Pediatric DXA: clinical applications

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Abstract Normal bone mineral accrual requires adequate dietary intake of calcium, vitamin D and other nutrients; hepatic and renal activation of vitamin D; normal hormone levels (thyroid, parathyroid, reproductive and growth hormones); and neuromuscular functioning with sufficient stress upon the skeleton to induce bone deposition. The presence of genetic or acquired diseases and the therapies that are used to treat them can also impact bone health. Since the introduction of clinical DXA in pediatrics in the early 1990s, there has been considerable investigation into the causes of low bone mineral density (BMD) in children. Pediatricians have also become aware of the role adequate bone mass accrual in childhood has in preventing osteoporotic fractures in late adulthood. Additionally, the availability of medications to improve BMD has increased with the development of bisphosphonates. These factors have led to the increased utilization of DXA in pediatrics. This review summarizes much of the previous research regarding BMD in children and is meant to assist radiologists and clinicians with DXA utilization and interpretation.

Keywords DXA · Bone mineral density · Pediatrics · Osteoporosis

Abbreviations

ALL acute lymphocytic leukemia
BMC bone mineral content
BMD bone mineral density
CF cystic fibrosis
CS corticosteroids
DXA dual energy X-ray absorptiometry
JRA juvenile rheumatoid arthritis
LS lumbar spine
TBBMC total body bone mineral content
TBBMD total body bone mineral density
WBI whole brain irradiation

Introduction

Peak bone mineral accrual occurs during early puberty and peak bone mass is achieved in young adulthood. Low BMD can result from a wide variety of childhood diseases or be due to the effects of their treatment. Increasingly, pediatric specialists are requesting evaluation of BMD and radiologists are expected to be knowledgeable in the technique, interpretation and clinical applications of DXA. A review of the technical and interpretive aspects of DXA has been recently presented [1]. The clinical uses of DXA in pediatrics are exceedingly broad. This paper reviews the clinical data regarding pediatric DXA and can be used to assist radiologists and clinicians in DXA utilization and interpretation.

Gastrointestinal disorders

Gastrointestinal diseases may impact bone health in several ways. Poor calcium intake, as in patients with a milk
allergy, and reduced calcium absorption, as in patients with untreated celiac disease, result in low BMD. Early correction of the underlying deficiency allows normal bone mineralization to occur. In addition to poor calcium absorption, inflammatory bowel disease likely impacts bone health through other factors including chronic diarrhea, decreased lean tissue mass, reduced physical activity, increased inflammatory cytokines, and CS therapy. As in all chronic conditions, correction of short stature and delayed maturation will allow better identification of those patients with abnormal DXA findings who will have significant bone mineral deficits.

Milk allergy

Henderson and Hayes [2] reported a positive correlation between LS and hip BMD and calcium intake in children with significant milk allergy. They found a 5–8% increase in LS Z-scores and a 9–13% increase in hip Z-scores in patients with daily calcium intake above the recommended dietary allowances. These findings were confirmed in children with reduced dairy intake due to a variety of other causes [3, 4]. There was a positive correlation between BMD and calcium intake with normal values in the subgroup with normal dietary calcium intake and decreasing BMD as the daily intake of calcium decreased. LS BMD was maintained, even with severe dairy restrictions when calcium intake was maintained through diet or supplementation.

Inflammatory bowel disease

Boot et al. [5] found decreased LS and TBBMD in children with Crohn disease or ulcerative colitis. The decreases were statistically significant even when they accounted for the delayed bone age in their patients. Similarly, Ahmed et al. [6] found reduced LS and TBBMD Z-scores in nearly 70% of children with Crohn disease and, to a lesser extent, ulcerative colitis, when compared to healthy age-matched controls. However, when height was taken into account, only 22% of their patients had low BMD. Burnham et al. [7] found decreased height, lean tissue mass and TBBMC in children with Crohn disease when compared to normal controls. However, with correction for height, age, race, Tanner stage and lean tissue mass, no statistically significant differences were found between the study and control groups. The authors also found no correlation between CS treatment and height-corrected BMC. Similar findings were reported by Walther et al. [8]. Thus, in patients with inflammatory bowel disease, the apparent low LS BMD and TBBMC is largely a result of short stature, delayed maturation and decreased lean tissue mass.

Celiac disease

Kalayci et al. [9] found lower LS BMD in untreated celiac disease patients compared to treated patients. They found that nearly all children with celiac disease whose treatment began before the age of 4 years reached normal BMD compared to only 50% of children whose treatment began after the age of 4 years. They also found that all patients who initially presented with gastrointestinal symptoms had normal BMD after 1 year of a gluten-free diet. In prepubertal children with celiac disease, Barera et al. [10], Tau et al. [11] and Szathmari et al. [12] found an increase in height, weight, BMC and BMD after 1.5 years of a gluten-free diet when compared to baseline measurements. These reports indicate that in patients with celiac disease, normalization of DXA findings can be expected with early diagnosis and treatment.

Liver disease

The effects of liver dysfunction on bone health are complex and may involve vitamin malabsorption, failure of vitamin D activation, calcium malabsorption, bile salt deficiency and chronic malnutrition. Argao et al. [13] 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. In a study of prepubertal children with Alagille syndrome, Olsen et al. [14] found reduced height, weight and TBBMC compared to healthy controls matched for age, gender, ethnicity and physical maturity. Malabsorption of fat-soluble vitamins, particularly vitamin D, significantly reduces LS and TBBMC. D’Antiga et al. [15] found normal LS BMC and BMD in patients with childhood liver failure who were at least 1 year out from orthotopic liver transplantation. Return to normal values appeared to be unaffected by the severity of bone disease or cholestasis prior to transplantation. Thus, liver dysfunction with disordered vitamin D metabolism results in early decreased bone mineral accrual. With successful liver transplantation, normalization of DXA findings can be expected.

Renal diseases

Chronic kidney disease results 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 other metabolites. Additional factors that affect the BMD in these patients include malnutrition, metabolic acidosis, anemia and
growth hormone abnormalities resulting in growth retardation. As with many chronic medical conditions, short stature will greatly affect BMD and needs to be accounted for in DXA interpretation.

Bakr [16] found reduced LS BMD in 60% of pre- and postdialysis patients. The degree of osteopenia correlated with biochemical markers of secondary hyperparathyroidism. However, the DXA BMD values were not corrected for height. Similar results were reported by Pluskiewicz et al. [17] following a 2-year longitudinal study of adolescents with chronic kidney disease. They found decreased or stable LS BMD (uncorrected for height) during a time when an increase would be expected. The most severe decreases in BMD were found in patients who were treated with CS. In contrast, Ahmed et al. [18] found normal TBBMD and TBBMC as well as normal LS BMD in children with chronic kidney disease when the DXA values were corrected for height. Similar findings were reported in children before transplantation [19]. Boot et al. [20] reported normal LS and TBBMD in patients with kidney disease 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 [21]. Several authors found that the height-corrected LS BMD was reduced for up to 2 years after transplantation; this was felt to be due to high-dose CS treatment required to suppress transplant rejection. However, by 3 years after transplantation, LS BMD had recovered to normal values [18, 22–24].

Idiopathic hypercalciuria results in excessive urinary excretion of calcium and has increasingly been identified as a cause of decreased BMD in children [25–28]. The degree of BMD reduction does not appear to correlate with the presence of urolithiasis or urinary uric acid concentration. Studies of children and their mothers with idiopathic hypercalciuria indicate that low LS and hip BMD persist into adulthood [25, 26].

In summary, the various metabolic disturbances resulting from altered renal physiology may compromise normal bone mineralization and remodeling, but children with chronic kidney disease often maintain normal BMD if calcium and vitamin D metabolism are normal. CS treatment, either before transplantation or when used to suppress transplant rejection, appears to contribute to low BMD but short-term follow-up indicates eventual normalization of LS BMD. Regardless of the nature of renal disease, correcting for height is essential for accurate interpretation of DXA results in these patients.

Endocrinological diseases

Skeletal development is significantly influenced by multiple hormone systems that are essential to normal bone mineral accrual. Both insufficient and excessive hormone levels can have deleterious effects, resulting in inadequate bone formation or disproportionate bone resorption. Pubertal hormones play a critical role in bone mass acquisition with major differences occurring based on sex and skeletal site [29]. Patients with early or delayed puberty will show early or delayed peak bone mass accrual, respectively [30]. Treatment of precocious puberty includes gonadotropin-releasing hormone analogs that could theoretically interfere with normal bone mineral acquisition. Short-term treatment does not interfere with normal BMD increases in these patients [31].

Disorders of growth hormone, insulin and glucocorticoids

Accurate DXA evaluation of children with growth hormone deficiency or idiopathic short stature must account for their smaller bones [1]. Children with growth hormone deficiency will present with low areal [32] and volumetric LS [33] BMD when first diagnosed. Children with idiopathic short stature have also been found to have low areal LS and hip BMD prior to therapy [34]. With sustained growth hormone replacement these values have been reported to remain stable [33] or normalize rapidly [34]. Children with growth hormone deficiency have a robust response to replacement therapy with increases in height, lean tissue mass and TBBMC [33]. Increases in BMD occur even after peak height is achieved, and this indicates the need to continue hormone therapy until peak BMD is achieved [35, 36].

Type 1 diabetes mellitus is a known risk factor for osteoporosis, but the underlying mechanisms are not fully determined. Adolescent patients have lower bone mass and bone size despite normal growth and maturation [37]. Studies suggest that children and adolescents with diabetes have reduced bone formation and increased bone resorption resulting in low bone mass and BMD [38, 39]. Hemoglobin A1C level, a measure of glycemic control, negatively correlates with BMD [40] and TBBMC [41].

The negative effects of chronic high-dose CS therapy on bone have been well documented. CS replacement therapy, as in congenital adrenal hyperplasia, has not been found to result in reduced BMD [42, 43]. However, young women with congenital adrenal hyperplasia are at risk of reduced BMD if there is biochemical evidence of androgen suppression due to CS therapy [44]. Patients with either childhood-onset or adult-onset Cushing disease often have severe reductions in BMD due to increased osteoclastic activity and bone resorption with normal or reduced bone deposition [45]. Additionally, concomitant reductions in sex and growth hormones contribute to their low BMD. Adolescents appear to be particularly vulnerable to reduced trabecular bone density as measured at the LS. BMD deficits and biochemical measures of bone turnover showed
marked improvement after 2 years remission from hypercortisolism when compared to baseline values, but low LS BMD persisted in the majority of patients [46].

Disorders of reproductive hormones

Reproductive hormones play an important role in the acquisition of bone mineral; estrogen is known to have a protective effect against the development of osteoporosis in postmenopausal women. The effects of hormonal birth control use on BMD in adolescent girls have been investigated by several researchers. The trend toward lower estrogen levels in oral contraceptives has been associated with decreased BMD in adolescent girls who use oral contraceptives [47, 48]. Progesterone-mediated contraceptives (Depo-Provera) have been shown to inhibit bone mineral acquisition in the LS and hip in adolescent girls [49–51]. The extent of this reduction appears to correlate with the duration of treatment and can be lessened with supplemental estrogen [51]. 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 [52–54]. These reductions are thought to be due to a combination of nutritional (decreased calcium and caloric intake), hormonal (decreased estrogen levels, delayed puberty), and mechanical (decreased lean tissue mass) factors. With resumption of 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 for at least 1 year [53]. It is not known if full BMD recovery will occur by early adulthood, but adult women who had adolescent-onset anorexia nervosa have more dramatic reductions in BMD than those with onset during adulthood [55, 56]. Estrogen replacement with oral contraceptives and vigorous exercise can protect against BMD loss in anorexia nervosa [57].

Untreated congenital hypothyroidism can result in markedly reduced BMD. Children with adequate long-term thyroid replacement therapy show normal LS and hip BMD and BMC [58, 59] and normal findings continue into young adulthood [60]. Later in childhood, hypothyroidism is usually caused by Hashimoto thyroiditis. LS and distal radial BMD are expected to be normal at diagnosis and to be maintained with thyroid hormone therapy, and normal peak bone mass is to be expected in these patients [61]. Hyperthyroidism in Graves disease markedly decreases LS and hip BMD, but these normalize within 1 year following thyroid ablation and hormone therapy [62].

In summary, hormonal imbalances from any of a large number of endocrine disorders are associated with abnormal DXA findings and reduced BMD. With hormone replacement therapy, improved bone mineral accrual is to be expected in most of the endocrine deficiencies. However, with anorexia nervosa, especially with onset in adolescence, there appears to be a sustained reduction in BMD even after resumption of normal caloric intake and menses.

Respiratory diseases

Cystic fibrosis

In cystic fibrosis (CF), low BMD may be caused by reduced gastrointestinal absorption of calcium and vitamin D, reduced testosterone levels, chronic hypoxia, chronic CS use, and reduced lean tissue mass. 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 [63–65]. However, adolescents and adults with CF have accelerated bone loss over time reflecting disease progression [66, 67]. Henderson and Madsen [68] and Buntain et al. [66] found progressively decreasing BMD Z-scores with increasing age in CF patients. LS, hip, and TBBMD in the prepubertal group were normal. TBBMD was reduced in adolescents; however, all other sites remained normal. In adult patients, BMD was reduced at all sites. In a follow-up study, Haworth et al. [69] reported that patients older than 25 years showed accelerated LS and hip BMD losses. Bhudhikanok et al. [70] found that LS, hip, and TBBMD were low at baseline and documented further bone loss at follow-up. CS use was identified as the most modifiable factor accounting for this bone loss and the authors suggested that bisphosphonates may be beneficial in these patients. The benefits of bisphosphonates in CF were confirmed by Aris et al. [71, 72] and Haworth et al. [73] who found increases in LS and hip BMD following treatment with intravenous or oral bisphosphonates, respectively.

Asthma

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 to CS-naive asthmatic controls but reduced BMD Z-scores when compared to normal controls when height is not taken into account [74–77]. Allen et al. [78] and Harris et al. [79] found significant reductions in BMD in asthmatic children receiving high doses of inhaled CS.
Hematological diseases

Anemia and hemophilia

Chronic anemias can affect bone structure and density through bone marrow hyperplasia (resulting in expansion of the medullary space, trabecular coarsening and cortical thinning), and vasoocclusion (resulting in medullary and diaphyseal infarction). Additional factors for reduced BMD include reduced lean tissue mass, decreased physical activity and hypogonadism, and in the case of thalassemia, endocrine dysfunction. Brinker et al. [80] found low BMD in children with sickle cell anemia. These findings confirmed those of Soliman et al. [81] who reported low LS BMD in prepubertal children with sickle cell anemia. Lal et al. [82] and Buisson et al. [83] noted markedly reduced BMD and BMC, which correlated with disease severity in these children. These changes were found to persist into adulthood [84]. Additionally, low calcium intake and low vitamin D levels may contribute to decreased BMD in these patients. Vogiatzi et al. [85] and Benigno et al. [86] evaluated children with thalassemia major who were fully treated with transfusion and chelation therapy and found reduced BMD at diagnosis and showed further reductions at follow-up.

Patients with hemophilia are at risk for osteoporosis due to 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, and this has been found to correlate with BMD [87]. Low BMD is independent of height and weight but correlates with disease severity and extent. These changes can be expected to persist into adulthood [88].

Oncological diseases

Acute lymphocytic leukemia

ALL is the most common childhood malignancy, but because of its excellent prognosis, most children with ALL survive into adulthood. Arikoski et al. [89] found reduced BMD in ALL survivors up to 20 years after treatment. Of their 29 patients, 20 had received cranial irradiation and four males had received testicular irradiation. The use of high-dose methotrexate and cranial irradiation were found to be significantly correlated with low BMD. Differing results were presented by Brennan et al. [90] 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 cranial irradiation, growth hormone status or height Z-scores. They suggested that the low BMD found in their patients was related to the effects of chemotherapy rather than cranial irradiation. Van der Sluis et al. [91] found normal LS and TBBMD a mean of 10 years after ALL treatment that included high-dose methotrexate and CS but not cranial irradiation. 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. The authors concluded that the deleterious effects of ALL and its treatment in childhood on BMD may be due to cranial irradiation but, in its absence, BMD will normalize by early adulthood. This conclusion is supported by other researchers [92, 93]. Jarfelt et al. [94] 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 prepubertal at the end of treatment and had been treated with high doses of CS and methotrexate. 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 methotrexate and CS therapy. 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 of persistently low BMD in adulthood if they have confounding factors such as gonadal dysfunction or if the course of their disease coincided with the period of expected rapid accrual of bone mineral that normally occurs during puberty.

Other malignancies

There are only limited data regarding the effects of other childhood malignancies on BMD. Aisenberg et al. [95] and Vassilopoulou-Sellin et al. [96] found reduced femoral neck and TBBMD in young adult survivors of various childhood cancers. Gonadal dysfunction due to pelvic or cranial irradiation was the factor most strongly correlated with reduced BMD. CS treatment did not correlate with low BMD. Nyssom et al. [97] reported normal size-adjusted TBBMC in adult survivors of childhood lymphoma and found no relationship between TBBMC and cumulative methotrexate or CS doses. Kelly et al. [98] evaluated adult survivors of various pediatric solid tumors and found reduced BMD in at least one site in half of their patients. Only the total number of chemotherapeutic agents correlated with reduced BMD. Five of six extremities involved with a bone sarcoma showed reduced BMD. Similar results...
were found in a group of sarcoma survivors reported by Ruza et al. [99]. Interestingly, they found that those diagnosed prior to puberty had more severe BMD reductions later in life. This may be due to the extensive physical disabilities associated with amputations and limb salvage procedures in these patients. Odame et al. [100] found that disabilities associated with amputations and limb salvage later in life. This may be due to the extensive physical activity and poorer quality of life. The authors postulated that the higher cranial radiation doses used for the treatment of brain tumors had a profound effect on long-term BMD compared to the relatively lower doses used in the treatment of ALL.

In summary, there are multiple factors that affect short- and long-term BMD in these patients/survivors. These include pubertal status at diagnosis, type of malignancy, local (sarcomas, central nervous system tumors) versus systemic (leukemia) disease, initial (malnutrition, immobilization) versus prolonged (amputation) disease-related disability, types of chemotherapy, and radiation ports and dosages that may cause gonadal or growth hormonal dysfunction.

**Neurological diseases**

Cerebral palsy

Because of decreased muscle development and ambulation, children with cerebral palsy are at increased risk of osteoporosis-associated fractures. Frequently, assessment of the LS and hips with DXA is impossible due to difficulties in positioning patients with contraction deformities, muscular spasm-induced motion artifacts or orthopedic hardware-related artifacts. Because of these limitations, Hareke et al. [101] suggested scanning the distal femur with these patients positioned on their side. Distal femoral BMD was found to be highly correlated with hip BMD and the technique yielded highly reproducible BMD data [102].

Henderson et al. [103] demonstrated reduced LS and hip BMD in children with cerebral palsy. Measures of nutritional and ambulatory status were found to be the best predictors of BMD. In children with moderate to severe disease, Henderson et al. [104] 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 these children grew older. 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 these patients. In a prospective longitudinal study of patients with cerebral palsy, Henderson et al. [105] found that low initial LS and distal femur BMD Z-scores were associated with poor growth, nutritional status and motor function, and these contributed to reduced bone mineralization at follow-up. Treatment with bisphosphonates for 1 year resulted in a substantial increase in distal femoral BMD in children with quadriplegic cerebral palsy [106]. The improvement was sustained for at least 6 months after the last treatment. However, Bachrach et al. [107] 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.

In summary, children with CP show decreased bone mineral status that reflects the duration and severity of their disease. Distal femoral measurements better reflect the bone status at the sites more at risk of fracture. Bisphosphonate therapy increases BMD during treatment and it appears to have sustained benefits with reduced fracture rates even after treatment is terminated.

**Meningomyelocele**

Quan et al. [108] found reduced forearm BMD in children with meningo(myel)ocele. Patients with a history of fracture had substantially lower forearm BMD than those without a fracture history. The reduced upper extremity BMD in these patients with preserved upper extremity function may indicate that both systemic and local factors affect bone mineralization. Hypercalcemia in nonambulatory patients with meningo(myelo)cele may be such a factor. Quan et al. [109] later evaluated the effect of thiazide treatment for hypercalcemia in these patients and found no change after 1 year in forearm BMD when compared to placebo-treated controls. Valtonen et al. [110] found normal forearm and LS BMD in adult patients with meningo(myelo)cele, but reduced hip BMD in one-third of the patients. There was a trend for low hip BMD in the nonambulatory compared to ambulatory patients but not for the LS. This dissociation of LS and hip BMD values was thought to be due to relatively preserved axial loading on the LS in upright patients with meningo(myelo)cele. The normalization of forearm BMD in these adult patients was attributed to increased upper extremity muscular stress with the use of crutches and manual wheelchairs.

**Connective tissue diseases**

Juvenile rheumatoid arthritis and systemic lupus erythematosus

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. [111] and Pereira et al. [112]
found decreased regional, LS, and TBBMD in patients with JRA. The decrease was more severe in children with longer disease duration and was similar for oligoarthritis and polyarthritis. Lien et al. [113] 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. [114] found no statistically significant difference in TBBMD in prepubertal children with mild-to-moderate JRA and no history of CS treatment when compared to normal controls. When a similar study was performed on CS-naive older girls with mild-to-moderate JRA, Henderson et al. [115] found decreased TBBMC. As with other chronic diseases of childhood, it appears that persistent disease activity through puberty will decrease when compared to normal controls. When a similar study was performed on CS-naive older girls with mild-to-moderate JRA, Henderson et al. [115] found decreased TBBMC. With other chronic diseases of childhood, it appears that persistent disease activity through puberty results in decreased BMC. Mul et al. [116] found marked reductions in LS BMD and BMC in children with rheumatic diseases treated for at least 1 year with high-dose CS. Bianchi et al. [117] found that long-term methotrexate for JRA did not result in reduced LS or TBBMD.

In summary, prepubertal children with JRA of mild or moderate severity without a history of CS treatment will have TBBMD similar to healthy children. With increasing disease severity and duration, especially through puberty, TBBMC will decrease when compared to normal children. These changes are in contrast to the normal DXA findings reported in patients with juvenile systemic lupus erythematosus [118, 119]. Unlike patients with JRA, these patients typically do not have bone and joint involvement and thus are more likely to have preserved BMD. However, factors that may negatively impact bone health in these patients include immobility, limited exposure to sunlight, and CS therapy.

**Musculoskeletal diseases**

For normal mineralization to occur, adequate muscle-induced mechanical stresses are required to induce bony remodeling. Insufficient muscle mass and activity result in poor bone accrual and low BMD. Additionally, therapy of primary muscle disorders with CS also inhibits normal bone mineralization.

**Duchenne muscular dystrophy and dermatomyositis**

In a longitudinal study of boys with Duchenne muscular dystrophy, Larson and Henderson [120] found that LS and hip BMD correlated with functional mobility level with ambulatory boys having higher LS BMD than nonambulatory boys. Hip BMD was decreased before loss of ambulation and showed progressive reduction over time. Fractures occurred in nearly half of patients, most typically involving the lower extremity and frequently resulting in loss of ambulation. Bianchi et al. [121] found decreased LS and TBBMD in ambulatory boys with Duchenne muscular dystrophy when compared to healthy boys. LS BMD was more severely reduced in the subset of Duchenne muscular dystrophy patients treated with CS. The authors noted greater lower extremity than upper extremity bone mineral loss using regional DXA analysis, especially in the CS-treated patients, and they attributed this to reduced mechanical stress on the lower extremities. Hawker et al. [122] found an increase in LS and TBBMD after 2 years of bisphosphonate treatment, supplemental calcium, and vitamin D. Improvement in TBBMD was inversely related to age at baseline.

In summary, patients with Duchenne muscular dystrophy have reduced LS BMD, especially in the setting of CS treatment. The low LS and hip BMD worsen with loss of ambulatory status and are frequently associated with fractures of the lower extremities. Studies of a small number of children with dermatomyositis have found low LS BMD that worsens with ongoing CS therapy [123, 124]. Patients treated with bisphosphonates for osteoporosis-related compression fractures show increases in LS BMD [123].

**Osteogenesis imperfecta**

Osteogenesis imperfecta 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 these children vary with subtype with few fractures and normal or near-normal DXA findings in type I osteogenesis imperfecta and more frequent fractures and marked reductions in BMD in types III and IV [125, 126]. (Type II typically results in perinatal demise.) Since as many as 40% of patients with osteogenesis imperfecta will have normal BMD and BMC, a normal DXA study does not preclude this diagnosis or distinguish these cases from non-accidental injuries [125]. In recent years, clinical trials using bisphosphonates in osteogenesis imperfecta have yielded impressive results with multiple studies demonstrating increases in LS, hip and TBBMD and improved quality of life [127–130]. 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 lead to improved quality of life, and the stimulus of physical activity is known to be beneficial to bone. Increased bone mass in the skull following bisphosphonate therapy in these patients implies that the drug also has a direct effect on bone accrual irrespective of physical activity [129]. The theoretical concern that this therapy might negatively impact linear growth in these children has not been shown to be true [131].
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