Mini Review

Assessing bone health in children and adolescents

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ABSTRACT

During normal childhood and adolescence, the skeleton undergoes tremendous change. Utilizing the processes of modeling and remodeling, the skeleton acquires its adult configuration and ultimately achieves peak bone mass. Optimization of peak bone mass requires the proper interaction of environmental, dietary, hormonal, and genetic influences. A variety of acute and chronic conditions, as well as genetic polymorphisms, are associated with reduced bone density, which can lead to an increased risk of fracture both in childhood and later during adulthood. Bone densitometry has an established role in the evaluation of adults with bone disorders, and the development of suitable reference ranges for children now permits the application of this technology to younger individuals. We present a brief overview of the factors that determine bone density and the emerging role of bone densitometry in the assessment of bone mass in growing children and adolescents.

Key words: Bone health, children, adolescents

Introduction

Senile osteoporosis begins as a pediatric disease. This seeming paradox is rooted in the fact that there is intense skeletal growth and development during childhood and adolescence, and much more bone is formed than lost. Later in life, the loss of bone tissue exceeds the rate of bone replacement. It, therefore, follows that lifelong bone health is dependent on maximizing peak bone mass during the critical periods of growth and maturation. One commonly cited notion is that each individual possesses a "Bone Bank," in which early deposits lay the foundation for skeletal health; later, during aging or in response to metabolic stresses, skeletal remodeling accelerates and withdrawals from the account exceed deposits, thereby compromising skeletal integrity. The natural process of bone remodeling makes youth the best time to "invest" in one's bone health.

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Skeletal development and growth

Development and growth of the skeleton occur through the coordinated interaction of osteoblasts and osteoclasts. Osteoblasts are bone-forming cells, and are derived from pluripotent mesenchymal stem cells that can also differentiate into muscle, adipocytes, cartilage, or fibrous tissue. Bone is resorbed by osteoclasts, large, multinucleated cells that can dissolve mineral and release calcium and phosphorus into the extracellular fluid. Osteoclasts are related to monocyte/macrophage cells. During embryogenesis, and after birth as the child grows, the skeleton continues to undergo changes in architecture and size that are termed "modeling," with coordinate increases in bone mineral mass and density. These changes are achieved through sustained modeling through puberty. In addition to modeling, bones are continuously reshaped by removing and replacing skeletal structures already present, a process termed remodeling.

Exquisitely complex cross-talk between osteoblasts and osteoclasts is required to effect these changes through the remodeling of existing bone and modeling of new

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bone as bone growth proceeds. Linear growth during childhood and adolescence occurs by growth of cartilage at the end plates of long bones, followed by endochondral bone formation. The width of the bones increases by periosteal apposition. During puberty and early adult life, endosteal apposition and trabecular thickening provide maximum skeletal mass and strength (peak bone mass). Locally and systemically produced factors and mechanical forces influence these processes and control the coordinated functions of osteoblasts and osteoclasts to preserve structural strength.[1] The adult skeleton continues to undergo remodeling throughout life, replacing approximately 15% of the mature skeleton each year to maintain mineral homeostasis, to repair damaged bone, and to respond to changes in skeletal stress.

Bone remodeling occurs most often in skeletal sites rich in cancellous (trabecular) bone, such as the vertebrae, proximal femur, calcaneus, and ultradistal radius. A second form of bone, termed cortical bone, is less metabolically active but provides great strength and integrity to the skeleton. Cortical bone comprises 80% of the skeleton, is dense and compact, and constitutes the outer part of all skeletal structures.

During the first two decades of life, the skeleton grows in both size and density, and it is estimated that more than half of peak bone mass is acquired during the teen years.[2] The process of bone growth is not uniform, and the axial and appendicular skeleton increase in size at different rates.[3,4] Specifically, there is proportionately greater growth in the limbs than the trunk prior to puberty. In early and mid-puberty, the relative rate of growth of the spine increases and growth slows at all sites in late puberty.[5,6] The rapid growth of the skeleton during puberty exceeds the rate of mineralization, and bone mineral accrual lags behind growth in height by 8 months.[7,8]

Bone mass continues to accumulate until around age 30.[9,10] At that point, bones reach their maximum strength and density, known as peak bone mass. Women tend to experience minimal change in total bone mass between age 30 and menopause. But, in the first few years after menopause, many women experience a period of rapid bone loss, which then slows but continues throughout the post-menopausal years. This loss of bone mass can lead to osteoporosis, a condition of weakened bones and increased risk of fragility fracture. In men, age-related bone loss occurs later and proceeds at a steady rate. In both men and women, declining bone mass is the primary cause of weak bones and fractures. It is estimated[11] that 10 million Americans over age 50 have osteoporosis, which represents significant health and economic costs to society. If osteoporosis has origins in childhood, then understanding the factors affecting bone accretion in childhood may be the key to early prevention of this common, disabling condition.

However, there is increasing recognition that many children fail to optimize bone accretion during childhood and adolescence and concern that inadequate skeletal mass will result in fragile bones and increased risk of fractures both in childhood and later as adults.[12] For example, many childhood conditions pose threats to bone health through primary disease effects such as mal-absorption, secondary effects such as prolonged periods of physical inactivity or treatment effects such as glucocorticoid therapy. Moreover, improvements in treatment now enable many children with severe medical conditions, such as cystic fibrosis, inflammatory bowel disease, and cancer, to enjoy significant improvements in life expectancy and in many cases, surviving to adulthood. Endocrine disorders such as growth hormone deficiency, hypothyroidism or hypoparathyroidism may limit growth, but apparently do not impair acquisition of bone mass. By contrast, primary hyperparathyroidism and hyperthyroidism, although uncommon in children, can have significant adverse effects on bone mass. And finally, many otherwise normal children experience nutritional deficiencies of calcium or vitamin D that can impair acquisition of optimal bone mass. Several studies estimate that 30% of children will experience a fracture before reaching adulthood.[13] Childhood fractures most commonly occur in the distal extremities, particularly the forearm. Several risk factors have been associated with childhood fracture, including lower bone density, a previous fracture, European ancestry, obesity, and low dairy intake.[14-17]

Based on these concerns, in 2000, the U.S. National Institutes of Health convened experts at a Consensus Development Conference on Osteoporosis Prevention, Diagnosis and Treatment.[18] Among other measures, the conference recommended developing research strategies to optimize bone mass during the first two decades of life, and to identify and intervene in disorders that compromise attainment of peak bone mass, particularly in children with chronic disease.

What affects bone mass in children

Bone mass is determined through a complex interaction of environmental, behavioral, and genetic traits. About 60% to 80% of the contribution to peak bone mass is thought to be genetically determined,[12] although not all the relevant genes have yet been identified.[19,20] The effect of heredity, and genetics, is manifest during childhood, prior to puberty.[12,21] These genetic effects can also account for

differences in bone density between population groups and are evident in childhood.[2] For example, areal bone mineral density (aBMD) is greater for African American compared to Caucasian, while Caucasians have greater aBMD than either Asians and Hispanics.

The identification of specific genetic mutations that cause low bone density in subjects with rare bone disorders (*e.g.* collagen 1 alpha 1 (*COL1A1*) in osteogenesis imperfecta and low-density lipoprotein receptor-related protein 5 (*LRP5*) in osteoporosis pseudoglioma syndrome) have stimulated large population studies to discover genetic variants that are associated with bone density and risk of osteoporosis. These population variants include polymorphisms in the regulatory region of *COL1A1* gene[22] that are associated with decreased bone mineral content and aBMD at several sites in pre-pubertal[23] or adolescent[24] girls. In adolescents, polymorphisms of the estrogen receptor, aromatase, interleukin-6, LRP5, and osteocalcin genes have also been shown to be independent predictors of bone size, BMC, or BMD.[25-35] Recent discoveries resulting from genome-wide association studies (GWAS) further confirm the relevance of genetic contributions to bone density.[36] There have been more than 40 published GWAS on skeletal phenotypes, predominantly focused on dual-energy x-ray absorptiometry (DXA)-derived aBMD of the hip and spine. Remarkably, 66 BMD loci have been replicated across all the published GWAS, confirming the highly polygenic nature of BMD variation. Only seven of the 66 previously reported genes (*LRP5, SOST, ESR1, TNFRSF11B, TNFRSF11A, TNFSF11, PTH*) from candidate gene association studies have been confirmed by GWAS. In addition, 59 novel BMD GWAS loci have been recently identified, including some that are involved in important biological pathways involving the skeleton, particularly Wnt signaling (*AXIN1, LRP5, CTNNB1, DKK1, FOXC2, HOXC6, LRP4, MEF2C, PTHLH, RSPO3, SFRP4, TGFBR3, WLS, WNT3, WNT4, WNT5B, WNT16), bone development and ossification (CLCN7, CSF1, MEF2C, MEPE, PKDCC, PTHLH, RUNX2, SOX6, SOX9, SPP1, SP7), mesenchymal-stem-cell differentiation (FAM3C, MEF2C, RUNX2, SOX4, SOX9, SP7*), osteoclast differentiation (*JAG1, RUNX2*), and TGF-signaling (*FOXL1, SPTBN1, TGFBR3*) (reviewed in.[37] By contrast, GWAS of BMD in children have been more limited and have identified few loci (e.g. near the Osterix (SP7) gene[35] and *WNT16* gene[38] that are associated with bone density. Each of these different genetic variants can explain only a very small effect on overall BMD, however.

Environmental and behavioral factors account for the remaining 20% to 40% of variability in bone mass, and variations in nutrition (particularly calcium and vitamin D) and physical activity are particularly important.[2,12,17,21,39-43] Calcium supplementation studies in children showed that children with calcium-deficient diets experience a modest (about 3%) increase in BMD with calcium supplementation.[44-46] The effect is most pronounced in pre-pubertal children. These effects of calcium are transient, however.[47,48] Nevertheless, other studies have suggested that increasing calcium intake during childhood through dietary fortification with dairy sources may provide more long-lasting improvements in BMD.[49,50] Optimal absorption of calcium from the gastrointestinal tract requires normal vitamin D homeostasis.[51] The primary source of vitamin D is the skin. High-energy UVB light, principally from sunlight, penetrates the epidermis and photochemically cleaves 7-dehydrocholesterol to produce previtamin-D_3. Previtamin-D3 then undergoes a thermally-induced isomerization to vitamin D_3 (cholecalciferol) that takes two to three days to reach completion. Therefore, after a single sunlight exposure, cutaneous synthesis of vitamin D_3 continues for many hours. It is not possible to generate too much vitamin D3 in the skin, as prolonged sunlight exposure activates a mechanism that converts excess previtamin D3 and vitamin D3 to biologically inert products. Vitamin D can also be obtained from the diet, from plant sources as ergocalciferol (vitamin D_2), and from animal sources as cholecalciferol (vitamin D_3). Dietary and endogenously-produced vitamin D can be stored in fat for later use. To become metabolically active, vitamin D must undergo two biochemical modifications. Vitamin D first undergoes 25-hydroxylation in the liver by the cytochrome p450 enzyme CYP2R1 to form 25(OH)D. Subsequently, 25-(OH)D_3 is directed to the kidney where it is either converted to 24,25-dihydroxyvitamin D_3 (an inactive derivative) or to 1,25-dihydroxyvitamin D_3 [calcitriol, the active hormone]. Activation to calcitriol requires hydroxylation by a 1α-hydroxylase enzyme (CYP27B1) that is tightly regulated and is the rate-limiting step in the bioactivation of vitamin D: Parathyroid hormone increases production of calcitriol by stimulating CYP27B1 activity while FGF23 decreases CYP27B1 activity. Dietary intake of vitamin D is inadequate in many parts of the world and, therefore, daily requirements for vitamin D depend upon cutaneous synthesis and sunlight exposure. Dark skin, use of UV sunblockers, or customs of dress that largely cover the skin can reduce cutaneous absorption of UVB light and thereby prevent adequate synthesis of vitamin D to meet daily or long-term requirements.

It is also important to note that other nutrients, such as vitamin D and K, copper, protein, phosphorus, magnesium, manganese, zinc, energy, and iron,[52] also appear important for bone health.

In addition to diet, physical activity, particularly weight-bearing activity, is an important determinant of bone mass. Bone contains a network of osteocytes that constitute a bio-mechanostat that can detect load and stress on the skeleton. Bone stress induces signals that stimulate osteoblast bone formation and reduces osteoclast bone resorption, leading to increased bone mass. Muscle mass provides an excellent index of the mechanical stimulation to bone and is highly correlated to bone mass, density, and architecture (Wetzsteon *et al.* 2011). Multiple studies in healthy children have shown an association between physical activity and aBMD,[41,42,53-55] and athletes, such as gymnasts[56] and tennis players,[57] have increased bone density, dimensions, and strength during growth. Moreover, modest increases in weight-bearing physical activity can result in significant improvements in bone density and strength in growing children and adolescents.[58] Importantly, the benefits of enhanced physical activity on bone density can persist beyond adolescence and result in greater bone density in young adulthood.[59] By contrast, children who are unable to bear weight or have neuromuscular disorders that reduce load on the skeleton have significantly reduced bone density and are at increased risk of fractures, particularly in the lower limbs.[60]

Other important factors include body mass. Although obese children typically have higher bone mass and density and larger bones,[61-64] their risk of fracture is increased and visceral fat mass is inversely related to bone mass. By contrast, lean body mass (i.e., muscle mass) is positively correlated to bone mass.[65] Hormonal influences (including estrogen, testosterone, and parathyroid hormone), infectious agents (such as HIV), metabolic disorders, and cancer. Because gonadal hormones secreted during puberty increase bone mass, delayed puberty has a limiting effect on BMD during adolescence that appears to resolve over time in males.[55,66,67] Chronic inflammatory diseases, such as Crohn's disease or juvenile idiopathic arthritis, may accelerate bone resorption due to inflammatory cytokines produced in the disease process. Childhood malignancy, particularly leukemia, can compromise bone health. And, endocrine disorders such as diabetes mellitus, hyperthyroidism, primary hyperparathyroidism, and glucocorticoid excess are associated with reduced bone mass and increased risk of fracture.

Quantitative bone assessment

A history of recurrent fractures, particularly low-impact or atraumatic fractures, should lead the clinician to carefully consider whether a child may have reduced bone strength, and the International Society for Clinical Densitometry has recommended that a child with a history of two upper extremity or one lower extremity fractures undergo an assessment of bone density.[68,69]

Early attempts to measure bone density utilized plain skeletal radiography. However, bone demineralization becomes visibly apparent only after bone density loss exceeds 40%, making this test too insensitive for clinical use. More quantitative imaging technologies for assessing bone health have been developed, and currently used modalities include metacarpal morphometry, quantitative ultrasound, quantitative computed tomography (QCT), and dual energy X-ray absorptiometry (DXA). At present, adequate databases for children are lacking for metacarpal morphometry and quantitative ultrasound. QCT has an advantage over the other techniques because it measures bone volume and thus accurately computes volumetric BMD (vBMD). In addition, it differentiates dense cortical bone from metabolically active trabecular bone. Its drawback is that it exposes the patient to a substantial amount of radiation (effective radiation dose 60 μSv), which limits utility for follow-up studies. Peripheral QCT is emerging as an attractive alternative technology because it is able to distinguish between the trabecular and cortical bone compartments, but exposes the patient to far less radiation than conventional QCT.

DXA provides considerable advantages: Low radiation exposure (1-3 μSv versus 50 μSv for adult PA chest x-ray and 8 μSv per day background radiation in the U.S.), precise results, and lower cost than QCT. However, unlike QCT, it does not directly measure true volume, and thus computes areal density, not volumetric density. Derived from the area of bone, areal density is a two-dimensional estimation of a three-dimensional property, and the algorithms that make the conversion to density are not entirely satisfactory.

Challenges in assessment of bone health in children

The measurement of bone density in children is less standardized than in adults and requires special consideration of the effects of growth and puberty on bone mass.[68,69] Interpretation of bone density in children relies on Z-scores—the number of standard deviations (SD) from the norm of a reference database of children. A Z-score of -2 SD represents low bone density, but indications for treatment and specific therapy are not yet established. In contrast, bone mass density in adults is measured in T-scores—standard deviations from peak bone mass, with a T-score of -2.5 SD or worse representing osteoporosis, as codified by the World Health Organization in 1994. In children, the relationship between bone density and fracture risk is less firmly established than in adults.[15,16]

There are important confounding factors to consider when performing DXA in children and adolescents, such as variations in age, race, gender, pubertal status, and height.[70,71] For example, many early reference data sets did

not distinguish between boys and girls. As girls experience an earlier puberty than boys, this can lead to an overestimation of low bone mass. For example, Leonard *et al*.[72] showed that reference ranges that are not sex-specific incorrectly identified 9–13% of girls and 24–44% of boys as having low bone mass compared to only 11–16% of girls 10% of boys when age- and sex-specific reference data were used. Racial differences may be relevant; in the U.S., bone density tends to be higher in African Americans than in other groups.[73] The lack of suitable reference ranges has been addressed by a multi-center U.S. study, 'The Bone Mineral Density in Childhood Study' (BMDCS), that evaluated 2014 children, aged 5–19 years at enrollment, annually for up to 7 years. This study now provides robust reference ranges for bone measurements at different sites and allows distinctions for race, age, and gender.[73]

It is also important to consider height and pubertal status. DXA measurements of aBMD are strongly influenced by bone size. Children who are tall for age have larger bones and hence, greater BMC and aBMD than those who are average or short for age.[71] This effect is attenuated when volumetric bone density is assessed, however. The effect of height on aBMD is intensified around the ages when pubertal development typically occurs, because taller children are often earlier maturing children in the early pubertal years and short children are often later maturing children in the later pubertal years. Consequently, DXA measurements should be adjusted for absolute height, preferably as height-specific Z-scores.[71,73] Similarly, a child's pubertal status must be considered when analyzing bone densitometry, as children with delayed maturation will have lower bone mass than their peers who have higher levels of estrogen or testosterone.

Technical considerations must also be addressed. DXA technology has addressed the lower bone density in children with the introduction of a low density software option for young children. This option uses a different bone edge detection algorithm to accommodate the lower attenuation values that occur in measuring young children. Differences between machines, particularly of different manufacturers, can introduce measurement differences that limit comparisons between studies. Recently, cross-calibration equations have been developed for whole-body bone density and composition derived using GE Healthcare Lunar and Hologic DXA systems.[74] These equations reduce differences between aBMD and body composition as determined by GE Healthcare Lunar and Hologic systems and will facilitate combining study results in clinical or epidemiological studies.[74]

Finally, errors in interpretation of pediatric bone densitometry can lead to spurious results that generate unnecessary worry and expense. A 2004 study found significant overdiagnosis of pediatric osteoporosis among children who had been referred to an osteoporosis trial on the basis of low aBMD scores inferred from DXA.[75] In that study, 88% of the scans had one or more errors in interpretation, including non-gender-specific reference data, inattention to short stature, and the incorrect use of a T-score instead of a Z-score. After correcting for these errors, 53% of the children who been referred for low BMD scores were found to have normal bone mineral density.

Conclusions

Clearly, refinements in reference data will improve the accuracy of clinical assessments of bone health in children and adolescents. Recently, the International Society for Clinical Densitometry (ISCD) issued recommendations for DXA interpretation in children. The ISCD stated that an appropriate reference dataset must include "a sample of the general healthy population sufficiently large to characterize the normal variability in bone measures that takes into consideration sex, age and race/ethnicity."[69]

Another recommendation stated that "In children with linear growth or maturational delay, BMC and BMD results should be adjusted for absolute height or height age, or compared to pediatric reference data that provide age-, sex-, and height-specific Z-scores."

Specific therapy for children with low bone density is best left to clinicians who are highly experienced in the evaluation and management of pediatric bone disorders. Available agents for adults with osteoporosis and other pharmacologic treatments may be useful in selected circumstances for children with low bone density, but such children must be treated very carefully as long-term safety data are not yet available.

In summary, evaluation of bone density by DXA is appropriate for children and adolescents who have a history of fragility fracture or specific risk factors for low bone density. As better diagnostic techniques become available and specific criteria for diagnosis are developed, it is likely that pediatric-specific pharmacologic agents will be forthcoming. Until that time, it is reasonable to refer children and adolescents who have a suspected metabolic bone disease to a pediatric bone specialist.

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