of methods have been developed, including pulse-echo (reflection) and transmission techniques. Devices have been developed that measure SOS and BUA at different peripheral sites, including the calcaneus, phalanx, tibia and radius. However, not all ultrasound devices are appropriate for use in pediatric populations due to inappropriate transducer sizes. For example, some of the calcaneal ultrasound scanners have fixed transducers and molded foot wells that are suited for an adult foot only. It is important that the appropriate normative data set is used when conducting pediatric ultrasound studies, and a variety of pediatric reference data bases do exist for several of the available ultrasound devices [30–32].

Since bone is not homogeneous, the physical distribution of trabecular and cortical bone within the measured site may influence SOS transmission. This is illustrated in Fig. 4 [33]. Briefly, the Plexiglas model, which is comparable to a finger measurement, shows that as the marrow cavity decreases the SOS increases. Even if the density, microstructure, and elasticity remain constant within the trabecular and cortical compartments, the distribution of cortical bone (i.e., varying cortical thickness in particular) may influence the SOS. There are significant changes in cortical bone distribution during growth [34], making interpretation of QUS results difficult. Since the calcaneus consists almost entirely of trabecular bone, the SOS measured at this site may be less problematic in this regard.

6.2 Advantages and disadvantages

There are several advantages in utilizing the QUS method for assessing bone health in children and adolescents (Table 1). First, QUS can be performed with a portable

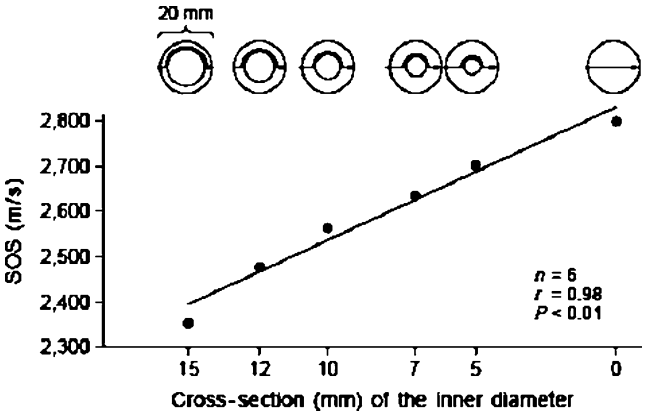


Fig. 4 The influence on geometry on the ultrasonic pathway. These measurements were carried out on a Plexiglas model, which correspond to changes of a growing tubular bone. The *inner space* was filled with water. Reproduced from Pediatric Nephrology 1998; 12:420-429 [33] with kind permission of the Springer Science and Business Media

scanner and it is technically simpler and more economical compared with DXA and pQCT. Second, there is no radiation exposure associated with QUS measurements. Third, some investigators have found that QUS measures are correlated with BMD [35, 36], although others suggest that since QUS measures more than just density there should not be a correlation between QUS and DXA [30, 37]. Pluskiewica and coworkers found that DXA and phalangeal QUS measurements do not identify the same patients with reduced bone mineral status and speculated that this was because these two techniques are measuring different bone properties [37].

Although QUS may be used as an overall indicator of bone health, a disadvantage is that it is not possible to determine where actual bone deficits are occurring if decreased SOS or BUA are observed since QUS is dependent not only density, but also the stiffness and the macro- and microstructure of bone. This inability to understand the bone biology behind DXA and QUS measurements has been discussed in a previous review [38]. Many of the size-related issues that are present with DXA bone measurements also may exist with BUA [39].

6.3 Bone measures and fracture

Jaworski and coworkers measured the calcaneus with the Achilles densitometer in 71 healthy children and 18 osteopenic children aged 6 to 13 years [40]. Children whose total body BMD scores were more than two standard deviations below the mean of age-matched children had significantly lower SOS (Z score=−1.9), BUA (−2.2) and estimated stiffness (−2.5) measures when compared to children with total BMD scores greater than −2 SD.

Fielding and coworkers compared SOS, BUA and spine aBMD among 42 children with chronic diseases known to influence bone density or with history of fragility fractures [35]. They found that Z scores for SOS and BUA correlated with several DXA Z scores, and the specificity for predicting osteopenia or pathological fractures was similar for spine aBMD, BUA and SOS. Baroncelli and coworkers found that SOS measurements in the phalanges were significantly lower in 135 children aged 3–21 years who had bone and mineral disorders [41]. Thirty eight percent of these children fractured during the previous six months and the ones who had fractured had lower SOS measurements than those children who had not fractured. As discussed above, SOS measurements are dependent on cortical thickness, and the longitudinal study of Clark et al. [28] found an increased fracture risk with decreased cortical thickness. Therefore, it is possible that the association between SOS measurements and fracture occurrence may be a result of the ability of SOS to indirectly measure cortical thickness.

7 Peripheral quantitative computed tomography (pQCT)

7.1 Method

Peripheral quantitative computed tomography (pQCT) is a type of computed tomography used to measure volumetric BMD (vBMD) in the peripheral skeleton. Ruegsegger et al. [42] developed the pQCT in Switzerland in 1976 and published work using the technology in the late 1980s [43, 44]. The first commercial pQCT scanners were produced in Germany and became available by the early 1990s [45], when studies using the scanners, also published in German, first appeared [46, 47]. An advantage of the new technology was the ability to separate trabecular bone tissue, generally found at the end of the long bones, from cortical bone tissue found in the shaft. By the mid to late 1990s, the technology was being assessed for accuracy and precision [48, 49] and being used to investigate geometric and biomechanical properties of bone [50, 51], establish reference data [52, 53], correlate muscle and bone strength [54–56] and obtain measurements in children [13, 57].

pQCT scan times vary depending on scan speed, voxel size and number of image slices chosen by the operator. In general, when using pQCT, a scout view is obtained to locate the endplate of the bone and place a reference line. Computed tomography (CT) slice images are taken at set distances from the reference line, generally a distance equal to some percentage of the bone length.

Bone size and geometric properties in terms of total cross-sectional bone area, cortical bone area, periosteal and endosteal circumferences, and cortical thickness can be obtained using pQCT. Properties of bone tissue, namely

$$CSMI = \Sigma (r^2 \times a)$$

$$\text{Section modulus} = \frac{\Sigma (r^2 \times a)}{r_{max}}$$

$$pSSI = \frac{\Sigma (r^2 \times a) \times CD/ND}{r_{max}}$$

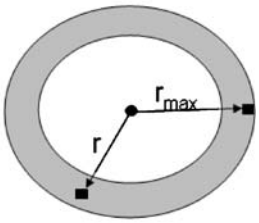


Fig. 5 Definitions of geometric properties of bone. A schematic view of a cross-section of cortical bone is shown. *r* is the distance from center of gravity to a voxel, r_{max} is the distance from the center of gravity to the voxel of maximum distance, *a* is the area (mm^2) of a voxel, CD is the measured volumetric cortical density, and ND is the maximum normal cortical density under physiologic conditions (1,200 mg/cm^3). Determination of bone strength is based on the calculation of the cross-sectional moment of inertia (*CSMI*); in this case the center of gravity or polar moment of inertia is used. The section modulus, which is directly proportional to maximum stress in bone, is calculated by dividing the CSMI by the maximum voxel distance from the center of gravity. The polar Strength Strain Index (*pSSI*) takes into account the material properties by multiplying the section modulus by the quotient of CD and ND

cortical and trabecular vBMD, also can be assessed. The cross-sectional moment of inertia (CSMI) and surrogate measures of bone strength, such as the bone strength index (BSI) and polar strength-strain index (pSSI) can be calculated from the geometric and material measures obtained using pQCT techniques (Fig. 5).

Non-invasive measures of these bone parameters using low dose radiation were not possible before the use of pQCT technology. Effective radiation doses using the XCT 3000 (Orthometrix, Inc., White Plains, NY, USA) ranges from 0.72 μSv in the distal tibia to 1.43 μSv in the distal femur [58]. According to the manufacturer, imaging of the forearm using the XCT 2000 (Orthometrix, Inc., White Plains, NY, USA) exposes the patient to effective radiation doses 0.22 μSv for a CT slice and 0.8 μSv for a scout view scan. As a comparison, the effective radiation dose in the USA varies depending on geographic location but is typically around 3,600 μSv/year based on data from the National Council on Radiation Protection and Measurements (Ionizing Radiation Exposures of the Population of the United States, Report no. 93, Washington, DC, 1987).

The use of pQCT in bone research has increased in the past decade. pQCT measures of healthy children have been used to establish reference ranges for bone growth patterns that can be used as a comparison when studying the bone status of children in disease states [53, 59, 60]. Other investigations in healthy children have been done to test the effects of activity, bone loading, diet, pubertal stage and hormonal status on bone [61–67]. pQCT images are generally acquired in the forearm or lower limb. Image slices are taken at the distal end of the bone (4% site; slice is at 4% of the bone length from the distal end of the bone) or in the shaft (14%, 20% or 33% site; slice image is at 14%, 20% or 33% of the bone length from the distal end).

Studies by Schoenau et al. have related bone strength and bone geometry of the forearm measured by pQCT to muscle strength measured by grip dynamometer in healthy children and in children with cystic fibrosis and Ullrich Turner Syndrome [55, 64]. Normal ranges and correlations of bone and muscle mass or strength lead to the perspective that bone diseases in childhood may be distinguished by comparing these measures [54]. pQCT measures of bone geometry, such as total cross-sectional area and cortical area, also have shown increases with increasing muscle strength, while trabecular and cortical vBMD do not [33].

7.2 Advantages and disadvantages

The advantage of pQCT is that the thickness of the X-ray beam adds a third dimension to the cross-sectional pQCT image slice thereby allowing for the measurement of true volumetric BMD (vBMD), which is reported in grams/cm^3.

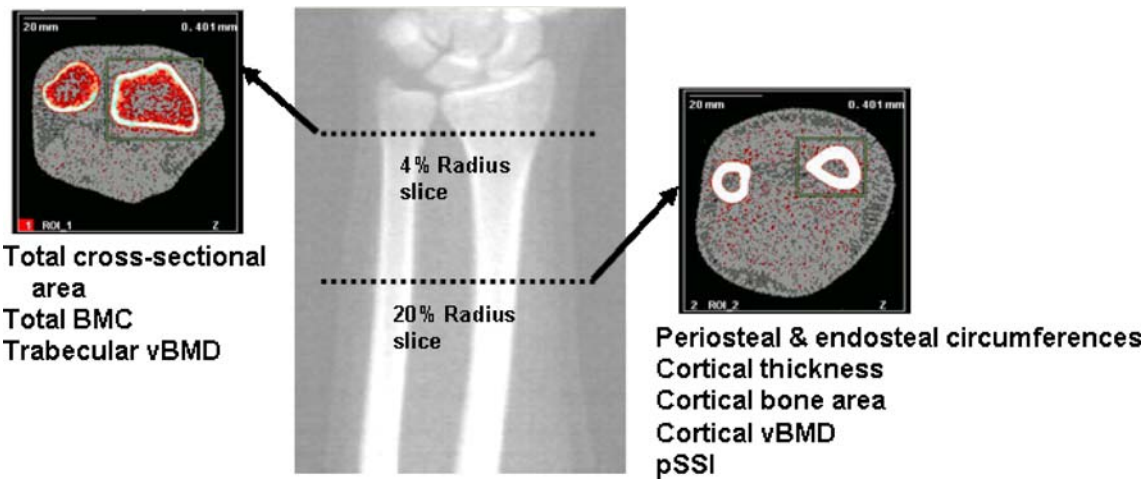


Fig. 6 pQCT slices at the 4% and 20% distal radius and various bone measurements that can be obtained

pQCT also offers several additional advantages over DXA including differentiation of bone tissue, measures of bone size, and estimates of geometric properties. As mentioned previously, images can be analyzed to differentiate cortical bone from trabecular bone (Fig. 6). The two types of bone tissue respond differently to stimuli such as pubertal changes, mechanical forces, and disease-related stresses, so the benefit of separating the two is extremely advantageous in bone research.

There are several disadvantages of pQCT. One has to do with the spatial resolution of the system and the underestimation of cortical vBMD when the thickness of the cortical bone shell is less than 2 mm [68]. This phenomenon is known as the partial volume effect and happens when a voxel in the image represents more than one tissue type (Fig. 7). The cortical rim of the bone has a considerable number of voxels with mixed tissue and therefore is more often affected by the partial volume effect compared to the trabecular bone sites, where the core area has more homogeneous voxels [69]. Algorithms for adjusting for the partial volume effect have been published [70]. Another disadvantage of pQCT is the inability to obtain repeated measurements at the same bone site in pediatric longitudinal studies due to variations in longitudinal bone growth rates. In addition, movement can cause errors in locating the measurement site, especially if it occurs between the scout view and slice imaging. Pediatric positioning devices were developed in the late 1990s and have reduced movement and increased the percent of valid scans. Both pQCT and DXA methods can be challenging when used in young children.

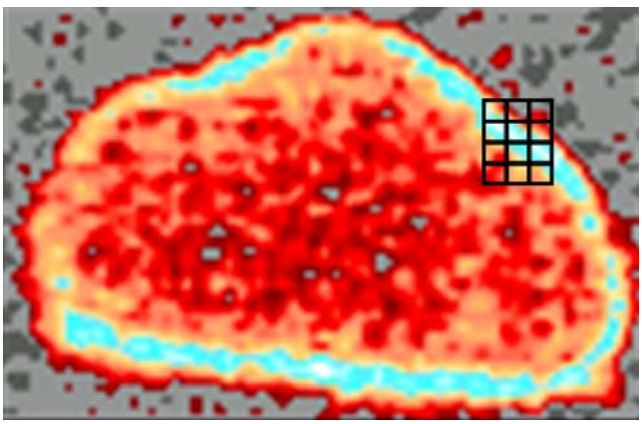


Fig. 7 Partial volume effect—the cross-sectional image of an 8-year-old female 4% distal radius. Each *square* in the grid pattern represents a voxel (volume equivalent of a pixel) and illustrates how a voxel may have more than one tissue type contained within it. The cortical rim of the bone has a considerable number of voxels with mixed tissue and therefore is more often affected by the partial volume effect compared to the trabecular bone area. This partial volume effect will result in a lower cortical $BMD_{compartment}$ and BMD_{total}

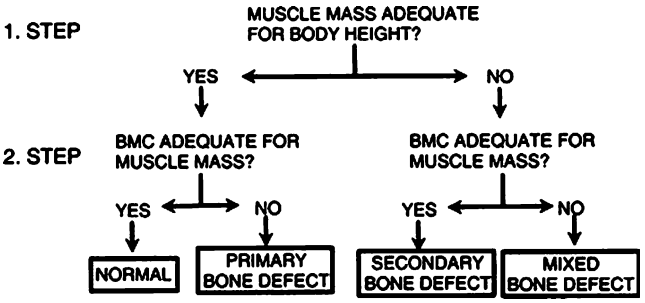


Fig. 8 Proposed diagnostic algorithm. Reproduced from *J Bone Miner Res* 2002;17:1095-1101 [74] with permission of the American Society for Bone and Mineral Research

7.3 Bone measures and fracture

pQCT measures of cortical thickness and estimates of bone strength have been shown to be associated with fracture risk in animal models [71] and in adults [72, 73]. However, there currently are no published studies showing an association between fracture risk and pQCT measurements in children.

8 Interpretation of bone measurements and current recommendations

Due to the close relationship between bone and muscle parameters it has been proposed that bone measurements, irrespective of how they are measured, should be considered in relation to muscle. Primary bone disorders are indicated by reduced bone strength with normal muscle strength. Since bone and muscle strength are difficult to measure directly, bone mass (BMC) and muscle mass are often used as surrogates of strength when trying to determine whether there is a primary or secondary bone defect that is present. As show in Fig. 8, a primary bone defect exists when BMC is not appropriate or adequate for the amount of muscle mass [74]. A secondary bone defect exists when BMC is appropriate for muscle mass, but muscle mass is not adequate for body size (height). A mixed bone effect is when muscle mass is reduced for body size (height) and there is reduced BMC for the mass of muscle present. A secondary bone defect can occur when muscle mass is reduced due to inactivity or chronic disease. In this case, BMC is reduced but appropriate for the amount of muscle measured. It is apparent from this algorithm that the treatment methods would differ depending upon the type of bone defect that exists.

There are no standard recommendations by either a US pediatric or bone organization on clinical reasons for obtaining bone measurements in children. The British Paediatric and Adolescent Bone Group published pediatric guidelines for the clinical use of DXA [75], suggesting that

children with conditions that may increase their risk of low bone density and fracture should be considered for a DXA scan if they also present with low trauma or recurrent fractures, back pain, spinal deformity or loss of height, change in mobility status, or malnutrition. Conditions considered to place children at increased risk include: chronic inflammatory disease, hypogonadism, osteogenesis imperfecta, idiopathic juvenile osteoporosis, prolonged immobilization, and osteopenia on x-ray. Rare diseases that also might place a child at increased risk of low BMD include congential neutropenia, certain inborn errors of metabolism, Ehlers Danlos syndrome, fibrous dysplasia, and hypophosphatasia. Long-term use of corticosteroids also increases a child's risk of low bone density or fracture. Due to variation between machines and the different pediatric reference databases and software programs that are available, it is important that clinicians consult with pediatric bone specialists before using DXA diagnostically or prescribing treatment based on DXA methodology.

An official position paper of the International Society of Clinical Densitometry (ISCD) made recommendations specific for pediatrics for performance and clinical application of bone density testing [22], including that:

- The WHO classification (for defining osteopenia and osteoporosis) should not be used.
- *T* scores should not appear in reports or on DXA printouts for children and *Z* scores should be used instead of *T* scores.
- Terminology such as "low bone density for chronological age" may be used if the *Z* score is below −2.0.
- The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone.
- *Z* scores must be interpreted in light of the best available pediatric databases of age-matched controls. The reference database should be cited in the report.
- The preferred skeletal sites for measurement are spine and total body.
- Standards for adjusting BMD or bone mineral content (BMC) for factors such as bone size, pubertal stage, skeletal maturity, or body composition have not been agreed upon; and, it should be clearly stated in the report what, if any, adjustments were made.
- Successive BMD studies should be done using the same machine, scanning mode, software, and analysis when appropriate, and changes may be required with growth of the child.
- Deviations from standard adult acquisition protocols, for example low-density software or any adjustment of ROI (region of interest), should be stated in the report.

As noted in the recommendations, the value of BMD to predict fractures in children has not been clearly demonstrated and standards for adjusting BMD or BMC for body size have not been agreed upon. The ISCD also has recently developed a position paper on the clinical utility of using pQCT in children and adolescents [76]. Although there are several advantages of this method for research purposes, concerns were raised regarding the lack of standardization of pQCT techniques and available reference data.

In summary, although there are specific methods available for assessing pediatric bone, there is no one method that can adequately assess bone health and identify the specific bone deficits that may be occurring. Understanding the biological basis for bone deficits that may be occurring and the ability of various bone assessment methods to discriminate or measure these deficits is important to understanding normal bone development and how to prevent and treat pediatric bone disease.

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