

## Position Statement

# Dual-Energy X-ray Absorptiometry Assessment in Children and Adolescents with Diseases that May Affect the Skeleton: The 2007 ISCD Pediatric Official Positions

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## Abstract

The Task Force focusing on the use of dual energy X-ray absorptiometry (DXA) in children and adolescents with diseases that may affect the skeleton reviewed over 300 articles to establish the basis for the Official Positions. A significant number of studies used DXA-based outcome measures to assess the effects of specific interventions and charted the natural history of incremental changes in bone size and mass in specific disease states in children. However, the utility of DXA in clinical practice has not been evaluated systematically, in large part due to the lack of a workable definition for childhood osteoporosis. Thus, in combination with the Official Positions addressing the diagnosis of osteoporosis in children, and the reporting of DXA results in children, this document presents clear guidelines from which clinicians and researchers alike can work. This report delineates a set of disorders in which it is appropriate to use DXA as part of the comprehensive assessment of skeletal health in children and adolescents, and provides guidance concerning the initiation of assessment and the frequency of monitoring. Importantly, this document also highlights significant gaps in our knowledge, emphasizing areas for future research.

**Key Words:** Body Size; chronic disease; frequency; low bone mass; monitoring; osteoporosis.

## Introduction

The Positions included in this section draw together advice for clinicians wishing to use dual energy X-ray

absorptiometry (DXA) in children. Fractures are not uncommon in healthy children; 27–40% of girls and 42–51% of boys sustain at least 1 fracture during growth (1,2). Up to one-third of children who fracture will go on to have another fracture (3). The principal activity in the growing skeleton is bone modelling, as opposed to remodelling in the adult skeleton. Bone mass increases with growth and development in most children and adolescents, including those with bone disease—albeit at a lower rate compared with healthy children. Absolute bone loss is unusual, but a low bone mass for age is not uncommon, often reflecting low body size. It is widely accepted that osteoporosis in children cannot be determined

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solely on the basis of low bone mass for age. However, the most appropriate method for adjusting raw measurements in children with chronic disease is not clear. Although a few studies have compared methods to adjust DXA results for differences in bone size in apparently healthy children (4), there are insufficient data to determine which adjustment methods provide better measures of bone fragility and fracture risk in children with disorders affecting skeletal health.

Most fractures in children take place in the peripheral skeleton and forearm fracture rates have increased over the last 30 yr (5). Dual energy X-ray absorptiometry instruments are designed to measure bone mass at sites commonly associated with adult osteoporotic fracture (typically sites with high trabecular bone content) and thus are not necessarily suited to the investigation of fractures in childhood (6). Nevertheless, low trauma fractures of the vertebrae or femoral neck have been observed in childhood chronic disease (7) and likely represent significant skeletal pathology.

Irrespective of these concerns, the starting point for inclusion of pediatric medical conditions within the field of interest of this task force was the association of the condition with an increased risk of fracture. Where such an association was thought to exist, a task group member was assigned to investigate the specific questions detailed below, in order to improve our understanding of the biological basis for the association and how this might be reflected in the measurement of projected bone area, bone mineral content (BMC) and areal bone mineral density (BMD) by DXA. This approach was cognisant of the fact that many chronic childhood disorders affect growth and hence both bone size and bone mass. However, given the absence of data comparing adjustment methods in distinct pediatric chronic disease, as relates to disease activity or fracture risk, we did not make recommendations regarding the methods to adjust for differences in body size. Rather, the DXA Reporting Task Force addresses this issue across all disorders associated with abnormal growth and maturation.

As stated previously, reduced growth of the skeleton does not of itself confer an increased risk of osteoporosis in childhood and young adulthood. However, there may be interactions between the processes underpinning growth and susceptibility to fracture, as evidenced by the increase in risk of fracture around the time of peak height velocity in children who are otherwise well (1,5). Other sections of this report examine the relationships between body size, bone size, bone mass, and fracture risk. We concur with their conclusions that there are consistent and reproducible associations between fracture risk, and bone size and mass adjusted for body size across the pediatric age range. Accordingly, we believe that fracture risk is likely increased by the disease processes and treatments as described below.

The numbers of subjects in the majority of paediatric studies have not been sufficient to disentangle the effects of such "intrinsic" risk due to the effects of the disease process from its treatment. Similarly, the distinct effects of most chronic diseases on trabecular and cortical bone density and architecture have not been established. For example, strategies to

assess total body bone size (i.e., total body DXA bone area) relative to bone height, such as proposed by Molgaard, et al (8), have been used in disparate diseases (9,10), and have not been widely adopted. Furthermore, studies using spine quantitative computer tomography (QCT) (11) in children with chronic diseases are very limited. Recent years have seen a significant increase in peripheral quantitative computer tomography (pQCT) studies in children with chronic disease (12–17), confirming the presence of significant cortical and trabecular deficits. Further discussion of the use of pQCT is found in the pQCT Task Force document.

It should be recognised that in adulthood low body mass and smaller skeletal mass are associated with an increased risk of osteoporotic fracture in later life. Nevertheless, this task force focused on those disorders that cause immediate problems for the health of the growing skeleton. The impact of peak bone mass and the long-term consequences of chronic disease in childhood require further study.

A number of disorders are associated with altered bone mass and increased risk of fracture in childhood. Broadly, the disorders can be classified as primary bone diseases such as osteogenesis imperfecta, where the defect lies in the bone tissue, and secondary disorders where the disease is not in the skeleton but factors associated with the disease affect bone strength through a variety of mechanisms, including inhibition of bone formation (18), reduced responsiveness to mechanical stimulation (19), and excessive and inappropriately sited bone resorption (15). In common with adult disease, at an ultrastructural level, the changes seen in bone include alteration of the material quality of bone tissue (in osteogenesis imperfecta (OI)); deterioration in trabecular architectural integrity with reduced trabecular number; thinner trabeculae; and reduced trabecular connectivity, as well as increased cortical porosity and reduced cortical thickness and bone width.

Most primary disorders are familial; a clear biological basis can be demonstrated in both OI, and some cases of idiopathic juvenile osteoporosis (IJO) where there are heterozygous mutations in LRP5 (20), and the osteoporosis pseudoglioma syndrome where both copies of LRP5 are abnormal. These disorders all give rise to defects in bone formation. Interestingly, disorders of constitutively increased bone resorption give rise to patchy alterations in bone mass, with cystic and expansile lesions being more typical than a generalised osteoporotic phenotype (22).

The disorders where reduced bone mass and increased risk of fracture are secondary to a non-skeletal primary disorder include a wide range of conditions characterised by one or more of the following: inflammation; reduced mobility; hormonal disturbances; haematological problems; and malnutrition. In some groups, the treatment used to ameliorate the primary disorder can worsen the effects of the disease on the skeleton. An important specific example of this is steroid therapy. In this document, we have considered the use of specific interventions in relation to the treatment of the primary condition, essentially because the cross-sectional data in subjects with complex treatment courses has not been presented

that would enable us to disentangle the effects of the treatment from the effects of the disease itself. In addition, for steroid therapy specifically, there is evidence that when used in some conditions (specifically idiopathic, steroid-sensitive, nephrotic syndrome (23,24)) steroids do not result in adverse skeletal effects. Nonetheless, a population-based study of the association of steroid use with fracture did show an association between four or more courses of oral steroids in 1 yr and an increased risk of fracture. It is not known if this effect was due to the greater steroid exposure, or the greater disease activity necessitating the greater steroid therapy. Therefore, the context of steroid use is important in considering the potential for harm and the effects that such a context and risk might have in setting guidelines for the use of bone mass measurement in children (25).

Finally, chronic kidney disease has not been included in the disorders assessed here. The National Kidney Foundation recently published clinical practice guidelines in children (26), concluding that the utility of DXA is not proven in a disorder characterized by opposing disease effects on trabecular and cortical bone mass (increase and decrease, respectively (27)).

The extent of disease the Task Force reported on, for the use of bone densitometric assessment, is as follows:

#### **Primary Bone Disorders**

- Idiopathic juvenile osteoporosis (IJO)
- Osteogenesis imperfecta (OI)

#### **Secondary to Inflammatory Diseases**

- Inflammatory bowel disease (IBD)
- Juvenile idiopathic arthritis (JIA)
- Cystic fibrosis (CF)

#### **Secondary to Chronic Immobilisation**

- Cerebral palsy (CP)
- Myopathic disease
- Epidermolysis bullosa (EB)

#### **Secondary to Endocrine Disturbances**

- Turner syndrome (TS)
- Anorexia nervosa (AN)

#### **Secondary to Cancer and Therapies with Adverse Effects on Bone Health**

- Acute lymphocytic leukaemia (ALL) and following chemotherapy for childhood cancer
- Transplant Bone Disease

#### **Secondary to Hematologic Disorders**

- Thalassaemia

All of these areas are associated with an increased risk of fracture according to one or more reports, although for TS, the increase in fracture risk is not present in childhood. There are some disorders where it could be argued that there are multiple factors that contribute to the increase in bone fragility; the categorisation of the disorders studied into the groups above represents simply an approach to defining the underlying disease, not the additional contributing factors. For example, children undergoing transplantation may suffer decreased physical activity following transplantation; may experience adverse effects of immunosuppressive drugs; and the underlying disease (e.g., liver failure, cystic fibrosis, or malignancy)

may have had adverse effects on bone health prior to transplant.

For each of the areas and specific conditions listed, the following questions were posed and answered by the task force member with responsibility for the specific area:

- What is the evidence for increased fracture risk in this condition?
- What is the relationship between DXA measures of BMC and areal BMD and fracture risk in this condition?
- Does measurement of DXA BMC and areal BMD influence management in this condition?
  - Subquestions:
    - When should DXA measurements commence?
    - How often should DXA scans be performed?
    - Are DXA measures of BMD and areal BMD accurate and precise in this condition?
- Is a DXA scan indicated for all children with this condition, or only in those with additional risk factors?
- Is there an effect of disease activity on DXA measures of BMC and areal BMD?
- Does disease management affect DXA BMC and areal BMD?
- What is the effect of stopping treatment on DXA BMC and areal BMD?

The answers to these questions generated the initial position statements that have been refined and presented here as ISCD Official Positions, facilitating the clinical application of DXA in paediatric practice.

## **Methodology**

A literature search was performed using the PubMed and OVID MEDLINE databases for the time period from 1966 to February 2007. Combinations of the terms “bone mineral density”, “BMD”, “BMAD”, “children”, “adolescents”, “pediatric” and “fractures” were used, along with the specific names for each of the diseases and disorders covered.

The methods used to develop, and grading system applied to the ISCD Official Positions, are presented in the Executive Summary that accompanies this paper. In brief, all positions were rated by the Expert Panel on quality of evidence (good; fair; 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 the 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), strength of the recommendation (A; B; C: where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion) and applicability (worldwide = W or variable, according to local requirements = L). Necessity was also considered with a response of “necessary”

indicating that the indication or procedure is “necessary” due to the health benefits outweighing the risk to such an extent that it must be offered to all patients and the magnitude of the expected benefit is not small.

## What is the Role of DXA in Pediatric Practice?

### *ISCD Official Position*

- DXA measurement is part of a comprehensive skeletal health assessment in patients with increased risk of fracture.

Grade: Fair-C-W-Necessary

### *Rationale*

As stated previously, fractures are not uncommon in healthy children; 27–40% of girls and 42–51% of boys sustain at least one fracture during growth (1,2). Up to one-third of children who fracture will go on to have another fracture (3). We thus identified a series of disorders where fracture risk likely exceeds that seen in normal children. The potential increase in fracture risk occurs in the context of specific clinical situations including primary bone diseases e.g., OI and IJO, or secondary to other problems e.g., immobilisation; inflammation; endocrine disturbance; malignancy and its treatment; following transplantation; and in thalassemia. In some but not all patients with these disorders, there is a reduction in bone mass that may contribute to the increase in fracture risk, and regular measurement of bone size, BMC, and areal BMD by DXA is part of the evaluation of these patients. In addition, according to clinical judgement, it may be appropriate to assess apparently healthy children with clinically significant fractures, as defined in the Official Positions.

### *Discussion*

Multiple cross-sectional and longitudinal studies attest to the increased propensity to fracture in both OI (21,29–31,35,45–70) and IJO (28–33); fracture might reasonably be considered a prerequisite for IJO, and an increase in fracture risk is always present in OI, although to a variable degree. The quality and extent of evidence for increased fracture risk is good; primarily observational but very consistent with a clear biological basis in both conditions. There is an increased risk of fracture both before and after starting anti-inflammatory therapy in IBD (88–100), JIA (34,35), and CF (36–40). The risk of fracture in IBD seems greater in Crohn’s disease rather than ulcerative colitis, although there may be some bias in fracture reporting; one population based study found no overall increase in fracture risk for Crohn’s disease (41). In contrast, a population based study encompassing the entire Danish population did show a minor elevation in risk for Crohn’s but not ulcerative colitis. Fracture is more common in both children and adolescents with arthritis compared to general population controls, becoming increasingly common with increasing age (34). The risk of fracture in childhood is increased by exposure to glucocorticoids (42), the principle anti-inflammatory agent used in all three conditions.

However, many studies did not report on fracture risk prior to starting interventions for the primary condition. A number of population-based studies have been undertaken which clearly indicate an increased risk of fracture in children with arthritis. The picture for the other conditions is less clear. It is, however, clear that exposure to corticosteroids increases fracture risk, and given the propensity for the use of steroids in these conditions it can be assumed that fracture risk will be increased in those with inflammatory disorders who receive steroids. Additional helpful reports are those that have given information regarding fractures likely to be attributable to significant bone loss, particularly vertebral fractures.

Fractures and reduced bone mass secondary to disuse have been reported in a number of different disease states, with the largest area being CP. There have also been multiple reports of osteoporotic fractures in Duchenne muscular dystrophy, both of vertebrae and long bones, particularly in those patients receiving steroids (43–45). Fractures can occur in other neuromuscular conditions such as spinal muscular atrophy (46), epidermolysis bullosa (EB) (47,48), following spinal cord injury (49), and in premature infants where the smallest and sickest are often relatively immobile and may also have additional risk factors, notably metabolic bone disease of prematurity (50–52). Evidence for an increase in fracture risk in CP overall, is sparse. A number of studies have undertaken interventions to increase bone mass in patients with CP (53–62), and some have recorded reductions in fracture frequency (53,55). Overall, fractures were recorded in 8 of 25 studies in which bone densitometry was undertaken (53,55,58,60,63–66), and recorded as definitely increased in only one (64). Furthermore, the use of anticonvulsant medication in immobilised children is reported as a major risk factor for fracture. In EB, in contrast to CP, vertebral compression fractures rather than long bone fractures are reported (47).

Increased fracture risk is reported in adult women with TS in some, but not all, studies (67–72). This may be related to variable adherence with estrogen replacement. There is no good evidence for increased fracture risk in girls and teenagers with TS. Increased risk of fracture is reported in epidemiological surveys of a mixed paediatric/adult population (69,70), but conflicting results come from the smaller observational studies in prepubertal TS girls (73,74). The overall risk of fracture in the population of TS patients (70) is similar to that in childhood for girls (approx 25%) (1).

By contrast, there is convincing data for an increase in fracture risk for girls with anorexia nervosa (AN). Vestergaard’s review of 2021 female and 128 males with AN, from the Danish national cohort study over the period 1977–1998, showed a clear increase in the odds ratio (OR) for fracture at both the spine (OR 3.49, 95% confidence interval [CI]: 1.50–8.11) and femoral neck (OR 7.12, 95% CI: 3.36–15.32), compared with age and sex-matched controls (75).

A recent retrospective review of fracture frequency in children with ALL in Innsbruck, using the UK General Practice Research Database as a comparator, found a doubling in the risk of fracture after controlling for age and gender, with higher risks in the younger children (age not greater than

5 yr) (76). In other studies looking at fractures in ALL (four following treatment and two during treatment) an increase in fractures was also demonstrated (77–82). However, there was a wide range in reported increases in risk between studies and some did not use a control group.

Fracture frequency is substantially increased in organ transplantation (83) with vertebral compression fractures being a particular issue. Liver transplant patients appear to be at particular risk (83,84), as are those with fractures prior to transplant (83). The long period of follow-up in the Helenius study (83) makes it particularly valuable in identifying the substantial increase in fracture risk in children undergoing solid organ transplantation, with a three-fold increase (compared to healthy controls) in the risk of recurrent fracture amongst this group.

For children with thalassaemia, there is no clear evidence of increased fracture risk generally. Most of the studies report historical fracture data that do not specify if fractures occurred in childhood or later on in life. Few studies report excessive numbers of fractures (28,85–88). Because of their study design, they do not address if fractures are related to trauma or are pathologic in nature. Increasing fragility with advancing age was found in a large retrospective study (85). Few studies reported increased fragility in young adults (87,88). Two studies report that fracture is associated with lower bone mass (28,85). The rest of the studies have not examined the relationship of bone mass with fractures.

## When Should DXA Scan Measurements be Initiated in Children at Increased Risk of Fracture?

### ISCD Official Positions

- In patients with primary bone diseases or potential secondary bone diseases (e.g., due to chronic inflammatory diseases; endocrine disturbances; history of childhood cancer, or prior transplantation (non-renal)), spine and total body less head (TBLH) BMC and areal BMD should be measured at clinical presentation.

Grade: Poor-C-W-Necessary

- In patients with thalassaemia major, spine and TBLH BMC and areal BMD should be measured at fracture presentation or at age 10 yr, whichever is earlier.

Grade: Fair-C-W-Necessary

- In children with chronic immobilization (e.g., cerebral palsy) spine and TBLH BMC and areal BMD should be measured at fracture presentation.
- DXA should not be performed if contractures prevent the safe and appropriate positioning of the child.

Grade: Poor-C-W-Necessary

### Rationale

In each of the conditions discussed there is some evidence to demonstrate that fracture risk is increased. Given that DXA forms part of the monitoring of skeletal health in disorders with increased fracture risk, the issue becomes one of

“when” to measure, rather than “if”. The rationale for obtaining a DXA scan at the outset is based on practicality and the need to generate a comprehensive picture of skeletal health. Not assessing bone status means that there is inadequate information on which to base clinical decisions aimed at maintaining or improving skeletal health; such measures include simpler interventions such as advice on diet and exercise, moving on to nutritional supplementation, and finally bone-active therapies such as bisphosphonates. For children with thalassaemia, the Official Position reflects the increased risk of fracture or skeletal ill health that is compounded by hypogonadism in the second decade of life, in many. The Official Positions also recognise the difficulty in positioning and reproducibility that can occur either as a result of very young children moving, or because children with deforming conditions cannot lie flat. In such instances, patient safety and comfort take priority. Alternative scan sites such as the lateral distal femur can be employed in children with contractures (160).

### Discussion

Measurements commence generally at the time of presentation in both IJO and OI (29,31–35,45–47,50,51,53,54,56,57,60,65,67,68,70,72–74,76–87); in mildly affected individuals they typically continue on a regular but less frequent basis (see below); and certainly before the commencement of therapeutic interventions. Increasing disease severity in OI is associated with worsening decrement in bone mass, and is also reflected in more severe growth retardation (generally not directly reported in the papers reviewed—assumed). In IJO, areal BMD is lowest in the acute phase of the disease (30–32) and higher in the recovery phase; this recovery in areal BMD may be spontaneous (31).

Studies are consistent in indicating that the more severe the phenotype in OI, the lower the bone mass. Some assessments may be confounded by reduced body size in OI. IJO patients are reported to have a low bone mass at diagnosis with gradual resolution. It may be difficult to disentangle whether the bone mass alters simply because of the passage of time and altered intrinsic effects of growth, or whether this indicates alteration in disease activity.

The rationale for measurement initiation was recorded in 2 of the 42 IBD studies (89,90) and 5 of the 45 CF studies (91–95). In all the CF studies, measurement initiation preceded interventions to increase bone mass. For the IBD studies, measurements were either started at diagnosis or for unstated reasons. Where measurements were taken at or around the time of diagnosis in IBD and JIA, there was typically a deficit in bone mass compared to healthy controls.

It is clear that bone mass is progressively lost in CF patients (37) from the first decade onwards; similar results have been obtained in cross-sectional studies of CF patients (96,97), indicating that skeletal disease is not simply a problem for older patients. Bone mass values are low compared to controls in both IBD (98) patients at diagnosis and JIA patients early in the course of their disease (99). To have a clear idea of how the disease and its treatment are impacting on the

skeleton, it is necessary to have a starting point, and from the available data it would appear the earlier the better.

For children with immobilising disorders, the available studies do not address the optimal timing for initiating bone mass measurements. The intervention studies (53–62) all undertook measurements prior to starting therapy, whether physical or pharmacological. In the non-intervention studies (18,20,201,209,210,218–225), measurements were made typically only once. The EB studies have been cross-sectional with only single measurements reported.

The TS data suggest no benefit to starting bone mass measurements in childhood, given the lack of association with fracture or influence on management decisions. Experienced adult physicians need to decide how often adult TS women should be measured, and when such measurements should start. There are no reported studies of measurement precision in TS. In AN, measurements tend to start at or around the time of diagnosis in late adolescence (5–17 yr typically) (100–103). The frequency of measurement in the cited studies of AN varied from only one measurement (101,104–109), to measures approximately every 6 mo (102,110–112), to intervals as long as 3–4 yr (102,103,110–113). There is no specific sub-group of children with either TS or AN that would be picked out for DXA measurement. However, duration of amenorrhoea (105,113), primary amenorrhoea (106), degree of loss of body tissue mass as assessed by reduction in body mass index (BMI) (105,114), and AN as opposed to bulimia (103) were all factors associated with lower BMC and areal BMD outcome measurements by DXA.

For ALL and post-chemotherapy patients, the literature suggests that measurements are typically undertaken in those with bone pain; fractures; previously diagnosed endocrinopathy (especially in those with prior cranial irradiation); poor linear growth (with potential occult vertebral fractures); and prolonged poor nutrition. In transplant studies, there is enormous variation in the time of initiation of measurement of bone mass, from pre-transplant (115,116) to up to 20 yr post-transplant (117).

In children with thalassaemia the current practice is to initiate measurements before intervention to increase bone mass (86,118–122). Many studies have reported DXA measurements starting in childhood and adolescence. However, these were done primarily for research interests rather than for clinical care.

## How Does DXA Measurement of BMC and Areal BMD Contribute to the Management of Pediatric Patients?

### ISCD Official Positions

- Therapeutic interventions should not be instituted on the basis of a single DXA measurement.  
Grade: Fair-C-W-Necessary
- When technically feasible, all patients should have spine and total body less head (TBLH) BMC and areal BMD measured:

- Prior to initiation of bone-active treatment
- To monitor bone-active treatment in conjunction with other clinical data

Grade: Poor-C-W-Necessary

### Rationale

Measurement of bone density by DXA is confounded by the fact that children grow. As detailed in the *Fracture Prediction and Definition of Osteoporosis Task Force* report, there is evidence that in apparently healthy children, after adjusting for age, gender, body size and bone size, there is a relationship between lower bone mass and increased fracture risk. It is likely that such relationships also exist in children with chronic disease, but few studies have convincingly demonstrated this, largely because the majority of studies in children have been small. Reliance on DXA alone to guide the initiation of bone-active interventions is thus inappropriate. However, if in combination with other markers of skeletal health it is decided to initiate bone-active treatment (for instance bisphosphonates, calcitonin or calcitriol), monitoring bone mass by DXA at baseline and clinically appropriate intervals as part of the assessment of the response was deemed appropriate by the Expert Panelists.

### Discussion

The relationships between fracture risk and bone mass measurements have not been established in children with OI or IJO. None of the prospective randomized clinical trials in children with OI have reported on this relationship. Land et al (123) found that spine areal BMD predicted vertebral height; Kok (124) found that spine areal BMD predicted prevalent vertebral deformity after adjusting for height and weight. Vallo (125) observed that two out of 10 patients with OI had normal spine areal BMD and did not fracture. In IJO, areal BMD is lowest at diagnosis and during the acute phase of the illness (30–32); the exact relationship with fracture risk has not been studied in this group either. In addition, the relationship between increases in areal BMD and reductions in fracture risk that might be expected to accompany an intervention has not been addressed in the published literature.

It is not discussed directly in any papers whether measurement of bone mass guides management of OI or IJO. However, for both conditions, measurement of spine and total body bone area, BMC and areal BMD, and derived estimates of volumetric BMD by DXA (BMAD) are frequently reported as outcomes of intervention (53,126–149). Peripheral quantitative computer tomography is less widely used but is gaining popularity (150,151).

Bone mass measurement is not the sole factor on which clinicians base the decision to intervene in OI and IJO; rather its role thus far has been to assess the effect of interventions such as bisphosphonates and growth hormone on bone mass accretion. However, the application of DXA has been uncritical in that most studies have failed to distinguish between the likely effect on the accretion of mineralised bone and of calcified cartilage.

Strength of evidence is limited in that the utilisation of bone densitometry in OI and IJO has been largely directed (in the available reports) at demonstrating that bone mass has increased following the institution of therapy (typically with bisphosphonates). It isn't clear whether further management decisions are based on the bone density measurements, e.g. deciding whether to change treatment frequency, dose or drug. One study has examined the effect of stopping bisphosphonate therapy, and documented the consequent reduction in trabecular bone mass by pQCT (127). Documented clinical practice in the UK includes reduction of dose or frequency, when bone mass is within the normal range and vertebral morphometry is normalising.

The relationship between bone mass and fracture risk has not been well studied in any of the inflammatory conditions. Three of the studies in children with CF have assessed the relationship of bone mass with fracture risk; two cross-sectional studies found such a relationship (36,39) one longitudinal study did not (37). In IBD, two studies found such a relationship (152,153) however, the youngest patient in those IBD studies was aged 17 yr; it is unclear whether the relationship is established in children as well. It is also unclear whether fractures were more likely to occur at higher areal BMD in the absence of steroid therapy. One of the JIA studies reported on vertebral fractures (35), but did not find a relationship with areal BMD. Further studies are needed to clarify whether there is a relationship between reduced areal BMD and other measures of bone mass and fracture risk in children with inflammatory conditions, whether there is a gradual increase in risk with reducing bone mass or whether bone mass and other risk factors in combination best predict fracture risk.

The pathological origin of bone loss in immobilising conditions has been widely assumed to be primarily due to lack of bone formation consequent upon reduced mechanical stimulation, and some intervention studies have investigated the role of mechanical stimulation in reversing the process (49,62,154). Other interventions have aimed to ameliorate bone loss by using anti resorptive interventions such as pamidronate(53,55,58,60,61), or by addressing the loss of mineral from the skeleton by simple nutritional supplementation(59).

Drugs that might exacerbate the adverse skeletal effects of disuse have also been considered here in their appropriate context. There is evidence that anti-convulsant medication can worsen loss of bone tissue in some settings (65,66,155–159), and is clearly identified as a major factor exacerbating fracture risk in these patients.

The use of bone mass measurement in immobilised children can present methodological difficulties, particularly where body shape has been altered by joint contractures or spinal deformity. Alternative sites such as the lateral distal femoral have been used by some investigators to try and overcome these difficulties (160).

The relationship of areal BMD and fracture risk has not been studied systematically in CP or EB. Only Henderson's early paper (64) looked at fracture risk and bone mass and found no difference in fracture risk between those with low

and very low lumbar spine areal BMD. The issue of accurate measurement in children with distorted body frames has been addressed carefully by Henderson and colleagues (160). Lateral distal femoral scans (scans of the distal femur with the patient in a lateral position) are reproducible with an inter-observer CV of 1.81% (averaged across four regions of interest) that is comparable to that of the spine and hip for children. Others have investigated the use of the forearm in non-ambulant children (161) and found it to be a reproducible site. Tibial and spine quantitative computer tomography (QCT) using a conventional spiral computer tomography (CT) scanner with in-line Mindways phantom and software was used in the studies of Caulton (162) and Ward (62). Earlier studies from the same group identified spine QCT CV as 3% (154). The CV was 2.1% for the tibia and 0.9% for the spine measurements. The intraoperator variability for ultrasound (Sunlight Omnisense 7000) at either the tibia or radius was 0.6–0.7% in Hartman's study (63), with a quoted manufacturer's CV of 1.68–0.8% at the radius and 0.3–1.03% at the tibia. Skeletal distortion does also occur in EB, but lumbar spine measurements can be made without undue difficulty.

AN and TS are linked by a hormonal disturbance—hypogonadism. However, there is little if any evidence that for children with TS, bone disease is a significant problem, and the supporting evidence for that is given below. By contrast, children with eating disorders such as AN are at significant risk of bone disease with lasting sequelae that compromise skeletal health into adult life (100,101,113,163).

Regarding the relationship between bone mass and fracture risk, only three observational studies have addressed this question in TS (73,74,164). No relation between fracture incidence and areal BMD has been reported. There was a tendency towards lower lumbar spine BMAD Z-scores in fractured patients in a mixed pediatric/adult TS population in one study (164). In AN, Grinspoon was unable to show any relationship between fracture risk and BMD at any of five separate sites (106).

For ALL and post-chemotherapy patients, only one study (80) looked at the relationship of bone mass and fracture risk and found there was no association between areal BMD and fracture. Low areal BMD was associated with vertebral compression fracture in two patients following heart-lung transplantation (165), and a reduction in BMC during the first 6 mo after bone marrow transplantation was associated with increased fracture risk in Atkinson's study (166).

For children with ALL and post-chemotherapy, the literature to date does not answer the question of bone mass measurement influencing therapy directly. Some children with initially low bone mass during the course of their acute therapy recover by the end of their two- to three-year course of treatment (167). The literature suggests that only those who have received cranio-spinal irradiation are likely to suffer long term deficits in bone mass (77,79,80,168–171). Exercise may be an important determinant of bone mass in these children (172). There are anecdotal reports of vertebral fractures occurring post-chemotherapy (without craniospinal irradiation); intervention in those children with agents designed to

prevent further adverse skeletal events would require monitoring including bone mass measurements. These cases are not typical and there is currently no indication that earlier measurement would have been predictive of the subsequent problems.

It is unclear from the available literature whether bone mass measurement following organ transplantation influences management directly in terms of the initiation of pharmacological interventions, but DXA has been used to monitor outcome following bone-directed interventions in some groups (173). There are insufficient data to determine if the risk of fracture post-transplant diminishes with time for children receiving solid organ grafts (83), in contrast to adult transplant recipients where fracture risk is highest in the first 2 yr post-transplant (174). This suggests that continued monitoring of skeletal health, of which DXA forms an essential part, should continue long term. In the comprehensive study of Helenius, volumetric BMD (Kroger method) was decreased in 20% (83). Studies of bone health in pediatric renal transplant recipients have produced variable and conflicting results; largely due to varied approaches to the adjustment for the severe growth failure in many of these patients, as well as the effects of renal osteodystrophy on trabecular and cortical bone mass (175). In children receiving bone marrow transplants, the risk of fracture may be greatest in the period immediately following the graft (77).

Any impact of areal BMD measurement on management in studies of thalassaemic children is unclear. A number of studies have documented low bone mass in children and adolescents (28,176–179). No definite relationship between transfusion and chelation parameters and bone mass was found, indicating that DXA measurements will not affect their haematological management. Hypogonadism has been shown to be a negative predictor of bone mass and fractures in thalassaemia, and gonadal steroid replacement usually improved areal BMD (85,177,180–185). This indicates that hypogonadal adolescents need to be diagnosed and treated in a timely fashion. However, such treatment relies on relevant clinical parameters and not directly on DXA measurement.

## What is the Optimal Timing for DXA Evaluation in the Follow-up of Children and Adolescents in Different Pathological Conditions, and in Relation to Therapy?

### ISCD Official Position

- The minimum time interval for repeating a bone density measurement to monitor treatment with a bone-active agent or disease processes is 6 mo.

Grade: Poor-C-W-Necessary

### Rationale

This Position reflects existing clinical practice. Where bone specific interventions are undertaken, skeletal health should be assessed regularly, but there is a paucity of data to indicate the optimal frequency of such assessment in these

children. No evidence exists for any benefit of monitoring bone mass at intervals of less than 6 mo in clinical practice. This Position defines a minimum time interval which will reduce radiation exposure in the growing child.

### Discussion

Bone density measurement is indicated on a regular basis in all children with a primary bone disease as part of their ongoing skeletal health assessment. In children with OI or IJO, the range of reported frequency of measurements is from three to 12 mo (53,126,130–149,151,186–189). No clear rationale has been provided in any of the papers for the specific frequency of measurements. There seems to be a general consensus to measure at three to 6 mo intervals when on treatment; and at 12 mo intervals when not on treatment. There is no clear evidence that measurement should be restricted to any particular subgroup in either condition.

There is little in the available literature to indicate optimal timing for the measurement of bone mass outcomes in patients with inflammatory conditions. There is no evidence that bone mass changes very rapidly in patients with inflammatory disease, although there are anecdotal reports of sudden multiple vertebral collapse in isolated cases following the initiation of steroid therapy. Anti-inflammatory therapy for the underlying disorder may need to be increased abruptly during disease activity flares, and this may pose some additional risk to growth and skeletal health, since the dose of steroids received is linked to the risk of fracture (42).

In terms of the frequency of measurement, observed practice in the reported longitudinal studies was 12–21 mo in IBD (190–192), and 6–24 mo in CF (37,91–95,193–195). No particular rationale was provided for the frequency of measurement, which likely reflects the performance of bone mass estimation as part of an annual review, in some studies. Increased measurement frequency (every 6 mo) followed the institution of specific therapies targeted at increasing bone mass (93,94). In only one study, that of Reeve, (196) was measurement undertaken more frequently, at 2 mo intervals.

There is no indication from the published data that measurement should be restricted to a specific subset of chronically immobilised children. There is evidence that children with cerebral palsy who also have epilepsy and are receiving anticonvulsant therapy (65,66,155–159), are osteopenic (158), are overweight, (197) or use standing equipment in therapy (157) are at increased risk of fracture. It may be that more frequent measurement should be undertaken in such children.

In those studies where measurements have been made more than once, measurement frequency has varied from every three to 18 mo (54–59,61,62,162,198,199). There was no clear justification for the frequency of measurements which likely reflected the frequency of administration of pamidronate (three monthly) (55) or an arbitrary end date following a period of observation (199).

In AN, therapies are directed at increasing body mass and the return of menstrual function. There is no evidence from the

cited papers that there are immediate strong effects of any of these interventions on bone mass accrual. Some authors report recovery in a proportion of AN patients (104,105,107,114), but in many of the cited papers normal bone mass was not achieved even after prolonged periods of follow-up (100–102,108,110,112,200,201). Frequency of measurement is not addressed in the studies reviewed.

All the studies in ALL survivors were undertaken in individuals with a variable time since completion for treatment. Recent studies seem to suggest that the longer the time since treatment, the greater the improvement in areal BMD anyway. A repeat areal BMD measurement 12 mo after an initial measurement may be justified to document an improvement in areal BMD over this time (78), which should occur in those who have completed treatment. The exceptions would be those who had received craniospinal irradiation (see above) who would need longer term monitoring. For post-transplant patients, measurement frequency is typically every six or 12 mo (83,116,202–204)—there is no indication that either is more informative or helps to direct therapy.

For children with thalassaemia, every 12–16 mo is the current practice (86,118–122,180). For thalassaemia patients, there is no clear effect of chelation therapy, irrespective of type, (118) on bone mass. Studies with additional interventions, including bisphosphonates, have shown increased bone mass (86,119–122,180); observational studies of gonadal replacement therapy suggest that they are of benefit to bone mass accrual (180,183,185), but this has not been formally tested in a randomized clinical trial.

### Additional Questions for Future Research

Much remains to be done. It is strongly recommended that work to address these issues is undertaken collaboratively, in order to create appropriately powered studies and a solid evidence base for future practice. Remaining questions include:

- How does DXA impact the management of the underlying disease in children with and without clinically significant fractures?
- What are the relationships between DXA BMC and areal BMD measurements and fracture risk in chronic disease, and does adjustment for bone size, maturation, and body composition improve fracture discrimination in chronic disease?
- How do steroids, used in the treatment of inflammatory disease, impact DXA BMC and areal BMD, and fracture risk, independent of the effect of the underlying disease?
- What is the optimal frequency of DXA measures in children with chronic disease to avoid unnecessarily irradiation and guide therapy?

### Summary

In summary, the majority of the published information concerning the use of DXA in children with metabolic bone disease comes from studies where DXA has been used to

describe BMC and areal BMD in cross-sectional studies of varied chronic disease, or where DXA has been used as a tool to assess changes in BMC or areal BMD consequent upon a specific intervention. There have been no studies that have sought to address directly the questions posed here, and hence the grading of the robustness of the evidence has, in most cases, been “Poor”. However, there was no doubt in the minds of the Expert Panelists that DXA measurements of bone size, BMC, and areal BMD have added significantly to our understanding of metabolic bone disease in children. There is no wish to denigrate the contribution that has been made in that respect.

Nevertheless, the gradings reflect more on the clinical art of the individual members of the Expert Panel and the members of the Task Force, than on hard scientific fact. As such, the recommendations for future research are targeted towards a better understanding of the appropriate use of this tool in clinical practice.

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