ELSEVIER

Seminars in
NUCLEAR
MEDICINE

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

Larry A. Binkovitz, MD,* Maria J. Henwood, DO,† and Paul Sparke‡

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.[1] 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[2] 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.[3] 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).[4]

*Department of Radiology, Columbus Children's Hospital, Columbus, OH.
†Department of Endocrinology, Columbus Children's Hospital, Columbus, OH.
‡Capital University, Columbus, OH.
Significant portions of this article were adapted from two of the authors' previous works: Binkovitz LA, Henwood MJ: Pediatric DXA: Technique and interpretation. Pediatr Radiol 37:21-31, 2007; and Binkovitz LA, Sparke P, Henwood MJ: Pediatric DXA: Clinical applications. Pediatr Radiol 2007 Apr 13 [Epub ahead of print]; with kind permission from Springer Science and Business Media.
Address reprint requests to Larry A. Binkovitz, MD, Department of Radiology, Columbus Children's Hospital, 700 Children's Way, Columbus OH 43205. E-mail: binkovil@chi.osu.edu

Areal Versus Volumetric BMD

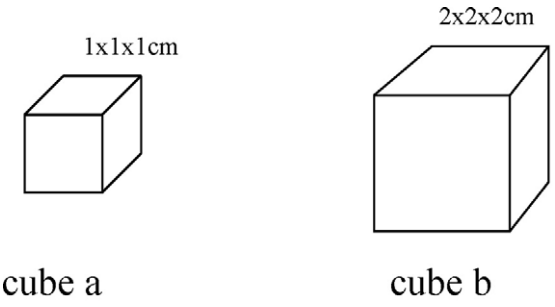
DXA relies on the differential absorption of x-rays to distinguish tissues of different radiographic density. Additionally, DXA can quantify (in grams) the bone mineral content (BMC) at various body sites. By selecting regions of interest (ROIs), a bone area (BA; units of cm^2) is delineated. The BMD is measured directly (in units of g/cm^2) 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.[5] Specifically, smaller bones will be found to have lower aBMD than larger bones even when the vBMD is the same (Fig. 1).[5] 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.[4]

Technical Aspects of DXA Performance

Patient positioning and ROI selection require precision[6] and need to be evaluated by the radiologist for each study. The specifics of patient positioning for DXA and details of ROI

0001-2998/07/$-see front matter
doi:10.1053/j.semnuclmed.2007.02.007



Two cubes with known vBMD of 1 g/ cm^3

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

	Volume	*Bone area*	*BMC*	*aBMD*
cube a	1 cm^3	1 cm^2	1 g	1 g/cm^2
cube b	8 cm^3	4 cm^2	8 g	2 g/cm^2

Figure 1 For 2 bones of known BMD = 1 g/cm^2, 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.[5])

selection can be found in standard DXA textbooks and are illustrated in Figure 2. Because of the normally low BMD in young children, software analysis is modified to improve edge detection of lower-density bone. Such algorithms have been validated in healthy, obese, and chronically ill children.[7] Using an adult algorithm will significantly overestimate BMD in a child compared with the results obtained using the pediatric low-density algorithm (Table 1) because lower density "bone pixels" will be excluded using the adult algorithm.[8,9]

The sites selected for BMD analysis needs to provide a robust evaluation of bone density status. If technically feasible, the DXA examination should include the lumbar spine and total body BMD.[3] There is normative DXA data for the adolescent hip, especially in girls,[10] and for these patients this site may be a useful addition to the standard examination. When evaluating group data of normal children, there is usually close correlation of BMD between the lumbar spine and hip[11] but for individuals, when the DXA results deviate from normal, there is less concordance between these 2 sites. If evaluation of the spine and hip is not feasible because of extensive orthopedic hardware or patient positioning issues, DXA of the forearm or distal femur[12,13] may be performed. However, there are few normative data for pediatric forearm studies and the value obtained may be useful only when compared with subsequent studies. Because of its lack of areal density-related errors, total body BMC is preferred for the assessment of bone status by some clinicians and researchers.[14] The identification of a thoracic body compression deformity in patients with low bone density has significant prognostic value, indicating a greater risk of subsequent 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.[15] 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[16] and is less than the dose of a PA chest x-ray.

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[17,18] 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).[16,19,20] This component varies with each technologist and should be calculated with a repeated measures procedure.[2] 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.[17]

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.[2] 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 pubertal,[21-23] especially in females.[22] 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.[24] 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

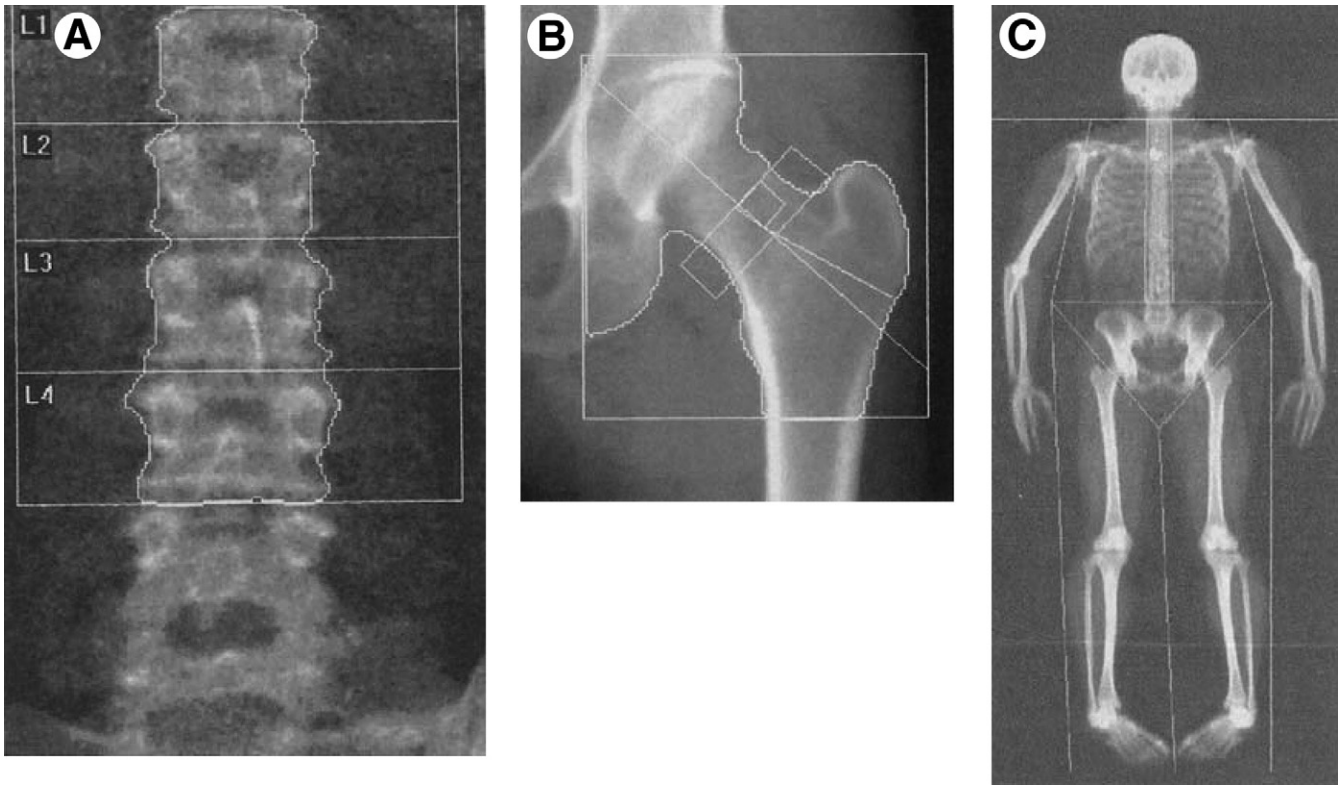


Figure 2 (A) Anteroposterior (AP) DXA image of the lumbar spine shows regions of interest from L1 to L4. The bone area and mineral content are used to derive the bone mineral density at each level. The areal density is based on the bone area; the depth dimension is not directly assessed with DXA. (B) 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

Region	Pediatric Area (cm^2)	Pediatric BMC (g)	Pediatric BMD (g/cm^2)	Adult Area (cm^2)	Adult BMC (g)	Adult BMD (g/cm^2)
Left arm	201	93	0.465	114	71	0.622
Right arm	196	97	0.497	116	76	0.655
Left ribs	79	40	0.507	75	39	0.511
Right ribs	98	51	0.525	92	48	0.525
T-spine	85	48	0.569	83	48	0.524
L-spine	49	28	0.50	33	20	0.599
Pelvis	179	136	0.760	115	95	0.829
Left leg	353	269	0.76	228	199	0.873
Right leg	338	245	0.724	226	187	0.829
Subtotal	1,577	1,008	0.639	1,081	782	0.723
Head	233	367	1.572	233	367	1.572
Total	1,810	1,375	0.759	1,315	1,149	0.874

Total body DXA from a 13-year-old patient processed using pediatric and adult software analysis. Note decreased BA (1,315 cm^2) and BMC (1,149 g) but increased BMD (0.874 g/cm^2) with the adult technique. Low-density portions of the bone are included using the pediatric technique and thus a larger BA (1,810 cm^2) with a greater BMC (1,375 g) are obtained, but the BMD (0.759 g/cm^2) 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.

Table 2 Normative Databases for Pediatric BMD

Year	M/F	Age Range	Input	Output	Reference
1992	28/29	Newborn	GA, weight, height, SA	LBMD, LBMC	29
1992	22 total	1-24 mos	GA, weight, height, SA	LBMD, LBMC	29
1996	82/68	GA 27-42 wks	Weight	TBMC, TBMD and TBA	30
1991	84/32	2-17 yrs	Weight and Tanner	LBMD	31
1993	86/68	5-18 yrs	Sex and Tanner	TBMC, % fat	32
1998	140/201	4-19 yrs (L)	Sex and Tanner	TBMC, TBMD, TBA	33,34
2002	188/256	4-20 yrs (L)	Sex and age	LBMD. LBMAD, TBMC, % fat	35,36
			Sex and Tanner	LBMD. LBMAD, TBMC and TBMD	35,36
2002	107/124	5-22 yrs	Sex and age	TBMC and TBA	37
			Sex and height	TBA	37
			Sex and TBMC	TBMD	37
2005	Up to 1,948	3-20 yrs	Sex and age	LBMD, FNBMD and TBMD	38
1991	109/98	9-21	Sex and Tanner or age	LBMC, LBA, LBMD and FN BMD	22
1996	110/124	8-17 yrs (L)	Sex and age	LBMC, LBMD, FN BMC, FN BMC, TBMC and TBMD	23,39
1999[1]	193/230	9-25 yrs	Sex, age, and ethnicity	LBMD, LBMAD, Hip BMD, Hip BMAD, FN BMD, FN BMAD, TBMD and BMC/Ht	40
2004	0/422	12-18 yrs	Age, weight, and ethnicity	LBMD, LBMAD, FN BMD and FN BMAD	10
2001[2]	0/151	9-14 yrs (L)	Breast stage and age	LBMC, LBMD, FN BMC, FNBMD, FA BMBMC and FA BMD	41
2003	210/249	3-30 yrs	Sex, height, or age	LTM, TBMC/LTM	49
2002	117/139	3-18.5 yrs	Age	Distal fem BMD	13

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 and http://www.bcm.edu/bodycomplab.

GA, gestational age; L, longitudinal study; SA, surface area; T, total; L, lumbar; FN, femoral neck; FA, forearm; and BMAD, bone mineral apparent density.

Adapted from Binkovitz and Henwood,[46] with permission from Springer Science and Business Media.

child being treated or considered for treatment of osteoporosis.[3] 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.[14] DXA is inappropriate for the evaluation for skeletal pain, chronic disease or traumatic fractures, without any of the additional risk factors listed previously.[16] 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.[25,26] The American College of Radiology lists DXA of the lumbar spine and hip as highly appropriate for children at risk factor for osteoporosis.[27]

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.[3] 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.[3] 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.[3] 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)[28-40] 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-

pretation, the sheer number of available normal databases has made DXA interpretation confusing and, at times, erroneous.[41] 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.[42] In fact, the diagnosis of osteoporosis in a child based on a DXA result often is a misinterpretation of the scan data.[43] 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 technologists but this is rarely possible. More complex and scientifically rigorous analyses of DXA results have been suggested[44,45] and are discussed in detail elsewhere.[46]

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.[43,47-49] A second approach has been to evaluate total body BMC, TBBMC, since it is determined with greater accuracy and precision than BMD.[50] 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.[31,34] 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.[31]

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,[51-53] and reduced calcium absorption, as in patients with untreated celiac disease,[54] resulted in low BMD. Early correction of the underlying deficiency allows for normal bone mineralization to occur.[55-57] 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.[58,59] As in all chronic conditions, correction for short stature and delayed maturation will show many of these patients have normal or near-normal BMD[60,61] 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[62] 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.[63] Normalization of LS BMC and BMD 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.[64]

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.[65-67] Boot et al[67] 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 transplantion because of CS treatment required for rejection, but by three years the BMD had normalized.[65,68-70]

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,[21] 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.[46] Children with GHD will present with low areal[71] and volumetric LS[72] BMD when first diagnosed. With sustained growth hormone replacement, GHR, these values have been reported to remain stable[72] or normalize rapidly.[73] Increases in BMD occurred even after peak height was achieved, indicating the need for GHR until peak BMD is achieved.[74,75] 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.[76,77] Progesterone-mediated implantable contraceptives (Depo-Provera) has been shown to inhibit bone mineral acquisition in the LS and hip in adolescent girls[78-80] The extent of this reduction appears to correlate with duration of treatment and can be lessened with supplemental estrogen.[80] 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.[81-83] 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.[80] 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.[84]

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,[85-87] and adolescents and adults with CF have accelerated bone loss over time reflecting disease progression.[88-91] Bhudhikanok[92] suggested that bisphosphonates might be beneficial in CF patients with accelerated bone loss who require CS therapy. The benefits of intravenous[93,94] and oral[95] 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.[96-99] Allen[100] and Harris[101] 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.[102-105] These changes were found to persist into adulthood.[106] Vogiatzi[107] and Beningo[108] 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.[109] Low BMD was independent of height and weight but correlated with disease severity and extent. These changes are expected to persist into adulthood.[110]

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[111] 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 Brennon,[112] 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[113] 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.[114,115]

Jarfelt[116] 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, Harcke[12] 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.

Quan[127] 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. Bianchi[135] 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.[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[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[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[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.[141,142] These patients showed improved LS BMD with bisphosphonate therapy for osteoporosis-related compression fractures.[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.[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.[143] 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.[145-148] 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.[147] The theoretical concern that bisphosphonate therapy might negatively impact linear growth in children with OI has not been shown to be true.[149]

References

1. Lentle BC, Prior JC: Osteoporosis: What a clinician expects to learn from a patient's bone density examination. Radiology 228:620-628, 2003
2. Bonnick SL, Johnston CC Jr., Kleerekoper M, et al: Importance of precision in bone density measurements. J Clin Densitom 4:105-110, 2001
3. The Writing Group for the ISCD: Position Development Conference; Diagnosis of osteoporosis in men, premenopausal women, and children. J Clin Densitom 7:17-26, 2004
4. Bachrach LK: Dual energy x-ray absorptiometry (DEXA) measurements of bone density and body composition: Promise and pitfalls. J Pediatr Endocrinol Metab 13:983-988, 2000
5. Carter DR, Bouxsein ML, Marcus R: New approaches for interpreting projected bone densitometry data. J Bone Miner Res 7:137-145, 1992
6. Hammami M, Koo WW, Hockman EM: Technical considerations for fan-beam dual-energy x-ray absorptiometry body composition measurements in pediatric studies. J Parenter Enteral Nutr 28:328-333, 2004
7. Leonard MB, Feldman HI, Zemel BS, et al: Evaluation of low density spine software for the assessment of bone mineral density in children. J Bone Miner Res 13:1687-1690, 1998
8. Cheng S, Nicholson PH, Kroger H, et al: Differences in estimates of change of bone accrual and body composition in children because of scan mode selection with the prodigy densitometer. J Clin Densitom 8:65-73, 2005
9. Simpson DE, Dontu VS, Stephens SE, et al: Large variations occur in bone density measurements of children when using different software. Nucl Med Commun 26:483-487, 2005
10. Cromer BA, Binkovitz L, Ziegler J, et al: Reference values for bone mineral density in 12- to 18-year-old girls categorized by weight, race, and age. Pediatr Radiol 34:787-792, 2004
11. Henderson RC: The correlation between dual-energy x-ray absorptiometry measures of bone density in the proximal femur and lumbar spine of children. Skeletal Radiol 26:544-547, 1997
12. Harcke HT, Taylor A, Bachrach S, et al: Lateral femoral scan: an alternative method for assessing bone mineral density in children with cerebral palsy. Pediatr Radiol 28:241-246, 1998
13. Henderson RC, Lark RK, Newman JE, et al: Pediatric reference data for dual x-ray absorptiometric measures of normal bone density in the distal femur. AJR Am J Roentgenol 178:439-443, 2002
14. Ellis KJ, Shypailo RJ, Hardin DS, et al: Z score prediction model for assessment of bone mineral content in pediatric diseases. J Bone Miner Res 16:1658-1664, 2001
15. Makitie O, Doria AS, Henriques F, et al: Radiographic vertebral morphology: A diagnostic tool in pediatric osteoporosis. J Pediatr 146: 395-401, 2005
16. National Osteoporosis Society: A Practical Guide to Bone Densitometry in Children. Bath, UK, National Osteoporosis Society, 2004
17. Wahner HW, Fogelman I: The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice. Cambridge, Martin Dunnitz, 1994
18. Ho CP, Kim RW, Schaffler MB, et al: Accuracy of dual-energy radiographic absorptiometry of the lumbar spine: Cadaver study. Radiology 176:171-173, 1990
19. Margulies L, Horlick M, Thornton JC, et al: Reproducibility of pediatric whole body bone and body composition measures by dual-energy x-ray absorptiometry using the GE lunar prodigy. J Clin Densitom 8:298-304, 2005
20. Glastre C, Braillon P, David L, et al: Measurement of bone mineral content of the lumbar spine by dual energy x-ray absorptiometry in normal children: Correlations with growth parameters. J Clin Endocrinol Metab 70:1330-1333, 1990
21. McCormick DP, Ponder SW, Fawcett HD, et al: Spinal bone mineral density in 335 normal and obese children and adolescents: Evidence for ethnic and sex differences. J Bone Miner Res 6:507-513, 1991
22. Bonjour JP, Theintz G, Buchs B, et al: Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab 73:555-563, 1991
23. Faulkner RA, Bailey DA, Drinkwater DT, et al: Regional and total body bone mineral content, bone mineral density, and total body tissue composition in children 8-16 years of age. Calcif Tissue Int 53:7-12, 1993
24. Sabatier JP, Guaydier-Souquieres G, Benmalek A, et al: Evolution of lumbar bone mineral content during adolescence and adulthood: A longitudinal study in 395 healthy females 10-24 years of age and 206 premenopausal women. Osteoporos Int 9:476-482, 1999

25. Osteoporosis Prevention, Diagnosis, and Therapy. Available at: http://consensus.nih.gov/2000/2000Osteoporosis111html.htm. Accessed March 14, 2007
26. American College of Rheumatology. Practice guidelines. Available at: http://www.rheumatology.org/publications/guidelines/index.asp?aud=mem. Accessed March 14, 2007
27. http://www.acr.org/sacr/bin.asp?TrackID=&SID=1&DID=11796&CID=1206&VID=2 &DOC=File.PDF
28. Salle BL, Braillon P, Glorieux FH, et al: Lumbar bone mineral content measured by dual energy x-ray absorptiometry in newborns and infants. Acta Paediatr 81:953-958, 1992
29. Koo WWK, Walters J, Bush AJ, et al: Dual-energy x-ray absorptiometry studies of bone mineral status in newborn infants. J Bone Miner Res 11:997-1002, 1996
30. Southard RN, Morris JD, Mahan JD: Bone mass in healthy children: Measurement with quantitative DX. Radiology 179:735-738, 1991
31. Hogler W, Briody J, Woodhead HJ, et al: Importance of lean mass in the interpretation of total body densitometry in children and adolescents. J Pediatr 143:81-88, 2003
32. Leonard MB, Propert KJ, Zemel BS, et al: Discrepancies in pediatric bone mineral density reference data: potential for misdiagnosis of osteopenia. J Pediatr 135:182-188, 1999
33. van Coeverden SCCM, de Ridder CM, Roos JC, et al: Pubertal maturation characteristics and the rate of bone mass development longitudinally toward menarche. J Bone Miner Res 16:774-778, 2001
34. Crabtree NJ, Kibirige MS, Fordham JN, et al: The relationship between lean body mass and bone mineral content in paediatric health and disease. Bone 35:965-972, 2004
35. Ponder SW, McCormick DP, Fawcett HD, et al: Spinal bone mineral density in children aged 5.00 through 11.99 years. Am J Dis Child 144:1346-1348, 1990
36. Boot AM, Bouquet J, de Ridder MAJ, et al: Determinants of body composition measured by dual-energy x-ray absorptiometry in Dutch children and adolescents. Am J Clin Nutr 66:232-238, 1997
37. van der Sluis IM, de Ridder MAJ, Boot AM, et al: Reference data for bone density and body composition measured with dual energy x-ray absorptiometry in white children and young adults. Arch Dis Child 87:341-347, 2002
38. Faulkner RA, Bailey DA, Drinkwater DT, et al: The densitometry in Canadian children 8-17 years of age. Calcif Tissue Int 59:344-351, 1996
39. Molgaard C, Thomsen BL, Michaelsen KF: Influence of weight, age and puberty on bone size and bone mineral content in healthy children and adolescents. Acta Paediatr 87:494-499, 1998
40. Rico H, Revilla LF, Villa ER, et al: Body composition in children and Tanner's stages: A study with dual-energy x-ray absorptiometry. Metabolism 42:967-970, 1993
41. Leonard MB, Propert KJ, Zemel BS, et al: Discrepancies in pediatric bone mineral density reference data: Potential for misdiagnosis of osteopenia. J Pediatr 135:182-188, 1999
42. Whyte MP, Wenkert D, Clements KL, et al: Bisphosphonate-induced osteopetrosis. N Engl J Med 349:457-63, 2003
43. Gafni RI, Baron J: Overdiagnosis of osteoporosis in children due to misinterpretation of dual-energy x-ray absorptiometry (DEXA). J Pediatr 144:253-257, 2004
44. Molgaard C, Thomsen BL, Prentice A, et al: Whole body bone mineral content in healthy children and adolescents. Arch Dis Child 76:9-15, 1997
45. Molgaard C, Michaelsen KF: Evaluation of whole body DXA scans in children. Bone 36:S73-S74, 2005
46. Binkovitz LA, Henwood MJ: Pediatric DXA technique and interpretation Pediatr Radiol 37:21-31, 2007
47. Katzman DK, Bachrach LK, Carter DR, et al: Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. J Clin Endocrinol Metab 73:1332-1339, 1991
48. Kroger H, Kotaniemi A, Vainio P: Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. Bone Miner 17:75-85, 1992
49. Lu PW, Cowell CT, Lloyd-Jones SA, et al: Volumetric bone mineral density in normal subjects, aged 5-27 years. J Clin Endocrinol Metab 81:1586-1590, 1996
50. Wren TAL, Liu X, Pitukcheewanont P, et al: Bone acquisition in healthy children and adolescents: comparisons of dual-energy x-ray absorptiometry and computed tomography measures. J Clin Endocrinol Metab 90:1925-1928, 2005
51. Henderson RC, Hayes PRL: Bone mineralization in children and adolescents with a milk allergy. Bone Miner 27:1-12, 1994
52. Infante D, Tormo R: risk of inadequate bone mineralizaton in diseases involving long-term suppression of dairy products. J Pediatr Gastroenterol Nutr 30:310-313, 2000
53. Rockwell JEP, Williams SM, Taylor RW, et al: Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. Osteoporos Int 15:1016-1023, 2005
54. Kalayci AG, Kkansu A, Girgin N, et al: Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. Pediatrics 108:e89, 2001
55. Barera G, Beccio S, Proverbio MC, et al: Longitudinal changes in bone metabolism and bone mineral content in children with celiac disease during consumption of a gluten-free diet. Am J Clin Nutr 79:148-154, 2004
56. Tau C, Mautalen C, De Rosa S, et al: Bone mineral density in children with celiac disease. Effect of a Gluten-free diet. Eur J Clin Nutr 60: 358-363, 2006
57. Szathmari M, Tulassay T, Arato A, et al: Bone mineral content and density in asymptomatic children with celiac disease on a gluten-free diet. Eur J Gastroenterol Hepatol 13:419-424, 2001
58. Boot AM, Bouquet J, Krenning EP, et al: Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 42:188-194, 1998
59. Ahmed SF, Horrocks IA, Patterson T, et al: Bone mineral assessment by dual energy x-ray absorptiometry in children with inflammatory bowel disease: Evaluation by age or bone area. J Pediatr Gastroenterol Nutr 38:276-281, 2004
60. Burnham JM, Shults J, Semeao E, et al: Whole body BMC in pediatric Crohn disease: Iindependent effects of altered growth, maturation, and body composition. J Bone Miner Res 19:1961-1968, 2004
61. Walther F, Fusch C, Radke M, et al: Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. J Pediatr Gastroenterol Nutr 43:42-51, 2006
62. Argao EA, Specker BL, Heubi JE: Bone mineral content in infants and children with chronic cholestatic liver disease. Pediatrics 91:1151-1154, 1993
63. Olsen IE, Ittenbach RF, Rovner AJ, et al: Deficits in size-adjusted bone mass in children with Alagille Syndrome. J Pediatr Gastroenterol Nutr 40:76-82, 2005
64. D'Antiga L, Ballan D, Luisetto G, et al: Long-term outcome of bone mineral density in children who underwent a successful liver transplantation. Transplantation 78:899-903, 2004
65. Ahmed SF, Russell S, Rashid R, et al: Bone mineral content, corrected for height or bone area, measured by DXA is not reduced in children with chronic renal disease or in hypoparathyroidism. Pediatr Nephrol 20:1466-1472, 2005
66. Acott PD, Crocker JFS, Wong JA: Decreased bone mineral density in the pediatric renal transplant population. Pediatr Transplant 7:358-363, 2003
67. Boot AM, Nauta J, de Jong MC, et al: Bone mineral density, bone metabolism and body composition of children with chronic renal failure, with and without growth hormone treatment. Clin Endocrinol 49:665-672, 1998
68. van der Sluis IM, Boot AM, Nauta J, et al: Bone density and body composition in chronic renal failure: Effects of growth hormone treatment. Pediatr Nephrol 15:221-228, 2000
69. Feber J, Cochat P, Braillon P, et al: Bone mineral density after renal transplantation in children. J Pediatr 125:870-875, 1994
70. Klaus G, Paschen C, Wuster C, et al: Weight-/height-related bone mineral density is not reduced after renal transplantation. Pediatr Nephrol 12:343-348, 1998
71. Saggese G, Baroncelli GI, Bertelloni S, et al: The effect of long-term

growth hormone (GH) treatment on bone mineral density in children with GH deficiency. Role of GH in the attainment of peak bone mass. J Clin Endocrinol Metab 81:3077-3083, 1996
72. Hogler W, Briody J, Moore B, et al: Effect of growth hormone therapy and puberty on bone and body composition in children with idiopathic short stature and growth hormone deficiency. Bone 37:642-650, 2005
73. Lanes R, Gunczler P, Esaa S, et al: The effect of short- and long-term growth hormone treatment on bone mineral density and bone metabolism of prepubertal children with idiopathic short stature: A 3-year study. Clin Endocrinol 57:725-730, 2002
74. Baroncelli GI, Bertelloni S, Sodini F, et al: Longitudinal changes of lumbar bone mineral density (BMD) in patients with GH deficiency after discontinuation of treatment at final height; timing and peak values for lumbar BMD. Clin Endocrinol 60:175-184, 2004
75. Baroncelli GI, Saggese G: Effect of GH treatment on bone mass in children with GH deficiency. J Endocrinol Invest 28:23-27, 2005 (10 suppl)
76. Shoepe HA, Snow CM: Oral contraceptive use in young women is associated with lower bone mineral density than that of controls. Osteoporos Int 16:1538-1544, 2005
77. Cromer BA, Stager M, Bonny A, et al: Depot medroxyprogestrone acetate, oral contraceptives and bone mineral density in a cohort of adolescent girls. J Adolesc Health 35:434-441, 2004
78. Cromer BA, Blair JM, Mahan JD, et al: A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. J Pediatr 129:671-676, 1996
79. Banks E, Berrington A, Casabonne D: Overview of the relationship between use of progestogen-only contraceptives and bone mineral density. BJOG 108:1214-1221, 2001
80. Cromer BA, Lazebnik R, Rome E, et al: Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. Am J Obstet Gynecol 192:42-47, 2005
81. Resch H, Newrkla S, Grampp S, et al: Ultrasound and x-ray-based bone densitometry in patients with anorexia nervosa. Calcif Tissue Int 66:338-341, 2000
82. Soyka LA, Misra M, Frenchman A, et al: Abnormal bone mineral accrual in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 87:4177-4185, 2002
83. Milos G, Spindler A, Ruegsegger P, et al: Cortical and trabecular bone density and structure in anorexia nervosa. Osteoporos Int 16:783-790, 2005
84. Seeman E, Szmukler GI, Formica C, et al: R: Osteoporosis in anorexia nervosa: The influence of peak bone density, bone loss, oral contraceptive use, and exercise. J Bone Miner Res 7:1467-1474, 1992
85. Sood M, Hambleton G, Super M, et al: Bone status in cystic fibrosis. Arch Dis Child 84:516-520, 2001
86. Haslam RHM, Borovnicar DJ, Stroud DB, et al: Correlates of prepubertal bone mineral density in cystic fibrosis. Arch Dis Child 85:166-171, 2001
87. Hardin DS, Arumugam R, Seilheimer DK, et al: Normal bone mineral density in cystic fibrosis. Arch Dis Child 84:363-368, 2001
88. Buntain HM, Greer RM, Schluter PJ, et al: Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. Thorax 59:149-155, 2004
89. Haworth CS, Selby PL, Webb AK, et al: Low bone mineral density in adults with cystic fibrosis. Thorax 54:961-967, 1999
90. Henderson RC, Madsen CD: Bone density in children and adolescents with cystic fibrosis. J Pediatr 128:28-39, 1996
91. Haworth CS, Selby PL, Horrocks AW, et al: A prospective study of change in bone mineral density over one year in adults with cystic fibrosis. Thorax 57:719-723, 2002
92. Bhudhikanok GS, Wang MC, Marcus R, et al: Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. J Pediatr 133:18-27, 1998
93. Aris RM, Lester GE, Renner JB, et al: Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. Am J Respir Crit Care Med 162:941-946, 2000
94. Aris RM, Lester GE, Caminiti M, et al: Efficacy of alendronate in adults with cystic fibrosis with low bone density. Am J Respir Crit Care Med 169:77-82, 2004
95. Haworth CS, Selby PL, Adams JE, et al: Effect of intravenous pamidronate on bone mineral density in adults with cystic fibrosis. Thorax 56:314-316, 2001
96. Boot AM, de Jongste JC, Verberne AAP, et al: Bone mineral density and bone metabolism of prepubertal children with asthma after long-term treatment with inhaled corticosteroids. Pediatr Pulmonol 24:379-384, 1997
97. Agertoft L, Pedersen S: Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. Am J Respir Crit Care Med 157:178-183, 1998
98. Bahceciler NN, Sezgin G, Nursoy MA, et al: Inhaled corticosteroids and bone density of children with asthma. J Asthma 39:151-157, 2002
99. Altzntas DU, Karakoc GB, Can S, et al: The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children. Allergol Immunopathol 33:204-209, 2005
100. Allen HDW, Thong IG, Clifton-Bligh P, et al: Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. Pediatr Pulmonol 29:188-193, 2000
101. Harris M, Hauser S, Nguyen TV, et al: Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. J Paediatr Child Health 37:67-71, 2001
102. Brinker MR, Thomas KA, Meyers SJ, et al: Bone mineral density of the lumbar spine and proximal femur is decreased in children with sickle cell anemia. Am J Orthop 27:43-49, 1998
103. Soliman AT, Bererhi H, Darwish A, et al: Decreased bone mineral density in prepubertal children with sickle cell disease: Correlation with growth parameters, degree of siderosis and secretion of growth factors. J Trop Pediatr 44:194-198, 1998
104. Lal A, Fung EB, Pakbaz Z, et al: Bone mineral density in children with sickle cell anemia. Pediatr Blood Cancer 47:901-906, 2006
105. Buison AM, Kawchak DA, Schall JI, et al: Bone area and bone mineral content deficits in children with sickle cell disease. Pediatrics 116: 943-949, 2005
106. Miller RG, Segal JB, Ashar BH, et al: High prevalence and correlates of low bone mineral density in young adults with sickle cell disease. Am J Hematol 81:236-241, 2006
107. Vogiatzi MG, Autio KA, Schneider R, et al: Low bone mass in prepubertal children with thalassemia major: Insights into the pathogenesis of low bone mass in thalassemia. J Pediatr Endocrinol Metab 17:1415-1421, 2004
108. Benigno V, Bertelloni S, Baroncelli GI, et al: Effects of thalassemia major on bone mineral density in late adolescence. J Pediatr Endocrinol Metab 16:337-342, 2003
109. Barnes C, Wong P, Egan B, et al: Reduced bone density among children with severe hemophilia. Pediatrics 114:177-181, 2004
110. Gallacher SJ, Deighan C, Wallace AM, et al: Association of severe haemophilia A with osteoporosis: A densitometric and biochemical study. Q J Med 87:181-186, 1994
111. Arikoski P, Komulainen J, Voutilainen R, et al: Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 20:234-240, 1998
112. Brennan BMD, Rahim A, Adams JA, et al: Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. Br J Cancer 79:1859-1863, 1999
113. van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, et al: Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 35:415-420, 2000
114. Boot AM, van den Heuvel-Eibrink MM, Hahlen K, et al: Bone mineral density in children with acute lymphoblastic leukaemia. Eur J Cancer 35:1693-1697, 1999
115. Marinovic D, Dorgeret S, Lescoeur B, et al: Improvement in bone

mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: A 1-year prospective study. Pediatrics 116:e102-e108, 2005
116. Jarfelt M, Fors H, Lannering B, et al: Bone mineral density and bone turnover in young adult survivors of childhood acute lymphoblastic leukaemia. Eur J Endoc 154:303-309, 2006
117. Aisenberg J, Hsieh K, Kalaitzoglou G, et al: J. Pediatr Hematol Oncol 20:241-245, 1998
118. Vassilopoulou-Sellin R, Brosnan P, Delpassand A, et al: Osteopenia in young adult survivors of childhood cancer. Med Pediatr Oncol 32: 272-278, 1999
119. Nysom K, Holm K, Michaelsen KF, et al: Bone mass after treatment of malignant lymphoma in childhood. Med Pediatr Oncol 37:518-524, 2001
120. Kelly J, Damron T, Grant W, et al: Cross-sectional study of bone mineral density in adult survivors of solid pediatric cancers. J Pediatr Hematol Oncol 27:248-253, 2005
121. Ruza E, Sierrasesumaga L, Azcona C, et al: Bone mineral density and bone metabolism in children treated for bone sarcomas. Pediatr Res 59:866-871, 2006
122. Odame I, Duckworth J, Talsma D, et al: Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. Pediatr Blood Cancer 46:357-362, 2006
123. Henderson RC, Lin PP, Greene WB. Bone-mineral density in children and adolescents who have spastic cerebral palsy. J Bone Joint Surg 77-A:1671-1681, 1995
124. Henderson RC, Lark RK, Gurka MJ, et al: Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. Pediatrics 110:1-10, 2002
125. Henderson RC, Lark RK, Kecskemethy HH, et al: Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placego-controlled clinical trial. J Pediatr 141:644-651, 2002
126. Bachrach SJ, Kecskemethy HH, Harcke HT, et al: Pamidronate treatment and posttreatment bone density in children with spastic quadriplegic cerebral palsy. J Clin Densitom 9:167-174, 2006
127. Quan A, Adams R, Ekmark E, et al: Bone mineral density in children with myelomeningocele. Pediatrics 102:E34, 1998
128. Valtonen KM, Goksor LA, Jonsson O, et al: Osteoporosis in adults with meningomyelocele: An unrecognized problem at rehabilitation clinics. Arch Phys Med Rehabil 87:376-382, 2006
129. Pepmueller PH, Cassidy JT, Allen SH, et al: Bone mineralization and bone mineral metabolism in children with juvenile rheumatoid arthritis. Arthritis Rheum 39:746-757, 1996
130. Pereira RMR, Corrente JE, Chahade WH, et al: Evaluation by dual x-ray absorptiometry (DXA) of bone mineral density in children with juvenile chronic arthritis. Clin Exp Rheum 16:495-501, 1998
131. Lien G, Flato B, Haugen M, et al: Frequency of osteopenia in adolescents with early-onset juvenile idiopathic arthritis. Arthritis Rheum 48:2214-2223, 2003
132. Henderson CJ, Cawkwell GD, Specker BL, et al: Predictors of total body bone mineral density in non-corticosteroid-treated prepubertal children with juvenile rheumatoid arthritis. Arthritis Rheum 40: 1967-1975, 1997
133. Henderson CJ, Specker BL, Sierra RI, et al: Total-body bone mineral content in non-corticosteroid-treated postpubertal females with juvenile rheumatoid arthritis. Arthritis Rheum 43:531-540, 2000
134. Mul D, van Suijlekom-Smit LWA, ten Cate R, et al: Bone mineral density and body composition and influencing factors in children with rheumatic diseases treated with corticosteroids. J Pediatr Endoc Metab 15:187-192, 2002
135. Bianchi ML, Cimaz R, Galbiati E, et al: Bone mass change during methotrexate treatment in patients with juvenile rheumatoid arthritis. Osteoporos Int 10:20-25, 1999
136. Trapani S, Civinini R, Ermini M, et al: Osteoporosis in juvenile systemic lupus erthematosus: a longitudinal study on the effect of steroids on bone mineral density. Rheumatol Int 18:45-49, 1998
137. Castro TCM, Terreri MT, Szejnfeld VL, et al: Bone mineral density in juvenile systemic lupus erythematosus. Braz J Med Bio Res 35:1159-1163, 2002
138. Larson CM, Henderson RC: Bone mineral density and fractures in boys with Duchenne muscular dystrophy. J Pediatr Orthop 2000; 20:71
139. Bianchi ML, Mazzanti A, Galbiati E, et al: Bone mineral density and bone metabolism in Duchenne muscular dystrophy. Osteoporos Int 14:761-767, 2003
140. Hawker GA, Ridout R, Harris VA, et al: Alendronate in the treatment of low bone mass in steroid-treated boys with Duchenne's muscular dystrophy. Arch Phys Med Rehab 86:284-288, 2005
141. Stewart WA, Acott PD, Salisbury SR, et al: Bone mineral density in juvenile dermatomyositis. Arthritis Rheum 48:2294-2298, 2003
142. Castro TCM, Terreri MTR, Szejnfeld VL, et al: Bone mineral density of Brazilian girls with juvenile dermatomyositis. Braz J Med Biol Res 38:309-313, 2005
143. Lund AM, Molgaard C, Muller J, et al: Bone mineral content and collagen defects in osteogenesis imperfecta. Acta Paediatr 88:1083-1088, 1999
144. Rauch F, Glorieux FH: Bisphosphonate treatment in osteogensis imperfecta: Which drug, for whom, for how long? Ann Med 37:295-302, 2005
145. Zacharin M, Kanumakala S: Pamidronate treatment in less severe forms of osteogenesis imperfecta. J Pediatr Endocrinol Metab 17: 1511-1517, 2004
146. Gatti D, Antoniazzi F, Prizzi R, et al: Intravenous neridronate in children with osteogenesis imperfecta: A randomized controlled study. J Bone Miner Res 20:758-763, 2005
147. Arikoski P, Silverwood B, Tillmann V, et al: Intravenous pamidronate in children with moderate to severe osteogenesis imperfecta: Assessment of indices of dual-energy X-ray absorptiometry and bone metabolic markers during the first year of therapy. Bone 34:539-546, 2004
148. Letocha AD, Cintas HL, Troendle JF, et al: Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. J Bone Miner Res 20:977-986, 2005
149. Zeitlin L, Rauch F, Plotkin H, et al: Height and weight development during four years of therapy with cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta types I, III, and IV. Pediatrics 111:1030-1036, 2003