Pediatric Dual-Energy X-ray Absorptiometry: Technique, Interpretation, and Clinical Applications

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This article reviews the dual-energy x-ray absorptiometry (DXA) technique, its interpretation, and clinical applications with emphasis on the considerations unique to pediatrics. Specifically, the use of DXA in children requires the radiologist to be a "clinical pathologist," monitoring the technical aspects of the DXA acquisition, a "statistician" knowledgeable in the concepts of Z-scores and least significant changes, and a "bone specialist," aware of the DXA findings in a large number of clinical diseases, providing the referring clinician with a meaningful context for the numeric result obtained with DXA.

Semin Nucl Med 37:303-313 © 2007 Elsevier Inc. All rights reserved.

The result of a dual-energy radiograph absorptiometry examination (DXA) is a number and a diagnosis and, thus, it is different than all other imaging studies. As a laboratory test, the DXA examination generates a numeric result, and the imaging specialist must have expertise in the processes by which that number is generated and insure that meticulous technique was used. He or she must be knowledgeable in the statistical limitations of a numeric result and be able to suggest appropriate follow-up intervals based on the examination’s precision and also must evaluate the result based on relevant patient factors and give a clinically meaningful interpretation. Imaging specialists should be knowledgeable of the limitations of the use of DXA in children. These limitations include the errors introduced in scan interpretation caused by the areal rather than volumetric density measurements DXA obtains, the impact the skeletal growth has on follow up measurements, the lack of consensus regarding the patient demographic and physiologic factors that should be incorporated into normative databases, and the uncertain prognostic value of pediatric DXA with regard to fracture risk or peak bone mineral density (BMD).

Areal Versus Volumetric BMD

DXA relies on the differential absorption of x-rays to distinguish tissues of different radiographic density. Additionally, DXA can quantify (in grams) the bone mineral content (BMC) at various body sites. By selecting regions of interest (ROIs), a bone area (BA; units of cm²) is delineated. The BMD is measured directly (in units of g/cm²) for each pixel in the ROI by comparing the x-ray attenuation of that pixel to a reference standard. This value is multiplied by the pixel’s area to derive that pixel’s BMC with units of grams. The summed areas of all the pixels in the ROI equals the BA, and BMD = BMC/BA.

The DXA-derived BMD is based on the 2-dimensional projected area of a 3-dimensional structure because the third dimension, depth, cannot be accounted for directly in that it is in the same direction as the x-ray beam. Therefore, BMD is an areal (aBMD), rather than a true volumetric (vBMD) density. Because the third dimension is unaccounted for, problems with DXA-derived BMD can arise. Specifically, smaller bones will be found to have lower aBMD than larger bones even when the vBMD is the same (Fig. 1). Also, a child’s bones grow over time and the growth of individual bones is not uniform in 3 dimensions. Errors caused by the measurement of an areal BMD with DXA make comparison of follow-up and baseline studies more challenging to interpret in pediatric patients.

Technical Aspects of DXA Performance

Patient positioning and ROI selection require precision and need to be evaluated by the radiologist for each study. The specifics of patient positioning for DXA and details of ROI
Two cubes with known vBMD of 1 g/cm³

The DXA bone area will reflect only one side of the cube.

<table>
<thead>
<tr>
<th>Volume</th>
<th>Bone area</th>
<th>BMC</th>
<th>aBMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>cube a</td>
<td>1 cm³</td>
<td>1 cm²</td>
<td>1 g</td>
</tr>
<tr>
<td>cube b</td>
<td>8 cm³</td>
<td>4 cm²</td>
<td>8 g</td>
</tr>
</tbody>
</table>

Figure 1 For 2 bones of known BMD = 1 g/cm³, the DXA-derived areal BMD will be greater in the larger bone because of the lack of accounting for the true volume of the measured bone. It should be noted that the larger cube will be stronger than the smaller cube. (Adapted from Carter et al.)

Accuracy, Precision, and Least Significant Change

It is important for the imaging specialist to understand the accuracy and precision of DXA. Accuracy refers to how closely a measured value approximates the true value as determined by a “gold standard” technique. For bone mineral content, the gold standard is the laboratory assessment of ashed bones and DXA measurements of BMC are within 7% to 9% these measurements. Precision is the reproducibility of a measurement and has short- and long-term components. It is expressed as the coefficient of variation (CV). Short-term precision reflects both the imprecision of the equipment (manufacturers report this to be less than 1%), as well as the variation in patient positioning and motion effects, (typical values are less than 2-3% for the spine, up to 5% for the hip, and 1-2% for the whole body). This component varies with each technologist and should be calculated with a repeated measures procedure. Long-term precision is a measure of machine drift and is normally less than 1%. Quality control scans of phantoms graphed over time should be reviewed by the imaging specialist for detection.

Because the DXA result is a number, the imaging specialist must be aware that the magnitude of change considered to be statistically significant varies with the precision of the measurement technique. This is expressed in terms of the least significant change (LSC) and is equal to 2.8 × %CV for the 95% confidence limit. If the %CV were 1.5%, then a change from the baseline measurement of 4.2% would be required for it to be considered significant. The LSC also can be used to suggest the timing of follow-up measurements, ie, if the LSC is 4.2% and the expected annual rate of change in the BMC or BMD is 2%, a follow-up study before 2 years have elapsed would likely result in a value not statistically different than the baseline. The annual rate of change in BMC and BMD varies considerably during childhood, with dramatic acceleration of bone mineral accrual during early puberty, especially in females. The annual rates of change for early-stage and late-stage adolescents are approximately 25% and 10% for BMC and 10% and 3% for BMD, respectively. For most pediatric conditions, follow-up examinations are obtained between 6 and 12 months.

Indications for Pediatric DXA

The International Society for Clinical Densitometry has suggested that a DXA examination should be obtained in any

vertebral compression fractures. Evaluation of the thoracic and lumbar spine can be achieved with modern DXA scanners and can identify thoracic compression fractures that would have been otherwise undiagnosed. Thus, vertebral morphologic assessment may be an important adjunct in the diagnosis of pediatric osteoporosis. DXA requires very low radiation doses. The effective dose for lumbar spine and whole body DXA is between 1 and 5 μSieverts and is less than the dose of a PA chest x-ray.
Figure 2  (A) Anteroposterior (AP) DXA image of the lumbar spine shows regions of interest from L1 to L4. The bone area and mineral content are used to derive the bone mineral density at each level. The areal density is based on the bone area, the depth dimension is not directly assessed with DXA. (B) AP DXA image of the lumbar spine shows regions of interest from L1 to L4. AP DXA image of the left hip shows regions of interest of the femoral neck, greater trochanter, and total hip. (C) Total body DXA scan with subregions of interests for trunk, extremities, and head. Note transitional lumbosacral vertebral body. (Adapted from Binkovitz and Henwood,46 with permission from Springer Science and Business Media.)

Table 1  Effect of Pediatric Versus Adult Software Analysis on Bone Area and Bone Mineral Content Results

<table>
<thead>
<tr>
<th>Region</th>
<th>Pediatric Area (cm²)</th>
<th>Pediatric BMC (g)</th>
<th>Pediatric BMD (g/cm²)</th>
<th>Adult Area (cm²)</th>
<th>Adult BMC (g)</th>
<th>Adult BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left arm</td>
<td>201</td>
<td>93</td>
<td>0.465</td>
<td>114</td>
<td>71</td>
<td>0.622</td>
</tr>
<tr>
<td>Right arm</td>
<td>196</td>
<td>97</td>
<td>0.497</td>
<td>116</td>
<td>76</td>
<td>0.655</td>
</tr>
<tr>
<td>Left ribs</td>
<td>79</td>
<td>40</td>
<td>0.507</td>
<td>75</td>
<td>39</td>
<td>0.511</td>
</tr>
<tr>
<td>Right ribs</td>
<td>98</td>
<td>51</td>
<td>0.525</td>
<td>92</td>
<td>48</td>
<td>0.525</td>
</tr>
<tr>
<td>T-spine</td>
<td>85</td>
<td>48</td>
<td>0.569</td>
<td>83</td>
<td>48</td>
<td>0.524</td>
</tr>
<tr>
<td>L-spine</td>
<td>49</td>
<td>28</td>
<td>0.50</td>
<td>33</td>
<td>20</td>
<td>0.599</td>
</tr>
<tr>
<td>Pelvis</td>
<td>179</td>
<td>136</td>
<td>0.760</td>
<td>115</td>
<td>95</td>
<td>0.829</td>
</tr>
<tr>
<td>Left leg</td>
<td>353</td>
<td>269</td>
<td>0.76</td>
<td>228</td>
<td>199</td>
<td>0.873</td>
</tr>
<tr>
<td>Right leg</td>
<td>338</td>
<td>245</td>
<td>0.724</td>
<td>226</td>
<td>187</td>
<td>0.829</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1,577</td>
<td>1,008</td>
<td>0.639</td>
<td>1,081</td>
<td>782</td>
<td>0.723</td>
</tr>
<tr>
<td>Head</td>
<td>233</td>
<td>367</td>
<td>1.572</td>
<td>233</td>
<td>367</td>
<td>1.572</td>
</tr>
<tr>
<td>Total</td>
<td>1,810</td>
<td>1,375</td>
<td>0.759</td>
<td>1,315</td>
<td>1,149</td>
<td>0.874</td>
</tr>
</tbody>
</table>

Total body DXA from a 13-year-old patient processed using pediatric and adult software analysis. Note decreased BA (1,315 cm²) and BMC (1.149 g) but increased BMD (0.874 g/cm²) with the adult technique. Low-density portions of the bone are included using the pediatric technique and thus a larger BA (1,810 cm²) with a greater BMC (1,375 g) are obtained, but the BMD (0.759 g/cm²) is lower because of the inclusion of low density “bone pixels.”

Adapted from Binkovitz and Henwood,46 with permission from Springer Science and Business Media.
child being treated or considered for treatment of osteoporosis. The National Osteoporosis Foundation lists the following indications for DXA in children: systemic long-term steroids, chronic inflammatory conditions, hypogonadism, prolonged immobilization, osteogenesis imperfecta, idiopathic juvenile osteoporosis, recurrent low-trauma fractures, and apparent osteopenia on radiographs. DXA is inappropriate for the evaluation for skeletal pain, chronic disease or traumatic fractures, without any of the additional risk factors listed previously. The National Institutes of Health and the American College of Rheumatology recommend a baseline DXA study when systemic corticosteroids will be used for greater than 2 months or when there is a significant risk for osteoporotic fracture. The American College of Radiology lists DXA of the lumbar spine and hip as highly appropriate for children at risk factor for osteoporosis.

**Pediatric DXA Interpretation**

As with other laboratory tests, the numeric value reported is meaningless without comparison to the appropriate normal controls. Once a comparison is made, the reported value is given as a percentile or a standard deviation score, the Z-score. The T-score (comparison of the current Z-score with peak adult BMD) is used in adult interpretation of DXA but should not be included in the pediatric DXA report. Because the T-score is a measure of bone density loss since early adulthood, its use in children whose BMD has yet to peak is meaningless. Because the World Health Organization’s DXA-based definitions of osteopenia and osteoporosis are in terms of T-scores, T \(-1.0\) and T \(-2.5\), respectively, a different terminology is needed for children. Some clinicians and researchers use the terms osteopenia and osteoporosis in children when Z-scores are less than \(-1.0\) and \(-2.5\), respectively. The phrase “low bone density” has been recommended for DXA reports. Importantly, the diagnosis of osteoporosis should not be made on DXA results alone but should take into account other patient factors.

Much of the research in pediatric DXA has focused on determining which factors most influence BMD and should be accounted for in the development of normative databases. Normative data provided by the DXA manufacturers historically have not included the parameters currently thought to be most important for interpretation. The factors of age, sex, ethnicity, and physiologic maturity level have been extensively studied. There are numerous published pediatric normative databases (Table 2) that were developed using a variety of scanners and processing software and are based on various combinations of demographic and physiologic patient variables. Rather than simplifying pediatric DXA inter-

<table>
<thead>
<tr>
<th>Year</th>
<th>M/F</th>
<th>Age Range</th>
<th>Input</th>
<th>Output</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>28/29</td>
<td>Newborn</td>
<td>GA, weight, height, SA</td>
<td>LBMD, LBMC</td>
<td>29</td>
</tr>
<tr>
<td>1992</td>
<td>22 total</td>
<td>1-24 mos</td>
<td>GA, weight, height, SA</td>
<td>LBMD, LBMC</td>
<td>29</td>
</tr>
<tr>
<td>1996</td>
<td>82/68</td>
<td>GA 27-42 wks</td>
<td>Weight</td>
<td>TBMC, TBMD and TBA</td>
<td>30</td>
</tr>
<tr>
<td>1991</td>
<td>84/32</td>
<td>2-17 yrs</td>
<td>Weight and Tanner</td>
<td>LBMD</td>
<td>31</td>
</tr>
<tr>
<td>1993</td>
<td>86/68</td>
<td>5-18 yrs</td>
<td>Sex and Tanner</td>
<td>TBMC, % fat</td>
<td>32</td>
</tr>
<tr>
<td>1998</td>
<td>140/201</td>
<td>4-19 yrs (L)</td>
<td>Sex and Tanner</td>
<td>TBMC, TMD, TBA</td>
<td>33,34</td>
</tr>
<tr>
<td>2002</td>
<td>188/256</td>
<td>4-20 yrs (L)</td>
<td>Sex and Tanner</td>
<td>LBMD, LBMD, TMC, % fat</td>
<td>35,36</td>
</tr>
<tr>
<td>2002</td>
<td>107/124</td>
<td>5-22 yrs</td>
<td>Sex and Tanner</td>
<td>LBMD, LBMD and TBA</td>
<td>35,36</td>
</tr>
<tr>
<td>2005</td>
<td>Up to 1,948</td>
<td>3-20 yrs</td>
<td>Sex and age</td>
<td>LBMD, FNBDM and TMD</td>
<td>37</td>
</tr>
<tr>
<td>1991</td>
<td>109/98</td>
<td>9-21</td>
<td>Sex and Tanner or age</td>
<td>LBMC, LBA, LBMD and FN BMD</td>
<td>37</td>
</tr>
<tr>
<td>1996</td>
<td>110/124</td>
<td>8-17 yrs (L)</td>
<td>Sex and age</td>
<td>LBMC, LBMD, FN BMC, FN BMC, TMC and TMD</td>
<td>23,39</td>
</tr>
<tr>
<td>1999</td>
<td>193/230</td>
<td>9-25 yrs</td>
<td>Sex, age, and ethnicity</td>
<td>LBMD, LBMD, Hip BMD, Hip BMD, FN BMD, FN BMAD, TMD and BMC/Ht</td>
<td>40</td>
</tr>
<tr>
<td>2004</td>
<td>0/422</td>
<td>12-18 yrs</td>
<td>Age, weight, and ethnicity</td>
<td>LBMD, LBMD, FN BMD and FN BMAD</td>
<td>10</td>
</tr>
<tr>
<td>2001</td>
<td>0/151</td>
<td>9-14 yrs (L)</td>
<td>Breast stage and age</td>
<td>LBMC, FN BMC, FN BMC, FA BMBMC and FA BMD</td>
<td>41</td>
</tr>
<tr>
<td>2003</td>
<td>210/249</td>
<td>3-30 yrs</td>
<td>Sex, height, or age</td>
<td>LTM, TBMC/LTM</td>
<td>49</td>
</tr>
<tr>
<td>2002</td>
<td>117/139</td>
<td>3-18.5 yrs</td>
<td>Age</td>
<td>Distal fem BMD</td>
<td>13</td>
</tr>
</tbody>
</table>

Input refers to patient parameters. Output refers to normative data provided in the reference database. Further data available online at: [http://www.stat-class.stanford.edu/pediatric-bones](http://www.stat-class.stanford.edu/pediatric-bones) and [http://www.bcm.edu/bodycomplab](http://www.bcm.edu/bodycomplab).

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interpretation, the sheer number of available normal databases has made DXA interpretation confusing and, at times, erroneous. To report the numeric result generated from the manufacturer's automated processing without consideration of factors specific to the patient being studied is unacceptable and often will lead to misdiagnoses and may result in inappropriate therapy. In fact, the diagnosis of osteoporosis in a child based on a DXA result often is a misinterpretation of the scan data. The most common causes for misdiagnosis are the use of T-scores, inappropriate normative data sets, inadequate ROIs, and inattention to short stature.

As with any other radiological study, a methodical evaluation of the results should be undertaken to minimize the risk of misdiagnosis. The imaging specialist needs to review patient data, including age, sex, ethnicity, weight, height, and Tanner stage (if provided). Patient positioning should be evaluated and ROIs analyzed for artifact and appropriateness. Comparison should be made to previous studies to insure consistency in positioning and ROI selection. Changes in patient height, weight, and Tanner stage should be noted. Once these steps have been taken, interpretation of the numeric result is performed with an appropriate database for comparison purposes selected. Ideally, this is based on data generated locally using the same equipment and technologies but this is rarely possible. More complex and scientifically rigorous analyses of DXA results have been suggested and are discussed in detail elsewhere.

**Bone Growth and BMD**

As mentioned previously, bone size affects the DXA result. Bone growth confounds DXA interpretation and is one of the major limitations of its use in pediatrics. The effect of bone size needs to be accounted for when the DXA result is compared with prior results or to normative values. These problems could be avoided, at least in part, if a true volumetric BMD was available with DXA. As this is not possible with current DXA technology, investigators have attempted to estimate bone volume using DXA and thus minimize the effect the growing skeleton has on the DXA BMD result. A second approach has been to evaluate total body BMC, TBBMC, since it is determined with greater accuracy and precision than BMD. A third approach focuses on the fundamental relationship between the mechanical stresses a bone experiences through muscle action and its mineral content. Changes in lean tissue mass explain greater than 95% of the variation in TBBMC. By incorporating lean tissue mass/height and height/age into the DXA interpretation, patients can be grouped as normal or as having a primary (bone), a secondary (muscle), or a mixed defect.

**Clinical Applications**

Normal bone mineral accrual requires adequate dietary intake and intestinal absorption of calcium and other nutrients, hepatic and renal activation of Vitamin D, normal hormone levels, and neuromuscular functioning with sufficient stress on bone to induce mineral deposition. Low BMD can result from a wide variety of childhood diseases and the treatments. This section summarizes clinical pediatric DXA and can be used to assist imagers and clinicians in DXA utilization and interpretation.

Gastrointestinal diseases may impact bone health in several ways. Poor calcium intake, as in patients with milk allergy or other causes of dairy restriction, and reduced calcium absorption, as in patients with untreated celiac disease, resulted in low BMD. Early correction of the underlying deficiency allows for normal bone mineralization to occur. In addition to poor calcium absorption, inflammatory bowel disease (IBD) likely impacts bone health through other factors, including chronic diarrhea, decreased lean tissue mass, reduced physical activity, and CS therapy. As in all chronic conditions, correction for short stature and delayed maturation will show many of these patients have normal or near-normal BMD and will better identify which patients with low lumbar BMD have significantly reduced bone mineralization. The effects of liver dysfunction on bone health are complex and may involve vitamin malabsorption, failure of vitamin D activation, calcium malabsorption, and malnutrition. Argao et al evaluated children with a variety of chronic cholestatic liver diseases and found distal radial BMC to fall quickly after birth and in infancy. The values remained low throughout childhood and reflected the severity of the underlying hepatic dysfunction. Malabsorption of fat-soluble vitamins, particularly vitamin D, was found to reduce LS and TBBMC significantly. Normalization of LS BMD and BMC in patients with childhood liver failure who were at least 1-year status after orthotopic liver transplantation is to be expected and this normalization is unaffected by the severity of bone disease or cholestasis before transplantation.

Chronic kidney diseases (CKDs) result in abnormal bone metabolism via disturbances in calcium and phosphate handling, altered vitamin D and parathyroid hormone levels and function, and altered renal clearance of aluminum and other metabolites. Additional factors that affect the BMD in patients with CKD include malnutrition, metabolic acidosis, anemia, and growth hormone abnormalities resulting in growth retardation. Several investigators have found normal TBBMD and TBBMC as well as normal LS BMD in children with CKD when the vitamin D levels were normal and DXA values were corrected for height. Boot et al reported normal LS and TBBMD in patients with CKD of relatively short duration and in the setting of adequate vitamin D replacement. Two-year follow-up of these patients demonstrated continued maintenance of normal BMD. Height-corrected LS BMD was reduced initially after transplantation because of CS treatment required for rejection, but by three years the BMD had normalized. Endocrinologic diseases disrupt the normal hormonal balance required for skeletal development. Rates of bone mineralization increase throughout puberty until peak bone mass is achieved in early adulthood. Although major differences occur based on sex and skeletal site, pubertal hormones play a critical role in bone mass acquisition. Accurate DXA evaluation of children with growth hormone deficiency...
(GHD) or idiopathic short stature (ISS) must account for their smaller bones. Children with GHD will present with low areal and volumetric LS BMD when first diagnosed. With sustained growth hormone replacement, GHR, these values have been reported to remain stable or normalize rapidly. Increases in BMD occurred even after peak height was achieved, indicating the need for GHR until peak BMD is achieved. Reproductive hormones play an important role in the acquisition of bone mineral and estrogen is known to have a protective effect against the development of osteoporosis in postmenopausal women. Several researchers have investigated the effects of hormonal birth control use on BMD in adolescent girls.

The trend toward lower estrogen levels in oral contraceptives (OCs) has been associated with decreased BMD in adolescent girls who use OCs. Progestrone-mediated implantable contraceptives (Depo-Provera) has been shown to inhibit bone mineral acquisition in the LS and hip in adolescent girls. The extent of this reduction appears to correlate with duration of treatment and can be lessened with supplemental estrogen. Partial or full BMD recovery can occur after cessation of treatment and can be facilitated with increased physical activity and adequate calcium and vitamin D intake. Girls with anorexia nervosa have been found to have decreased BMD at multiple skeletal sites. These reductions are thought to be the result of a combination of nutritional (decreased calcium and caloric intake), hormonal (decreased estrogen levels and delayed puberty), and mechanical (decreased lean tissue mass) factors. With normal caloric intake and return of menses, there is biochemical evidence of increased bone turnover; however, BMD levels remain low and Z-scores may continue to fall. It is not known if full BMD recovery will occur by early adulthood. Estrogen replacement with OC and vigorous exercise can protect against BMD loss in anorexia nervosa.

Chronic pulmonary diseases result in low BMD because of chronic hypoxia, chronic CS use, and reduced lean tissue mass. Additional factors affecting many patients with cystic fibrosis (CF), such as reduced gastrointestinal absorption of calcium and vitamin D and reduced testosterone levels, will also result in low BMD. Because of the multifactorial nature of reduced BMD in CF, BMD Z-scores often reflect the severity of illness. Clinically stable children with mild CF have been shown to have normal BMD, and adolescents and adults with CF have accelerated bone loss over time reflecting disease progression. Bludhikanok suggested that bisphosphonates might be beneficial in CF patients with accelerated bone loss who require CS therapy. The benefits of intravenous bisphosphonates and oral bisphosphonate treatment in CF have been confirmed with increases in LS and hip BMD. Asthma may inhibit normal bone metabolism due to chronic hypoxia and decreased physical activity. Additionally, asthmatic patients are treated with both oral and inhaled CS to reduce airway inflammation. Patients treated with low or moderate levels of inhaled CS have been shown to have normal BMD Z-scores when compared with asthmatic controls but reduced BMD Z-scores when compared with nonasthmatic controls because of the shorter stature of asthmatics. Allen and Harris found significant reductions in BMD in asthmatic children receiving high doses of inhaled CS.

Hematologic diseases, including chronic anemias, can affect bone structure and density through bone marrow hyperplasia, resulting in an expansion of the medullary space, trabecular coarsening, cortical thinning, and vaso-occlusion leading to medullary and diaphyseal infarction. Additional factors for reduced BMD include reduced lean tissue mass, decreased physical activity, low calcium intake, and low vitamin D levels and hypogonadism and, in the case of thalassemia, endocrine dysfunction. Investigators found low BMD in both pre- and postpubertal children with sickle cell anemia and that low BMD correlates with disease severity. These changes were found to persist into adulthood. Vogiatzi and Beningo evaluated children with thalassemia major and found reduced BMD at diagnosis and showed further reductions at follow-up. Patients with hemophilia are at risk for osteoporosis because of reduced levels of physical activity and sports, particularly those involving running, jumping, and axial loading of the skeleton. The severity of hemophilic arthropathy can be quantitated using a clinically derived joint score, which has been found to correlate with BMD. Low BMD was independent of height and weight but correlated with disease severity and extent. These changes are expected to persist into adulthood.

Oncologic diseases can result in low short- and long-term BMD in patients/survivors through multiple factors. These include pubertal status at diagnosis, type of malignancy, local versus systemic disease (sarcomas and central nervous system tumors versus leukemia), initial versus prolonged disease-related disability (malnutrition and immobilization versus amputation), chemotherapy, and radiation therapy that may cause growth hormone or gonadal dysfunction. Acute lymphocytic leukemia (ALL) is the most common childhood malignancy, but because of its excellent prognosis, most children with ALL survive into adulthood. Arinoski found reduced BMD up to 20 years after treatment. The use of high-dose methotrexate (MTX) and whole brain irradiation (WBI) were found to correlate with low BMD. Differing results were presented by Brennan, who also reported significantly reduced LS, hip, and distal radial BMD in long-term survivors of ALL but found no statistically significant correlation of BMD with WBI, growth hormone status, or height Z-scores. These results suggest that the low BMD found in their patients was more likely related to effects of chemotherapy rather than WBI. van der Sluis et al found normal LS and TBBMD a mean of 10 years after ALL treatment that included high-dose MTX and CS but not WBI. Their patients had all been prepubertal at the time of initial diagnosis and none had signs of significant gonadal or growth hormone dysfunction at the time of follow-up. These and other authors concluded that the deleterious effects of ALL and its treatment in childhood on BMD may be caused by WBI but, in its absence, BMD will normalize after puberty in early adulthood.

Jarfelt examined bone turnover and growth hormone status with respect to physical activity levels and BMD in adult survivors of childhood ALL. The patients were all pre-
pubertal at the end of treatment and had been treated with high doses of CS and MTX. No patient had evidence for gonadal or endocrine dysfunction. The BMD values were normal for the group. Only the level of physical fitness at follow-up correlated positively with BMD. The authors stressed the importance of physical activity in restoring and maintaining normal BMD in survivors of childhood ALL. In summary, children with ALL will have reduced BMD during treatment and shortly thereafter. The recuperative capacity in young children is high, and normal BMD should be expected even after high dose MTX and CS. The role of adequate physical activity is being increasingly stressed as an important factor in normal BMD recovery. Children who have survived ALL may be at risk for low BMD as adults if they have confounding factors such as gonadal dysfunction.

There are only limited data regarding the effects of other childhood malignancies on BMD. Aisenberg et al.117 and Vassilopoulou-Sellin et al.118 found reduced femoral neck and TBBMD in young adult survivors of various childhood cancers. Gonadal dysfunction caused by pelvic or WBI was the factor most strongly correlated with reduced BMD. CS treatment did not correlate with low BMD. Nysom et al.119 reported normal size-adjusted TBBMC in adult survivors of childhood lymphoma. They found no relationship between TBBMC and cumulative MTX or CS doses. Kelly et al.120 evaluated adult survivors of various pediatric solid tumors and found reduced BMD in at least one site in half of the patients. Only the total number of chemotherapeutic agents was correlated with reduced BMD. Five of 6 extremities involved with a bone sarcoma showed reduced BMD. Similar results were found in a group of sarcoma survivors reported by Ruza.121 Interestingly, they found that those diagnosed before puberty had more severe BMD reductions later in life, which may be attributable to the extensive physical disabilities associated with amputations and limb salvage procedures in these patients. Odame et al.122 found that patients with childhood brain tumors treated with cranial irradiation had reduced LS and TBBMD and that these were correlated with reduced physical activity and poorer quality of life. The authors postulated that the higher radiation doses used for the treatment of brain tumors had a profound effect on long-term BMD compared with the relatively lower doses used for WBI in the treatment of ALL.

Neurologic, connective tissue, and muscular diseases interfere with the fundamental relationship between mechanical forces exerted on bone and bone accrual. Children with cerebral palsy, CP, are at increased risk for osteoporotic fractures and frequently, the assessment of the LS and hips with DXA will be impossible due to difficulties in positioning patients with contraction deformities, muscular spasm-induced motion artifacts, or orthopedic hardware-related artifacts. Because of these limitations, Harcke12 suggested scanning the distal femur with these patients positioned on their side. Distal femoral BMD was found to correlate with hip BMD and this technique yielded highly reproducible BMD data.13

In a study of children with CP, Henderson et al.123 demonstrated reduced LS and hip BMD. Nutritional and ambulatory status were found to be the best predictors of BMD. In children with moderate to severe CP, Henderson et al.124 found distal femur and LS BMD to be markedly reduced and both closely correlated with disease severity. Distal femoral BMD was negatively correlated with age, indicating progressive bone mineral deficits as children with CP age. The lack of a strong correlation between LS BMD and fracture risk in the lower extremities emphasizes the need for direct assessment of the distal femur with DXA in CP patients. In a prospective longitudinal study in CP patients, Henderson et al.125 found treatment with bisphosphonates for 1 year resulted in a substantial increase in distal femoral BMD in children with quadriplegic CP. The improvement was sustained for at least 6 months after the last treatment. However, Bachrach et al.126 found that LS BMD returned to baseline values 2 years after bisphosphonate therapy was terminated. Importantly, despite the lack of sustained BMD improvement, no patient had a fracture during the treatment or follow-up periods.

Quan127 found reduced forearm BMD in children with meningomyelocele, MMC. Patients with a history of fracture had substantially lower forearm BMD than those without a fracture history. The low upper-extremity BMD in these patients with preserved upper-extremity function may indicate systemic as well as local factors affecting BMD. Valtonen et al.128 found normal forearm and LS BMD in adult patients with MMC, but reduced hip BMD in one-third of the patients. There was a trend of low hip BMD in the nonambulatory compared with ambulatory patients but not for the lumbar spine. This dissociation of LS and hip BMD values was thought to be due to axial loading on the LS in upright patients.

Rheumatoid diseases have long been known to affect bone health negatively. Disease extent, severity, subsequent disability, and CS therapy negatively impact bone mineralization. Pepmueller et al.129 and Pereira et al.130 found decreased regional, LS, and TBBMD in patients with juvenile rheumatoid arthritis (JRA). The decrease was more severe in children with longer disease duration and was similar for oligoarthritis and polyarthritis. Lien et al.131 found decreased TBBMC and TBBMD in patients with juvenile idiopathic arthritis. Disease duration and severity correlated with TBBM but not CS therapy. Henderson et al.132 found no statistically significant difference in TBBMD in prepubertal children with mild-to-moderate JRA and no history of CS treatment when compared with control patients. When a similar study was performed on CS naive older girls with mild-to-moderate JRA, Henderson et al.133 found decreased TBBMC.

As with other chronic diseases of childhood, it appears that persistent disease activity through puberty results in decreased BMC. Mul et al.134 found marked reductions in LS BMD and BMC in children with rheumatic diseases treated for at least 1 year with high-dose CS. Bianchi135 found that long-term MTX therapy for JRA did not result in reduced LS or TBBMD. In summary, prepubertal children with JRA of mild or moderate severity without history of CS treatment will have TBBMD similar to normal children. With increasing disease severity and duration, especially through puberty, TBBMC will decrease when compared with normal children. These changes are in contrast to the normal DXA findings
reported in patients with juvenile systemic lupus erythematosus, JSLE.\textsuperscript{136,137} Unlike patients with JRA, JSLE patients typically do not have bone and joint involvement and thus are more likely to have preserved BMD. Factors that negatively impact bone health include immobility, limited exposure to sunlight, and CS therapy.

In a longitudinal study of boys with Duchenne muscular dystrophy, DMD, Larson et al\textsuperscript{138} found LS and hip BMD correlated with functional mobility level, ie, ambulatory boys had higher LS BMD compared with nonambulatory boys. Hip BMD was decreased before loss of ambulation and showed progressive reductions over time. Bianchi\textsuperscript{139} found decreased LS and TBBMD in ambulatory boys with DMD when compared with healthy boys and was more severely reduced in the subset of DMD patients treated CS. Hawker\textsuperscript{140} found an increase in LS and TBBMD after 2 years of treatment with alendronate, supplemental calcium, and vitamin D. Studies of a small number of children with dermatomyositis have found low LS BMD that worsens with ongoing CS therapy.\textsuperscript{141,142} These patients showed improved LS BMD with bisphosphonate therapy for osteoporosis-related compression fractures.\textsuperscript{141}

Osteogenesis imperfecta (OI) includes a spectrum of genetic disorders of collagen synthesis resulting in abnormal skeletal and connective tissues. Reduced BMD and other factors result in fragile bones and multiple fractures. Fracture occurrence and DXA findings in children with OI vary with subtype with few fractures and normal or near normal DXA findings in type I and more frequent fractures and marked reductions in BMD in types III and IV.\textsuperscript{143,144} Type II typically results in perinatal demise. Because as many as 40% of patients with OI will have normal BMD and BMC, a normal DXA study does not preclude the diagnosis of OI or distinguish cases of OI from nonaccidental injuries.\textsuperscript{145} In recent years, clinical trials using bisphosphonates, especially IV pamidronate, in OI have yielded impressive results with multiple studies demonstrating increases in LS, hip and TBBMD and improved quality of life.\textsuperscript{145,146} Patients with the lowest baseline bone mass experienced the most significant gains with treatment. Improved mobility, ambulation, muscle force and reduced chronic pain and fatigue not only lead to improved quality of life, but also afford patients the stimulus of physical activity that is known to be beneficial to bone. Increased bone mass in the skull following pamidronate therapy for patients with OI implies that the drug also has a direct effect on bone accrual irrespective of physical activity.\textsuperscript{147} The theoretical concern that bisphosphonate therapy might negatively impact linear growth in children with OI has not been shown to be true.\textsuperscript{149}

References


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