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Bone Health in Children and Adolescents With Chronic Diseases That May Affect the Skeleton: The 2013 ISCD Pediatric Official Positions

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Abstract

The aim of this Task Force was to review the use of dual-energy X-ray absorptiometry (DXA) in children and adolescents with underlying chronic diseases that pose risk factors for compromised bone health, such as inflammation, glucocorticoid therapy, or decreased mobility. The Task Force systematically analyzed more than 270 studies, with an emphasis on those published in the interval since the original 2007 Position Statements. Important developments over this period included prospective cohort studies demonstrating that DXA measures of areal bone mineral density (aBMD) predicted incident fractures and the development of robust reference data and strategies to adjust for bone size in children with growth impairment. In this report, we summarize the current literature on the relationship between DXA-based aBMD and both fracture (vertebral and non-vertebral) outcomes and non-fracture risk factors (e.g., disease characteristics, ambulatory status, and glucocorticoid exposure) in children with chronic illnesses. Most publications described the aBMD profile of children with underlying diseases, as well as the cross-sectional or longitudinal relationship between aBMD and clinically relevant non-fracture outcomes. Studies that addressed the relationship between aBMD and prevalent or incident fractures in children with chronic illnesses are now emerging. In view of these updated data, this report provides guidelines for the use of DXA-based aBMD in this setting. The initial recommendation that DXA is part of a comprehensive skeletal healthy assessment in patients with increased risk of fracture is unchanged. Although the prior guidelines recommended DXA assessment in children with chronic diseases at the time of clinical presentation with ongoing monitoring, this revised Position Statement focuses on the performance of DXA when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture and when the DXA results will influence that management.

Key Words: Bone mineral density; children; chronic disease; DXA; fractures.

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Introduction

Dual-energy X-ray absorptiometry (DXA) is the most widely used technique for the evaluation of bone status in children and adolescents affected by various diseases that may influence bone health. In the recent years, there has been greater attention given to the short-term and lifelong consequences of childhood chronic diseases and their therapies on bone health. In light of multiple important new developments, a reassessment of current and potential uses of DXA in children and adolescents with chronic diseases is required. As detailed below and in the accompanying 2013 Position Statements, advances since the 2007 Statements include the development of robust reference data, the validation of strategies to adjust for bone size in children with growth impairment and numerous longitudinal studies relating DXA measures to fracture (vertebral and non-vertebral) outcomes and non-fracture risk factors (disease characteristics, ambulatory status, glucocorticoid exposure) in children with chronic illnesses.

It is well established that DXA measures of bone mineral content (BMC) and areal BMD are confounded by short stature. DXA is a 2-dimensional technique in which bone is presented as the combined sum of cortical and trabecular bone within the projected bone area, concealing the distinct structural characteristics. DXA provides an estimate of BMC per anatomical region, dividing the BMC (g) by the projected area of the bone (cm²) then derives “areal-BMD” (g/cm²). This aBMD is not a measure of volumetric density (g/cm³) because it provides no information about bone depth. Bones of larger width and height are thicker. Since bone depth is not factored into DXA results, reliance on areal-BMD systematically underestimates bone density in shorter people. This limitation is of paramount importance in children and adolescents with chronic diseases complicated by poor growth. For example, in the evaluation of a children receiving glucocorticoid therapy, one could falsely attribute the decreased areal-BMD as evidence for osteopenia, rather than a glucocorticoid-induced reduction in height.

Failure to address short stature is pervasive in publications describing DXA in children with chronic disease and restricted our interpretation of these data. The literature is further limited by myriad strategies used to adjust for short stature and delayed maturation. Fortunately, as described in the accompanying Position Statement entitled *Dual Energy X-ray Absorptiometry Interpretation and Reporting in Children and Adolescents*, the Position Development Conference (PDC) was able to reach a consensus regarding adjustment strategies (1). The Official Position states: in children with short stature or growth delay, spine and total body less head (TBLH) BMC and areal BMD results should be adjusted. For the spine, adjustment is recommended using either bone mineral apparent density (BMAD) or the height Z-score. For TBLH, adjust using the height Z-score.

Insufficient age, sex, and race-specific reference data to generate Z-scores was recognized as a critical barrier to the assessment of bone health in the 2007 statements. The earliest reference datasets resulted in markedly different Z-scores

when applied to children who were at risk for low bone density (2). As described in the 2013 Position Statement on DXA Reporting, new reference data are now available (1). For example, the US National Institute of Child Health and Human Development’s Bone Mineral Density in Childhood Study (BDMCS) was designed to meet the majority of requirements for pediatric reference data and included longitudinal data on a multi-ethnic cohort of 1554 children from across the US (3–6). These data were obtained with Hologic scanners and have been converted to “GE equivalents” using the transformation equations developed by Shepherd et al and are currently available as an optional reference database with the latest versions of General Electric Lunar scanners (7). Although these reference data do not meet the needs of clinicians worldwide, their availability will result in more uniform reporting of DXA results and provide a standard moving forward. Finally, the recent availability of reference data for the lateral distal femur for use in children with contractures and spines is an important advance (8).

Despite the above limitations, numerous studies have demonstrated clear associations between DXA outcomes and increased fracture risk (9–12). Other studies have demonstrated associations between DXA outcomes and risk factors for bone deficits such as glucocorticoid therapy, disease activity, and muscle deficits (13–17). This document presents a systematic assessment of the literature in children and adolescents with chronic disease, in support of the revised recommendations.

Methods

Evidence Review

This Task Force was charged with updating the 2007 Position Statement entitled *Bone Health in Children and Adolescents with Chronic Diseases that May Affect the Skeleton* (18). The Task Force members were each assigned one or more of the primary or secondary bone diseases outlined below. Each member completed a thorough bibliographic search to find the relevant literature from 2007 through August 2013 using the PubMed, Ovid, and Embase databases. Search terms included bone mineral density, BMC, DXA, fracture, and children, along with the specific names of the assigned diseases. Each manuscript was reviewed for relations between DXA outcomes with disease and fracture outcomes. For those topics not included in the 2007 PDC, such as chronic kidney disease (CKD), studies before 2007 were also considered.

The methods used to develop the ISCD Official Positions and grading system applied to the positions are presented in the Executive Summary that accompanies this task force document. In brief, all positions were graded on quality of evidence as Good; Fair; or Poor: where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies,

important flaws in their design or conduct, gaps in the chain of evidence, or information. Second, positions were graded on strength of recommendation as A, B, or C: where A is strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion. Third, positions were graded on applicability as worldwide (W) or variable, according to local requirements (L).

Changes in the grading of each of the position statements previously presented in the original 2008 document (18) represent a revision in of the quality of evidence, the strength of recommendation and its worldwide applicability. In addition, the new data and their interpretation by the Expert Panel resulted in substantial refinement of the scope of the prior guidelines.

Selection of Diseases

According to the literature, primary and secondary bone diseases characterized by an increased risk of fractures were included in the review for the 2013 PDC, even if studies on large pediatric populations are still few. The diseases were characterized as primary and second bone disorders. The review of primary bone disorders was limited to osteogenesis imperfecta (OI) and juvenile idiopathic osteoporosis (JIO) because these are the only diseases for which sufficient data on DXA outcomes in children and adolescents are available. The secondary diseases were broadly categorized as endocrine diseases (e.g., type 1 diabetes mellitus [T1DM]), disorders resulting in impaired mobility (e.g., myopathic diseases and cerebral palsy [CP]), hematologic disorders (e.g., thalassemia), leukemia, cystic fibrosis (CF), inflammatory disorders (e.g., inflammatory bowel disease [IBD]), CKD, and solid organ and bone marrow transplantation.

The Questions

For each chronic disease, the Task Force reviewed the literature published between 2007 and 2013 with the aim of answering the following 4 key questions addressed in the prior guidelines:

1. Is there a role for DXA in pediatric practice?
2. When should DXA scan measurements be initiated in children at increased risk of fracture?
3. How does measurement of bone mass contribute to the management of pediatric patients?
4. What is the optimal timing for DXA evaluation in the follow-up of children and adolescents in different pathologic conditions and in relation to therapy?

Results

The following is a summary of the disease-specific reviews, highlighting those studies that informed the new Position Statements.

Primary Bone Diseases

OI

OI is a heritable bone fragility disorder that in the majority of cases is caused by mutations in COL1A1 or COL1A2, the

genes that encode the 2 collagen type I alpha chains, alpha1 (I) and alpha2 (I). Over 30 manuscripts reporting DXA results in children and adolescents with OI and published since 2007 were identified: The majority measured DXA results in the lumbar spine (LS) and total body (TB), whereas 3 measured the proximal femur, one measured the distal femur, and one measured the radius. DXA was measured in different OI types: mostly in type I and less frequently in type II, III, and IV. Most studies used DXA to evaluate aBMD before starting treatment and, more rarely, at presentation.

It is well established that OI is characterized by bone fragility and increased fracture risk. Two recent noteworthy studies reported the relation between areal BMD results and fractures (10,19). Aglan et al observed lower LS aBMD in the patients with severe OI types that also presented with a greater number of fractures (19). Ben Amor et al reported a negative association between LS aBMD Z-score and vertebral fracture severity, quantified as the spine deformity index (20) and between LS aBMD and long-bone fractures (10). These authors concluded “it is noteworthy that the LS areal BMD Z-score was associated with both the incidence of long-bone fractures and the prevalence of vertebral compressions. This observation indicates that LS areal BMD provides some indication about fracture risk also in young patients with OI due to COL1A1 haploinsufficiency mutations.”

Additional studies examined the associations between OI disease severity and aBMD. As expected, the observed aBMD values were lower than the values expected for healthy children of the same age, including adjustments for height, at different skeletal sites (LS, hip) and for the TB, and were lower in untreated compared with treated patients. In a series of 19 children with OI, a greater degree of scoliosis was associated with a lower spine aBMD Z-scores (21). More recent studies have examined genotype-phenotype correlations, including DXA outcomes (22,23). For example, a large series of 192 children demonstrated that patients with COL1A1 haploinsufficiency on average were taller and heavier and had higher LS aBMD, compared with patients with helical mutations. After adjustment for age, sex, and height Z-scores, the mean LS aBMD Z-scores were -4.0 for the haploinsufficiency group and -4.7 for both helical mutation groups.

The measurement of BMC/aBMD was considered useful in monitoring pediatric patients with OI undergoing bisphosphonate therapy. All prospective studies used DXA to evaluate aBMD changes after starting treatment with oral or IV bisphosphonates (24–26); in a single study, a subgroup was also treated with growth hormone (27). All studies observed lower aBMD before starting treatment and demonstrated that aBMD increased at the LS, hip, and TB after treatment (although studies evaluating the last 2 skeletal sites were relatively few). In most studies, both retrospective and prospective, DXA was repeated at intervals of 6 or 12 mo; shorter intervals (2–4 mo) were very rarely used.

Idiopathic Juvenile Osteoporosis

Idiopathic juvenile osteoporosis, a disease of unknown etiology, manifests typically as pain, bone deformities, fractures,

and low BMD (28). A prior longitudinal study documented that both LS and TB aBMD Z-scores were lower during the acute phase than the recovery phase (28). A recent study examined the impact of pamidronate: (29) 9 patients were randomized to intravenous pamidronate or no treatment. Pamidronate was associated with higher LS aBMD and lower fracture rates over a 3-yr interval.

There are no conclusive data on the optimal timing for DXA scans during follow-up: the only prospective study performed spine DXA every 12 mo throughout the follow-up in the context of a clinical trial (29).

Secondary Bone Diseases

Endocrine Diseases

Anorexia Nervosa. The majority of the studies of anorexia nervosa were conducted in females and included DXA scans in LS. A few also evaluated the hip and TB. These studies consistently demonstrated reduced aBMD in males and females, compared with controls. Four of the studies assessed estrogen replacement therapies and demonstrated that DXA aBMD was preserved or increased compared with the controls (30–33). Only one study evaluated the association between DXA aBMD results and fractures detected on DXA lateral thoracolumbar images (34), concluding vertebral fractures were not predicted by disease duration, severity of malnutrition, or DXA aBMD. DXA studies have demonstrated correlations with disease characteristics. For example, weight gain and menstrual recovery was associated with a halting of deterioration in aBMD parameters, and baseline ghrelin, cortisol, and peptide YY predicted changes in LS and TB DXA outcomes (16,35). The longitudinal studies typically assessed aBMD at 6-mo intervals.

T1DM. A meta-analysis published in 2007 reported that the relative risk of hip fracture in adults was 6.94 and 1.38 in T1DM and T2DM, respectively, compared with healthy controls. Furthermore, aBMD Z-score was decreased in LS and hip in T1DM (36). To our knowledge, increased fracture rates have not been reported in children with T1DM. However, insulin receptors are present on osteoblast lineage cells and it is hypothesized that children with T1D have impaired skeletal development due in part to poor bone formation (37). Between 2007 and 2013, multiple cross-sectional studies using DXA in children and adolescents with diabetes mellitus were identified. With one exception (38), all studies reported that DXA measures of aBMD and/or BMC were significantly lower in T1DM, compared with controls. Peripheral quantitative computed tomography (pQCT) studies also documented bone deficits (39,40). Interestingly, the longitudinal pQCT study suggested recovery of bone deficits following diagnosis (39). Although none of the studies reported fracture events, multiple DXA studies consistently reported that poor metabolic control (HbA1c value) was associated with worse aBMD outcomes (15,38,41,42). Of note, one study reported that concurrent celiac disease was

associated with lower aBMD, compared with those with T1DM alone (43).

Overall, there are inadequate data to support routine DXA evaluation in these patients. However, the above studies illustrate that those with poor metabolic control or celiac disease are likely at greater risk, and future longitudinal studies are needed to determine the associations with fracture risk.

Hypothyroidism. Prior studies in adults have reported that hypo- and hyperthyroidism are associated with increased fracture risk (44,45). A study in 35 children with hypothyroidism reported no differences in DXA LS or hip Z-scores, compared with matched controls (46). In contrast, a study in 60 children and adolescents with congenital hypothyroidism reported significantly lower TB aBMD (47).

Turner Syndrome and Hypogonadism. Bone phenotype in Turner syndrome is affected by SHOX haploinsufficiency and hypogonadism. The fracture prevalence in girls and adolescents has not been well characterized. The majority of recent studies were performed with pQCT, providing insights into the structural basis for bone fragility. Isolated SHOX mutations (48) and TS (48–51) are associated with wider bone diaphyses with lower cortical thickness, but normal trabecular density before puberty, with somewhat opposing results reported in adult TS women (52). Trabecular BMD and bone mass accrual decreases with delay in pubertal induction (50,53–55) and improves with estrogen supplementation (56–58), which is no surprise because lack of estrogen causes osteoporosis in males and females.

In contrast, delayed puberty and male hypogonadism in boys and young men has an effect on periosteal expansion and total bone mass accrual (59) but not on bone density or fractures.

Growth Hormone Deficiency. Children and adults with severe, isolated growth hormone deficiency (GHD) or severe GH resistance do not have an increased risk of fractures. GHD only causes lower cortical thickness, due to reduced periosteal expansion, but cortical and trabecular density is normal when proper size corrections are applied (60). Risk of traumatic fractures is increased only in subjects with hypopituitarism (61–67), which may be associated with pituitary surgery, vision impairment, risk of falls, overtreatment with glucocorticoids and insufficient sex hormone replacement.

In a recent article, Hogler and Shaw (60) concluded that there is no evidence that isolated childhood-onset GHD, or severe GH resistance, causes an increased fracture risk in children or adults. Short children and adults with GHD are at risk of being misdiagnosed with low bone mass and may consequently receiving inappropriate treatment. The authors advised against the use of DXA and concluded that GHD should not be regarded as a cause of osteoporosis in children and young people.

Because of the increased fracture risk in hypopituitarism, compliance and optimization of estrogen and glucocorticoid

replacement is essential, and in case of vision impairment or other neurological deficits, appropriate support and fall protection should be provided. DXA measurement should be performed in young adulthood in patients with hypopituitarism.

Neuromuscular Disorders

Children with limited or no ability to ambulate frequently sustain fragility fractures. CP and Duchenne muscular dystrophy (DMD) were identified as 2 disorders with substantial skeletal morbidity related to chronic immobilization.

Special Considerations Regarding DXA Measurement Site.

Although some studies reported aBMD in the LS or proximal femur, joint contractures, scoliosis, hip dysplasia, and metallic implants often prevent reliable DXA measures of aBMD at these sites. DXA lateral distal femur scans are often feasible in children for whom other sites are not measurable. In 2009, Zemel et al published lateral distal femur reference data based on over 800 children and adolescents (8). The lateral distal femur Z-scores were strongly and significantly associated with weight, body mass index, LS, and TB aBMD Z-scores. This study demonstrated the comparability of lateral distal femur measurements to other clinical aBMD assessment modes. In a related study, the relation between lateral distal femur aBMD Z-scores and fracture history was assessed in a cross-sectional study of 619 children aged 6 to 18 yr with muscular dystrophy (n = 112) or moderate-to-severe CP (n = 507) compiled from 8 centers (12). There was a strong correlation between fracture history and aBMD Z-scores in the distal femur; 35% to 42% of those with aBMD Z-scores less than -5 had fractured compared with 13% to 15% of those with aBMD Z-scores greater than -1. Risk ratios were 1.06 to 1.15 for each 1.0 lower aBMD Z-score.

CP. It is well established that children with CP suffer increased fracture rates and have reduced DXA BMD Z-scores (68–70). A substantial number of manuscripts describing DXA results in children and adolescents with CP were published between 2007 and 2013, including multiple prospective controlled trials of medications or physiotherapy interventions. It is noteworthy that the physical activity intervention (virtual cycling training) in the study by Chen et al resulted in significant improvements in distal femur BMD but not spine BMD (71). DXA evaluation was considered useful in the management of pediatric patients with CP, to estimate the risk of fracture and the effects of intervention.

In addition to the study relating DXA BMD to fractures in 507 children with CP described previously (12), multiple studies have examined the associations with CP disease characteristics. For example, a study conducted in 113 children with CP identified tetraparesis, severe mental retardation and epilepsy as significant risk factors for low BMD Z-scores (17). Other studies have identified limited ambulation, feeding difficulties, previous fractures, anticonvulsant use,

and lower body fat mass as risk factors for low BMD Z-scores, as reviewed by Mergler et al (72).

DMD. It is also well established that DMD is associated with low BMD and increased fracture rates, especially in the setting of glucocorticoids. In one noteworthy study, symptomatic vertebral compression fractures were found in 32% of boys treated with glucocorticoids (73). Furthermore, 38% of boys on glucocorticoids and 33% of those not on glucocorticoids had a history of femoral or humeral fractures. The international DMD Care Considerations Working Group recommends annual DXA scans (74,75). DXA was considered helpful to evaluate BMD changes in relation to the progression of disease and glucocorticoid use. Although small series have failed to demonstrate an association between BMD and fractures in DMD (76), the larger study by Henderson et al (described previously (12)), of a combined sample of children with CP and DMD, showed an association with BMD at the lateral distal femur.

Mayo et al recently reported the results of a longitudinal study of BMD and fracture in 39 boys with DMD on long-term deflazacort therapy (77). Height-adjusted BMD Z-scores remained stable with years of deflazacort until loss of ambulation and weight gain occurred, with marked reductions in BMD Z-scores thereafter. Nine long-bone fractures occurred in 8 ambulating boys and 7 vertebral fractures occurred in 6 non-ambulatory boys after more than 5 yr of glucocorticoid therapy. Therefore, body fat and ambulatory status may also be useful bone health indicators (77).

Hematologic Diseases

Thalassemia. In thalassemia, studies of bone mass and frequency of fractures were reported in children in 6 prospective cross-sectional studies (78–83) and 2 retrospective studies between 2007 and 2013 (84,85). Three studies reported fracture rates without BMD measurements (78,79,85).

Children and adolescents with thalassemia had lower BMD than controls (also after adjustment for height and Tanner stage) (81,83) and suboptimal peak bone mass (81). Fracture rates were increased overall in thalassemia and rose with age (80,81). However, results among children and adolescents were not consistent. Although most studies documented that peripheral fractures were not increased (78,80,81), 2 studies reported increased fragility (79,85). Rates of vertebral fractures are unclear because studies performed so far included both children and adults (78,84). In a large study on 163 children/adolescents, Vogiatzi et al found that BMD predicted fracture risk (81), and 2 other studies reached the same conclusion (79,84).

Low bone mass was found in all thalassemia syndromes and regardless of frequency of transfusions (81). However, the associations between BMD and disease parameters were not consistent across all studies. Ferritin and hemoglobin levels were not independent predictors of BMD or fractures (84,86). High bone turnover and hypogonadism predicted BMD Z-score in a number of studies,

whereas associations with vitamin D status were inconsistent (81,83,84).

Sickle Cell Disease. Four articles were found for the period from 2007 to 2013 on DXA measurements and fractures in children: all prospective studies, 3 cross-sectional and one observational (80,87–89). Children with sickle cell disease had a significantly reduced BMD compared with matched healthy subjects, and boys showed a greater BMD deficit than girls (88). Garrido et al reported a 5.3% fracture rate in children with SCD; however, this study was not powered to estimate the relationship between BMD and fractures (89). BMD was associated with hemoglobin and reticulocyte levels in this study.

Acute Lymphoblastic Leukemia. Acute Lymphoblastic Leukemia (ALL) is associated with substantial skeletal morbidity, with an increased risk of fractures, osteonecrosis, and bone pain observed during maintenance therapy (90). Two prospective longitudinal studies that were published in the interval since the 2007 PDC provide important evidence that patients with leukemia are at high risk for vertebral compression fractures, and DXA LS BMD Z-score predicts future fracture events.

Rayar et al enrolled children and adolescents at the time of the first clinical remission. Baseline DXA LS scans were available in 46 at enrollment and 124 during continuation therapy. Twenty-three (18.5%) patients developed fractures (fracture sites not reported). Dexamethasone therapy and lower LS-BMD during the continuation therapy were independent predictors of fracture (91).

Investigators conducting the national multicenter Steroid-associated Osteoporosis in the Pediatric Population study published the first prospective cohort study of children with newly diagnosed ALL (9,11). Vertebral morphometry was carried out by the Genant semiquantitative method. Overall, 29 of 186 patients (16%) had a total of 75 prevalent vertebral compression fractures within 30 d of diagnosis. Children with fractures had significantly greater back pain and lower LS BMD Z-scores, compared with those without fractures: every 1 standard deviation (SD) reduction in LS BMD Z-score was associated with an 80% greater odds of prevalent fracture. Over the subsequent 12 mo following initiation of chemotherapy, 25 of 155 (16%) children had a total of 61 incident vertebral fractures, of which 32 (52%) were moderate or severe. Vertebral fractures at baseline were highly associated with increased odds of a new incident fracture at 12 mo (OR = 7.3). In addition, for every 1 SD lower LS BMD Z-score at baseline, there was 1.8-fold increased odds of incident vertebral fracture at 12 mo.

Taken together, these studies identify back pain, low LS BMD, and prevalent fractures as important risk factors for future fractures in ALL. Future studies are needed to examine fracture events following completion of chemotherapy. Finally, a recent longitudinal pQCT study in patients following completion of maintenance chemotherapy

demonstrated significant increases in trabecular volumetric BMD and cortical area (92).

Cystic Fibrosis

Low bone mass and fractures are common in young adults with CF. A meta-analysis reported a prevalence of vertebral fractures of 14% (93), and a Canadian cohort (mean age 25 yr) study found a baseline vertebral fracture prevalence of 16%, rising to 21% over a 3-yr period (94). To our knowledge, no studies have evaluated the prevalence of vertebral fractures in children with CF, and no studies have related DXA results to vertebral or non-vertebral fractures.

Many new studies reporting DXA results in children with CF were published between 2007 and 2013; the majority was cross-sectional and 2 were intervention studies (95,96). One study reported normal anthropometric and DXA BMD results in young pre-pubertal children with CF (97), whereas 2 other studies reported low BMD in young children, adolescents, and young adults (98,99). Multiple studies have identified risk factors for bone deficits in CF, including frequent exacerbations (100), dysglycemia (101), lactose malabsorption (102), disease activity score (e.g., Shwachman-Kulczyki score) (103), low vitamin D levels (98), and glucocorticoid therapy (104).

Importantly, a study by Kelly et al illustrated the confounding effects of poor growth and delayed maturation on DXA BMD results: (105) Children with CF have significantly lower LS and TB BMC, compared with healthy controls ($p < 0.001$). However, when the results were adjusted for height Z-score, the TB deficits were attenuated and LS deficits were absent. Height Z-score, lean body mass Z-score, and pulmonary function were independently associated with TB and LS BMC. Given that many of the risk factors associated with low BMD and BMC in CF are also risk factors for poor growth, it is important to incorporate adjustments for short stature in the interpretation of the DXA results.

The European Cystic Fibrosis Mineralization Guidelines recommend that “In children, routine bone density scans should first be performed from around the age of 8 to 10 yr and should be repeated approximately: every 5 yr if the BMD Z-score is > -1 ; every 2 yr if the Z-score is between -1 and -2 ; and every year if the Z-score is < -2 or if the child has experienced low trauma fractures. Bone density measurements can be first done at an earlier age and/or yearly in children with significant risk factors for low BMD and in children before prescribing specific treatments for low BMD.”

Inflammatory Disorders

IBD. Numerous descriptive studies have documented that IBD has an adverse effect on bone modeling and the muscle bone unit. DXA aBMD is lower in Crohn disease, compared with ulcerative colitis (106). Inflammation, poor growth, delayed puberty, lean mass deficits, and glucocorticoid therapy all contribute to poor bone acquisition. Bone deficits are evident at diagnosis, before glucocorticoid exposure, and do not fully recover (107–109). A study in newly diagnosed patients identified significant deficits in pQCT measures of

trabecular volumetric BMD and cortical dimensions (110) and DXA measures of lean body mass at diagnosis (111). Despite significant improvements in lean mass over 1 yr, bone deficits persisted. A cross-sectional study in children with IBD demonstrated an inverse correlation between disease activity indices and BMAD (112). Treatment with infliximab was associated with higher BMAD Z-scores. A small randomized clinical trial of zoledronate (113) demonstrated increases in BMD Z-score, whereas a large study using calcitonin did not have a sustained effect (114).

An early case series reported vertebral compression fractures in children with Crohn disease (115); however, this study reflected fracture events before the era of biologic therapies. In 2010, Kappelman et al reported fracture rates in 733 children with Crohn disease, 488 with ulcerative colitis, and 3287 controls (116). IBD was not associated with increased fracture rates at any site. The impact of peak bone mass and lifetime fracture risk has not been determined (117). To our knowledge, no studies have examined the association between aBMD and fracture events in children and adolescents with IBD.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition clinical practice guideline on skeletal health recommends BMD screening and monitoring in children with IBD and other identified risk factors (118). DXA will also provide important information on body composition. DXA evaluation is advisable in the presence of malnutrition, short stature, prolonged glucocorticoid therapy, or frequent disease relapses.

Celiac Disease. A gluten-free diet is associated with restitution of bone health in children with celiac disease. There is no strong evidence for routine DXA scans at baseline or follow-up of children with celiac disease, with the exception of those with severe growth retardation and malnutrition or those who do not improve, despite strict adherence to a gluten-free diet. In these cases, DXA may provide helpful information on body composition as well as on BMD. As noted previously in the discussion T1DM, celiac disease is a risk factor for low aBMD in these patients (43).

The fracture risk in children with celiac disease is still unknown. A large population-based study in Sweden reported that celiac disease in childhood was associated with a 2.6-fold greater risk for hip fractures (119). However, the absolute numbers were low: 6 hip fractures/100,000 person-years compared with 2 fractures/100,000 person-years among controls. In a meta-analysis of 8 studies (120), Olmos et al considered 20,955 celiac disease patients having 1819 (8.7%) fractures and 96,777 controls with 5955 (6.1%) fractures (pooled odds ratio = 1.43); however, the study was limited by considerable heterogeneity among studies. To our knowledge, no studies have evaluated the association between BMD and fracture risk in celiac disease.

Rheumatologic Diseases. The Task Force did not perform a systematic review of rheumatologic conditions. However, the study by Rodd and the Steroid-associated Osteoporosis

in the Pediatric Population investigators was considered at the PDC deliberations (121). The study was conducted to determine the frequency of incident vertebral fractures over a 12-mo period after glucocorticoid initiation in children with rheumatic diseases. A total of 136 participants enrolled and 118 completed the 12-mo visit. Of these, 7 (6%) developed an incident vertebral fracture in a previously normal vertebrae. One child had symptomatic vertebral compression fractures requiring bisphosphonate therapy and was excluded from the longitudinal analyses. Children with incident fractures received higher glucocorticoid doses, had greater increases in BMI, and had greater declines in spine aBMD Z-scores in the first 6 mo.

CKD and Renal Transplantation

CKD and renal transplantation were not included among the indications for DXA in the 2007 ISCD positions. This decision was based on concerns that DXA usefulness was not proven in a disorder characterized by opposing effects on the trabecular and cortical bone mass (increase and decrease, respectively). These opposing effects were confirmed in a cross-sectional and longitudinal pQCT study in children and adolescents with mild-to-severe CKD published in the interval since the 2007 PDC (122,123). However, a subsequent study by the same investigators demonstrated that changes in the LS BMD and TB BMC Z-scores mirrored the trabecular and cortical changes observed by pQCT following renal transplantation and captured the associations with parathyroid hormone (PTH) and glucocorticoid therapy (13).

Moreover, until 2007, studies on the associations between DXA results and fractures in CKD were limited to cross-sectional analyses of prevalent fractures in adults, and many suggested that DXA results were poorly associated with fractures. However, 3 recent prospective studies have demonstrated that femoral neck BMD predicted fractures in CKD (124–126). In a prospective study in adult patients on hemodialysis, femoral neck and total hip BMD predicted incident fractures; however, radius, spine, and whole-body BMD did not (125). A study in adult kidney transplant recipients documented that osteopenia (T-score < -1 and > -2.5 SD) as well as osteoporosis (T-score ≤ -2.5 SD) at hip were independent risk factors for fractures, with relative risks of 2.7 and 3.5, respectively, independently of sex, age, and diabetes (126). The association was not significant for spine or total body BMD. To date, there are no studies relating DXA results to incident fractures in children with CKD. However, the growing evidence that DXA provides fracture discrimination in CKD suggests that there is inadequate evidence to exclude children with CKD from the PDC recommendations for children with chronic disease.

The Task Force reviewed numerous articles on BMD in CKD and renal transplantation dating back to 1994 since CKD was not included in the 2007 PDC. The studies were complicated by marked heterogeneity in the severity of CKD. None of the studies related DXA BMD to fracture events. Two studies reported an inverse relation between LS BMD Z-score and PTH levels (127,128).

The study by Griffin et al compared pQCT and DXA results in 88 children with advanced CKD and 650 healthy controls (129). LS and TB DXA suggested greater trabecular BMD and lower cortical BMC in CKD, compared with controls—consistent with pQCT results. Z-scores were modestly correlated at the trabecular (DXA LS BMD and pQCT trabecular BMD: $R = 0.36$) and cortical (TB BMC-Z and pQCT cortical BMC-Z: $R = 0.64$) sites in CKD, similar to correlations in reference participants. This study also illustrated the importance of adjusting for growth failure in CKD. The mean height Z-score among the participants was -0.96 with a range from -4.87 to 1.66 . The mean TB BMC Z-score relative to age was -1.31 and increased to -0.36 with adjustment for height Z-scores, using the method of Zemel et al that is endorsed in this PDC (5). Similarly, the LS Z-scores increased from a mean of -0.02 to 0.50 with adjustment for height Z-scores.

Transplantation. Children undergoing transplantation frequently have compromised bone health pre-transplantation due to the underlying disease. The majority of studies following renal, liver, heart-lung, and bone marrow transplantation were cross-sectional and performed DXA at highly variable intervals following transplantation—limiting our ability to draw conclusions regarding change in BMD following transplantation. In addition, few addressed growth status and the confounding effects of short stature on areal BMD results.

The largest study of fractures following pediatric transplantation included a population-based sample of 196 children undergoing solid organ transplantation (130). Overall, the incidence of all fractures was 6-fold higher and vertebral fractures was 160-fold higher in the transplant recipients compared with the control population. In a multivariate analysis, older age, male sex, liver transplantation, and fractures before transplantation were the most significant independent risk factors. The relation between BMD and fractures was not reported. The authors conclude that screening of vertebral fractures at regular intervals is recommended.

Bone Marrow Transplantation. All but one of the DXA studies were cross-sectional and none related DXA BMD to fracture events. The single prospective longitudinal study enrolled 49 children and adolescents at the time of transplantation (131). The mean LS BMD Z-score decreased from -0.56 at baseline to -1.10 by 6 mo in 27 children and -0.94 at 12 mo in 21 children. The reduction in LS BMD at 6 mo was correlated with the cumulative glucocorticoid dose.

Although none of the studies addressed fracture risk, one study related DXA BMD to non-fracture outcomes: the risk of low BMD was greatest among survivors who received central nervous system irradiation, were older, female, and had greatest fat mass (132).

Mostoufi-Moab recently examined a sample of long-term survivors, enrolled a median of 7 yr after transplantation. Despite years off all therapies, including glucocorticoids, tibia pQCT scans revealed substantial trabecular and cortical deficits, especially among those treated with total body

irradiation (133). TB DXA scans in these survivors documented significant cachexia and excess adiposity (134).

Liver Transplantation. The majority of studies were cross-sectional. The studies evaluated patients of different ages, ranging from infancy to 23 yr. Multiple studies demonstrated recovery of BMD following liver transplantation (135–138). Valta et al reported that vertebral fractures (estimated with DXA vertebral fracture assessment) were associated with lower Z-scores at LS, hip, and TB (139).

The most recent study enrolled 18 cholestatic infants and young children at the time of transplantation, with 4 yr follow-up in 16 patients (135). DXA TB BMD and BMC improved markedly over the first 18 mo, then declined at the time of the 4-yr visit in association with increases in PTH levels. The changes in TB BMC over the 4 yr correlated with insulin growth factor-1 levels.

Heart and Lung Transplantation. The few studies that were identified were limited to cross-sectional studies and retrospective chart reviews. The most recent study examined BMD in 26 pediatric heart transplant recipients a median of 3.4 yr after transplant. The median TB and LS BMD Z-scores were -0.09 and -1.10 . Three patients had vertebral fractures and/or avascular necrosis (140).

Official Positions

What is the Role of DXA in Pediatric Practice?

- DXA measurement is part of a comprehensive skeletal health assessment in patients with increased risk of fracture.
 - Grade: Good-B-W.

Rationale

This Official Position is unchanged since the 2007 report; however, the rating of the quality of the evidence has improved from Fair to Good. The rationale for this Official Position is further strengthened by the substantial new data and advances summarized previously. We have identified a series of disorders where fracture risk exceeds that seen in healthy children, and in many of these disorders there is a reduction in bone mass that may contribute to the increased fracture risk. Furthermore, there are substantial new data relating DXA BMD to fracture outcomes and modifiable risk factors, such as glucocorticoid therapy, inflammation, decreased muscle mass, immobilization, and disease activity. Last, there are multiple studies demonstrating increases in BMD in response to therapies.

Discussion

The utility of DXA as part of a comprehensive health assessment is supported by 3 major considerations. First, there are now multiple prospective studies demonstrating that DXA aBMD predicts vertebral and non-vertebral fractures in children and improves in response to therapies. For those diseases with lack of data on fracture events, multiple

studies have demonstrated associations with disease and treatment characteristics. In general, the studies reviewed in this report suggest that DXA is useful as part of the bone health evaluation of children with chronic illnesses. An increasing number of studies have been published which show an inverse relationship between DXA-based aBMD (most often measured at the spine) and vertebral as well as non-vertebral fractures; furthermore, the relationship between aBMD and clinically relevant non-fracture outcomes (such as ambulatory status, glucocorticoid therapy, and PTH) has also been explored and confirmed in childhood chronic disorders. In diseases where the vertebral and non-vertebral fracture rates are still unknown, additional studies are needed to define the epidemiology of fractures and the ability of aBMD to predict bone strength loss. Second, the newly available robust reference data for conventional DXA sites (3–6) and for the distal lateral femur (8) will facilitate clinical applications. And, third, the adoption of accepted strategies to adjust for short stature by the 2013 PDC is an important advance since many of the DXA studies cited previously confounded by the effects of growth failure in children with chronic disease.

1. When should DXA scan measurements be initiated in children at increased risk of fracture?
2. How does measurement of bone mass contribute to the management of pediatric patients?
3. What is the optimal timing for DXA evaluation in the follow-up of children and adolescents in different pathologic conditions and in relation to therapy?
 - In patients with primary bone disease, or at risk for a secondary bone disease, a DXA should be performed when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture and the DXA results will influence that management.
 - Grade: Fair-B-W.
 - DXA should not be performed if safe and appropriate positioning of the child cannot be assured.
 - Grade: Fair-C-W.

Rationale

These new recommendations represent a significant change from the original guidelines that recommended (18): (1) In patients with primary bone diseases or potential secondary bone disease, spine and TBLH BMC and areal BMD should be measured at clinical indication (Poor-C-W); (2) in patients with thalassemia major, spine and TBLH BMC and areal BMD should be performed at fracture presentation or age 10 yr, whichever is earlier (Fair-C-W); (3) therapeutic interventions should not be instituted on the basis of a single DXA measurement (Fair-C-W); and (4) when technically feasible, all patients should have spine and TBLH BMC and areal BMD measured before initiation of bone active treatment and to monitor bone-active treatment in conjunction with other clinical data (Poor-C-W). It is noteworthy that all of these were graded C, that is, supported by expert opinion only.

The 2013 Expert Panel felt that there was insufficient evidence that routine DXA scans at diagnosis in all primary and secondary diseases (or as specified previously in thalassemia major) are indicated and would have a beneficial effect on bone health. For example, one could monitor vitamin D levels and ensure adequate calcium and vitamin D intake in patients with well-controlled diseases without performing a DXA scan. Similarly, the disease-specific literature review above identified very high risk populations, such as Duchenne's muscular dystrophy, where a DXA may be indicated before starting glucocorticoids, or new onset ALL, where a DXA assessment may identify those at high risk for incident fractures. However, even in these conditions, the positive and negative predictive value of a low DXA BMD for fracture events has not been established. As noted in the accompanying *Fracture Prediction and the Definition of Osteoporosis in Children and Adolescents* Position Statement, vertebral compression fractures have been observed in the absence of a low BMD. Therefore, the 2013 Expert Panel felt that the recommendation for DXA scans should be refined to include only those where the patient may benefit from interventions and the DXA will influence management. Of note, the level of evidence for this revised guideline is improved at B, that is, supported by the evidence.

With regard to the safe and appropriate positioning of the child, this Position Statement is a revision of the prior statements which stated: (1) In children with chronic immobilization (e.g., CP) spine and TBLH BMC and areal BMD should be measured at fracture presentation, and (2) DXA should not be performed if contractures prevent the safe and appropriate positioning of the child. These combined statements were rated as Poor-C-W. This first statement was eliminated as the new Position Statement provides recommendations as to the timing of the scans in all children with primary or secondary bone disease. This minor amendment specifies that the scan should not be performed if safe and appropriate position cannot be obtained for any reason, such as contractures or other disabilities.

Discussion

It is important to note that literature describing the acquisition of DXA scans before initiation of bone-targeted treatment and at routine intervals in the diseases discussed previously was typically performed as part of a prospective study protocol. This does not mean that these are the clinical recommendations. For example, one study performed DXA scans every 3 mo following pediatric renal transplantation to characterize the tempo of bone loss and identify high risk periods (13), but these data do not serve as recommendations for such frequent measurements. Importantly, the data on responses to therapy, such as the use of bisphosphonates in OI, can inform the frequency of measurements in certain diseases. However, the breadth of diseases, their severity, and the therapeutic options prevent standardized recommendations.

The literature does not suggest that a single DXA measurement is sufficient to dictate specific therapeutic interventions.

One should rely instead on the fracture history, risk factors, and aBMD trajectory. This is evident in the large number of cross-sectional studies that provide an incomplete picture of the effects of the disease and its therapies. The timing of the first DXA scan, and the number of aBMD re-evaluations depend on the magnitude of the ongoing risk of fracture, the magnitude of low aBMD, the aBMD trajectory, and periods when significant clinical changes are expected.

Last, 2 important studies published since 2007 will facilitate the use of distal lateral femur scans in children with chronic immobilization in whom LS and TB DXA cannot be performed with safe and appropriate positioning. The first described robust reference data (8) and the second demonstrated that BMD Z-scores generated using these reference data were associated with fractures in children with CP or DMD (12).

Future Directions

Although there have been numerous important advances since the last report that have informed our understanding about the clinical utility of DXA-based BMD in children, many of the Position Statements are not evidence based. There is an ongoing need for further studies which elucidate the relationship between DXA aBMD parameters and non-vertebral and vertebral fractures in the various disease states, the positive and negative predictive value of aBMD in forecasting incident fractures and the nature of the relationship between aBMD treatment response and subsequent reductions in fracture (and other adverse health outcome) risk.

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