

ABSTRACT

Osteoporosis is a disease characterized by low bone mass and micro architectural alterations of bone tissue leading to enhanced bone fragility and increased fracture risk. Although research in osteoporosis has focused mainly on the role of bone loss in the elderly population, it is becoming increasingly clear that the amount of bone that is gained during growth is also an important determinant of future resistance to fractures. Thus, considerable interest is being placed on defining preventive strategies that optimize the gain of bone mass during childhood and adolescence. Knowledge of the determinants accounting for the physiologic and genetic variations in bone accumulation in children will provide the best means toward the early diagnosis and treatment of osteoporosis. This article reviews the techniques available for bone mass measurements in children and the major determinants and diseases influencing bone accretion during childhood and adolescence. (**Arq Bras Endocrinol Metab 2006;50/4:775-782**)

Keywords: Low bone mass; Bone mass measurement; DXA in childhood and adolescence; Update; Controversy

RESUMO

Baixa Massa Óssea em Crianças e Adolescentes.

Osteoporose é uma doença caracterizada pela baixa massa óssea e alterações de micro arquitetura do tecido ósseo, levando ao aumento da fragilidade óssea e aumento do risco de fratura. Apesar da pesquisa em osteoporose ter focalizado principalmente no papel da perda óssea na população idosa, está começando a ficar claro que a quantidade de osso que é ganho durante o crescimento é também um determinante importante de resistência futura para fraturas. Portanto, interesse considerável está sendo colocado na definição de estratégias preventivas que otimizam o ganho de massa óssea durante a infância e adolescência. O conhecimento dos determinantes responsáveis pelas variações fisiológicas e genéticas, na acumulação óssea nas crianças, irá levar aos melhores meios para o diagnóstico precoce e tratamento da osteoporose. Este artigo revê as técnicas disponíveis para a medida da massa óssea em crianças e os maiores determinantes e doenças que influenciam a aquisição óssea durante a infância e adolescência. (**Arq Bras Endocrinol Metab 2006;50/4:775-782**)

Descritores: Baixa massa óssea; Medidas da massa óssea; DXA na infância e adolescência; Atualização em DXA; Controvérsia em DXA

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THE PEAK BONE MASS

THE FOUNDATION FOR LIFELONG skeletal health is established during childhood and adolescence. Although there is controversy regarding the exact timing of peak bone mass, bone size and strength reach a maximum by early adulthood (1-3). Failure to accrue optimal peak bone mass has been linked to an increased risk of osteoporosis (4). The variables that contribute to optimal bone health have been delineated in studies of healthy youth (1-3).

Approximately 90% of adult bone mass is gained in the first two decades of life. Optimizing peak bone mass and bone strength early in life and stabilizing it during young adulthood is believed to play a significant role in preventing osteoporosis and fractures later in life. Adequate weight-bearing physical activity, nutrition, body mass, and hormonal balance are essential in achieving optimal skeletal health. A growing list of chronic diseases has also been linked to low bone mass or fragility fractures (5-30). Disorders causing rickets and osteomalacia are reviewed by Durval elsewhere in this issue. In some chronic conditions, a single factor (e.g., immobilization or hypogonadism) accounts for the increased risk of low bone mass. In most of these disorders, however, skeletal health is threatened by a combination of risk factors including malnutrition, vitamin D insufficiency, malabsorption, deficiency or resistance to sex steroids or growth hormone, immobilization, and increased cytokine production. Medications that are used to treat these disorders, such as glucocorticoids, calcineurin inhibitors, and chemotherapeutic agents, may also contribute to bone loss (6). The magnitude of effect that these disorders or medications will have on an individual patient varies, depending upon genetic factors, disease severity, activity, and other variables. For this reason, clinicians seek diagnostic tools to identify patients at greatest risk for bone fragility.

Obese and less-active children also have been shown to have decreased BMD or bone mass compared with non-obese children of similar weight (31,32). It is not clear whether this decreased BMD among obese children is a direct effect of fat on bone or due to decreased muscle mass or reduced activity levels, or a combination of both of these factors. However, the epidemic of childhood obesity may in part directly or indirectly explain the increase in childhood fracture incidence that has recently been reported (33). Identifying children with low bone mass early in life could be an important strategy for preventative or therapeutic efforts to optimize bone accrual and, consequently, bone strength (table 1).

ASSESSING PEDIATRIC BONE HEALTH

DXA is the most widely used densitometric method for diagnosing osteoporosis in adults. DXA was developed in the late 1980s for use primarily in postmenopausal women. Pediatric software became available in the early 1990s after improvements in algorithms for detecting bone edges in children with low bone density. The advantages of DXA are its wide availability, short scanning times, and relatively low radiation exposure. The radiation exposure is comparable to that received during a round trip transcontinental airplane flight. DXA has several important limitations, however (34-36). The technique does not provide a measure of volumetric bone mineral density

Table 1. Disorders associated with low bone mass or fractures in childhood and adolescence (60).

Genetic disorders (6,42)

Ehlers-Danlos
Fibrous dysplasia
Homocystinuria
Hypophosphatasia
Idiopathic hypercalciuria
Marfan's syndrome
Menkes' kinky hair syndrome
Osteogenesis imperfecta

Chronic disease

Anorexia nervosa (7,8)
Athletic amenorrhea (9)
Celiac disease (10)
Cystic fibrosis (11)
Diabetes (type I) (12)
Hematologic thalassemia, sickle-cell anemia (13)
Inflammatory bowel disease (14)
Malignancy (15-17)
Post transplantation (18)
Renal failure (19)
Rheumatologic disorders (20)

Endocrine disorders

Glucocorticoid excess (21)
Growth hormone deficiency (22)
Hyperparathyroidism (23)
Hyperthyroidism (26)
Sex steroid deficiency or resistance (25,26)

Immobilization

Cerebral palsy (27)
Muscular dystrophy (28)
Paraplegia
Spina bifida

Miscellaneous

Idiopathic juvenile osteoporosis (29)
Idiopathic scoliosis (30)

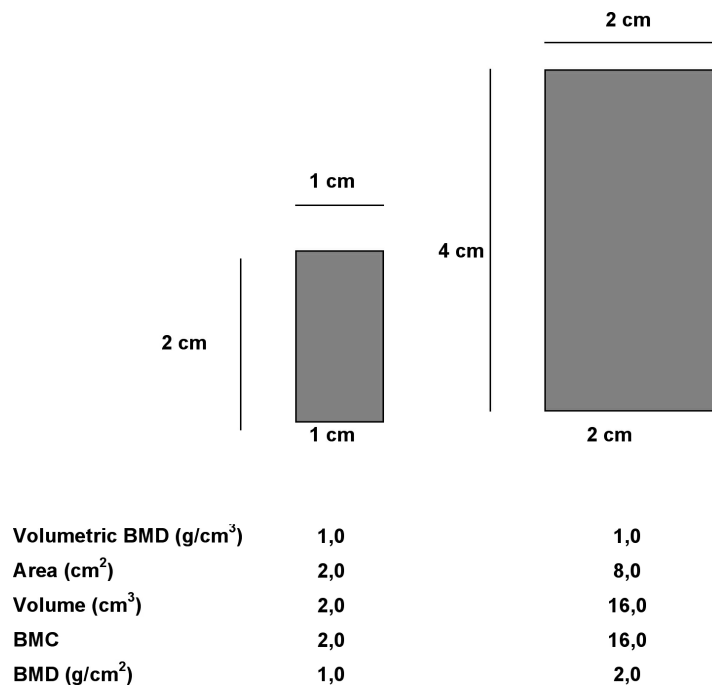


Figure 1. Areal BMD measurements are influenced by bone size, with larger bones of similar volumetric BMD having higher areal BMD values.

or of bone geometry nor does it distinguish between cortical and trabecular bone. Although bone size and geometry can be adjusted for mathematically, these are only estimates of these parameters. Because this is a 2-dimensional measurement and not a true volumetric density, measurements using DXA are often referred to as *areal BMD* (aBMD). Measurements of aBMD are influenced by bone size, with larger bones having artificially inflated aBMD measurements (figure 1). This is an important problem in pediatric bone assessment because of the large differences in body size and bone size within and across different ages. Studies show that aBMD by DXA increases with age, but computed tomography evaluations indicate that true volumetric BMD (vBMD) is relatively constant during childhood until puberty, at which time there is a large increase in vBMD (37). BMC increases with age, and the increase in aBMD that is observed is likely the result of greater bone size.

Although adult aBMD has been shown to be predictive of future fracture risk in longitudinal epidemiologic studies (Data on the Bone Densitometry Chapter), there is no evidence indicating this in children. The aBMD results are often presented as T- and Z-scores. Because T-scores compare the observed aBMD with that of young adults, they are not appropriate for growing children and should never be used.

Z-scores, defined as the SD score based on age and gender-specific norms, must be used to determine how a child's aBMD compares with other children's (figures 2 and 3). This is a more appropriate method of comparison of aBMD in pediatrics. As previously described, however, aBMD is highly correlated to body and bone size, and in children with chronic diseases in whom weight or height for age may be severely affected, the comparison of aBMD measurements to age-matched norms is difficult to interpret.

Total body and lumbar spine (L1-L4) DXA scans are reported in pediatric studies. Total body is a predominantly cortical bone measurement while lumbar spine is mainly trabecular bone. Thus different skeletal sites will be affected by different factors. Dietary calcium intake has been shown to affect primarily appendicular bone sites that are predominantly cortical bone (38), whereas hypogonadism and steroid use affect primarily axial bone sites or the ends of long bones, which are predominantly trabecular bones (39,40).

Although regional DXA scans can measure BMD and BMC at sites that are predominantly trabecular or cortical bone, it is not possible to obtain separate cortical and trabecular BMD results using DXA. The aBMD assessed by DXA is a function of both the amount of bone within the periosteal envelope and the size of the bone.

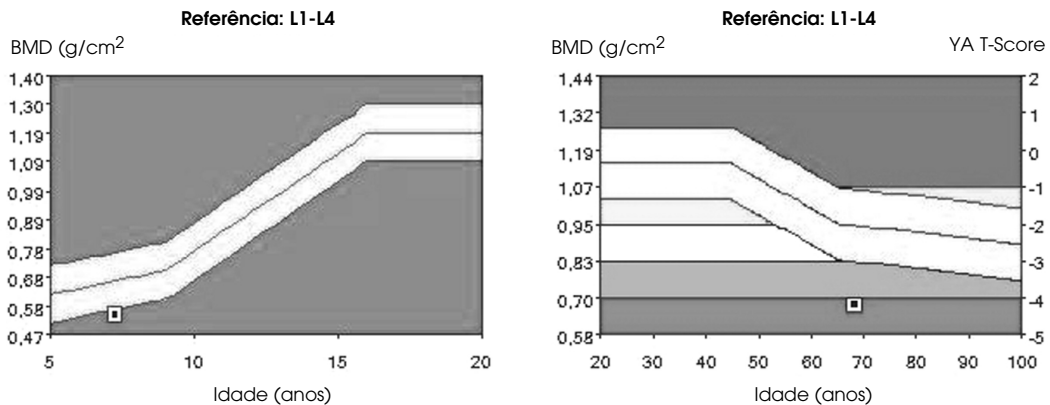


Figure 2. Shows the different graphs for the interpretation of bone densitometry. Pediatric bone density is compared for patients of the same age, the Z-score. Adult bone density is read comparing young adults, 20 to 40 years old, density, and T-score.

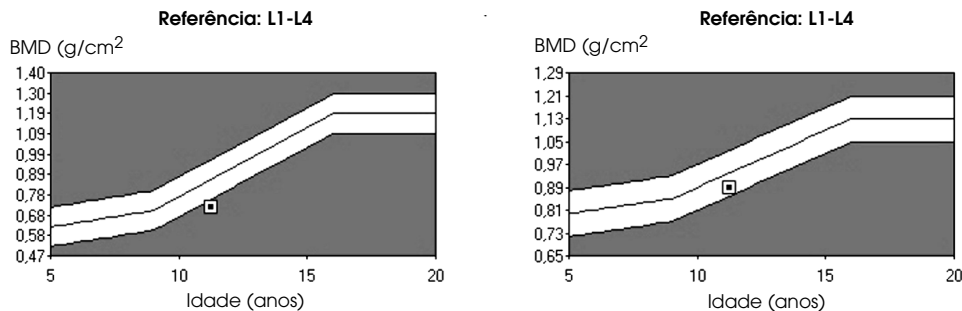


Figure 3. Spine and total body scan of a 11-year-old girl, 40,1 kg, 142,0 cm height, referred to evaluation for previous use of anticonvulsants for five years. Her BMI is 20, at the 80 th percentile for age, according to CDC Growth Charts, and Tanner Stage B2P2, no menarche. The Z-score for total skeletal is -0,6 and for lumbar spine (L1L4) is -1,4. The diagnosis is "adequate bone mass density for chronological age" since the Z-score values are less than -2,0 within the normal pediatric range.

BONE MASS MEASUREMENT GENERAL GUIDELINES

There are currently no standard recommendations by either a U.S. pediatric or bone organization regarding who should have bone measurements for clinical purposes. The British Paediatric and Adolescent Bone Group recently published pediatric guidelines for the clinical use of DXA (41). They suggested 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 low trauma or recurrent fractures, back pain, spinal deformity or loss of height, change in mobility status, or malnutrition. The list of conditions that place children at increased risk is given in table 1, along with some of the more rare conditions that also may be associated with decreased BMD. Because of the lack of pediatric reference databases, the variation between machines, and the different software analyses that are performed, it is important that clinicians consult with

pediatric bone specialists before using DXA diagnostically or prescribing treatment on the basis of DXA methods.

The International Society of Clinical Densitometry recently published an official position paper on recommendations for performance and clinical application of bone density testing, which included recommendations specific for diagnosis in children (table 2).

INTERPRETING PEDIATRIC DUAL-ENERGY X-RAY

Interpreting bone mineral measurements is far more complex in children than in adults and goes beyond calculating a Z-score (34,36,43,44). Unlike the adult whose bone dimensions are stable with time, children and adolescents are moving targets whose bone size, geometry, and mineral content are changing. These processes evolve at varying rates in different regions of the skeleton, with appendicular growth preceding spinal mineral acquisition (44). Furthermore, within a given

region of interest, trabecular and cortical compartments respond variably to sex steroids, calcium intake, and mechanical loading. The tempo of mineral accrual is linked more closely to pubertal and skeletal maturation than to chronological age, and these processes vary with gender and ethnicity (43,44,45,49,50). For this reason, the influence of bone size and maturation must be considered in evaluating DXA results.

In fact it is very important to correlate bone acquisition in young subjects not only with chronological age or sex, as it is done in commercial softwares, but also with anthropometrical parameters, particularly in longitudinal evaluations. On the basis of many studies published on literature (45-48), the pubertal development and weight are the most important parameters in monitoring bone mass in adolescents. When children have delayed growth or puberty and altered body composition, these factors must be considered in interpreting BMC and BMD. For children with delayed growth and maturation, it is also reasonable to adjust for pubertal stage rather than for chronological age. Unfortunately, only a few studies have reported normative data by pubertal stage (16,44,51). Alternatively, a bone age can be obtained and BMD data compared with norms for the patient's skeletal rather than chronological age.

Additionally, BMC and BMD are strongly influenced by bone size; BMD corrects only for the area of bone studied but not the thickness of bone. For this reason, true (volumetric) bone density may be underestimated in patients with smaller bones and overestimated in larger children. Several methods have been proposed to adjust bone mass for the influence of bone size or lean body mass (52-55). Estimates of volumetric bone density at the spine and femoral neck

divide BMC by the estimated volume of bone in the region; total body BMC is corrected for relative height (55). None of these correction models has been established as best by the gold standard of predicting childhood fracture. Furthermore, given two bones of equal density, the larger bone will be more resistant to fracture than the smaller one. Nonetheless, it is possible to estimate how much reduced BMD can be attributed to smaller bone size by calculating volumetric BMD. Limited pediatric norms for volumetric BMD have been published (49,55-57). An example of a pediatric DXA interpretation is provided in figure 2.

INTERPRETING LOW BONE MASS

The fracture risk associated with low BMD is far less certain in children and young adults. Patients with mild forms of osteogenesis imperfecta (OI), for example, have very low BMD but do not suffer spontaneous fractures. The International Society for Clinical Densitometry has determined that the diagnosis of osteoporosis in a young patient "should not be made on the basis of densitometric criteria alone". The WHO criteria for osteopenia and osteoporosis are not appropriate for use in children, adolescents, and young adults. Terms such as "low bone density for chronological age" may be used if the Z-score is less than -2.0; the term "osteoporosis" must be avoided since it is better conditions of loss of bone. By implication, the diagnosis of "low bone density for chronological age" in a child requires additional clinical findings such as a history of low impact fracture.

Finding low bone mass on a pediatric DXA does not necessarily imply bone loss. Low bone mass

Table 2. Position of the International Society for Clinical Densitometry (ISCD) on the Use of DXA in Diagnosis in Children (males or females less than 20 years of age) (32).

- The WHO classification (for defining osteopenia and osteoporosis) should not be used.
- Z-scores should be used instead of T-scores in children.
- T-scores should not appear in reports or on DXA printouts for children.
- 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 light of the best available pediatric databases of age-matched controls. The reference database should be cited in the report.
- Preferred skeletal sites for measurement are spine and total body.
- The value of BMD to predict fractures in children is not clearly demonstrated.
- 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. Clearly state any adjustments in the report.
- Successive BMD studies should be done using the same machine, scanning mode, software, and analysis when appropriate. 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.

in a child can result from inadequate gains of bone mineral, bone loss, or a combination of the two (8,58,59). Understanding this is critical, because most drugs used to treat osteoporosis in adults are anticatabolic agents that reduce bone loss. Children who fail to gain adequate bone mineral may require therapy that is anabolic or bone building. It is beyond the scope of this article to review the current therapies for pediatric low bone mass (5,6). At the very minimum, however, the finding of low bone mass should prompt a search for possible cause(s), including a review of overall nutrition, calcium intake, vitamin D stores (serum 25 hydroxyvitamin D), hormonal status, physical activity, and underlying disease status. All risk factors should be addressed.

CONCLUSIONS

Bone acquisition early in life is considered an important predictor of osteoporosis risk later in life. DXA is the most common method for assessing bone health in pediatric populations. There are, however, several problems with interpreting DXA scans in children that need to be considered by clinicians before therapeutic interventions are implemented on the basis of DXA results. PQCT is a promising method that is currently being used in pediatric bone research that may find its way into clinical use for assessing bone strength and fracture risk. Further research is needed to determine whether QUS could be used as a radiation-free alternative for assessing bone development clinically and in epidemiologic studies.

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