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'A CLINICAL REPORT ON SKELETAL HEALTH OF CHILDREN AND ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE"

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Abstract

Objectives—Current evidence, albeit sparse, points to suboptimal bone health in children and adolescents with inflammatory bowel disease (IBD) when compared to healthy peers. In this clinical report we aimed to: a) review the current literature regarding the pathogenesis of suboptimal bone health and its clinical consequences and long term outcome in children with IBD, b) provide recommendations regarding screening and monitoring bone health, c) review the evidence on available measures and agents to prevent compromise and improve bone health d) summarize the gaps in knowledge and point to research directions.

Methods—Six experts in pediatric bone health and IBD reviewed the available literature specific to their area of expertise. Evidence was rated using an adjusted evidence rating system.

Results—The mechanism of suboptimal bone health in children with IBD lays in reduced bone formation and resorption. This could lead to reduced bone mineral density (BMD), which may predispose to fractures and suboptimal peak bone mass. Factors contributing to this derangement are: inflammation, delayed growth and puberty, lean mass deficits, and use of glucocorticoids. Improvement in linear growth and repletion of lean mass may help improve bone health in children with IBD. The role of vitamin D, calcium, exercise, biologics and bisphosphonates is under investigation.

Conclusions—We recommend: screening and monitoring BMD in children with IBD and certain identified risk factors, control of inflammation with steroid-sparing techniques, nutritional

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support in children with growth delays and/or lean mass deficits, optimization of vitamin D status, and weight bearing physical activity. Gaps in knowledge are numerous and require investigation.

PART A. SCREENING AND MONITORING BONE HEALTH IN CHILDREN AND ADOLESCENTS WITH IBD

A. 1. INTRODUCTION

A. 1. a. Differences of skeletal homeostasis and response to inflammation between adults and children/adolescents—The skeleton serves as a mechanical scaffold for motor activities, protects internal organs, is the largest reservoir for calcium, and hosts and interacts with the hematopoietic bone marrow. Each one of these functions is tightly regulated by a variety of homeostatic factors, both local and systemic. The skeleton has the ability to adapt to mechanical loading exerted by weight bearing exercise and large muscle forces that stimulate bone apposition, especially during periods of rapid linear growth such as puberty [1]. Bone readily responds to increased calcium demands by releasing calcium in response to parathyroid hormone [2]. Blood stem cell development is modulated by bone-forming osteoblasts [3]. Therefore, bone is metabolically active and functionally dynamic throughout the lifespan.

The skeleton has a built-in mechanism for self-repair, called *bone remodeling*. In response to mechanical stress or damage, osteoclasts develop from hematopoietic precursors under the influence of RANKL (receptor activator of nuclear factor kappa-B-ligand). RANKL is produced by osteoblasts, stromal cells and activated T cells [4, 5]. Osteoclasts then latch on to damaged or stressed bone surfaces and dissolve them. This triggers mechanisms that recruit a secondary wave of osteoblasts, which repair the defects with collagenous matrix that later becomes mineralized with calcium and phosphate crystals. Resorption of bone takes an average of 3 weeks, while the repair phase takes about 3 months, so the activities of osteoclasts and osteoblasts need to be precisely synchronized to prevent bone loss. Bone remodeling occurs in adult and pediatric bone. Post-menopausal osteoporosis is a disease of abnormal bone remodeling, where bone resorption outpaces bone formation, resulting in micro-architectural deterioration, bone fragility, and increased risk of fractures [6].

In growing children bones elongate and change shape. This occurs by the combination of *bone modeling* and the activity of the growth plate in long bones [7, 8]. Bone modeling and linear growth are fundamentally different than bone remodeling. While in bone remodeling there is sequential activation of osteoclasts and osteoblasts on the same bone surfaces, in bone modeling both osteoblasts and osteoclasts are *active simultaneously on different parts of the bone*. In modeling, osteoclasts expand the medullary cavity, osteoblasts lay periosteal bone, and osteoclasts and osteoblasts work together to sculpt the metaphyses of long bones. Bone modeling results in faster, larger changes in bone mass compared to bone remodeling. Bone modeling occurs almost exclusively in children, and is fastest post-natally and during the pubertal growth spurt. Consequently, chronic inflammatory diseases that affect children are likely to have unique consequences on bone metabolism, affecting bone remodeling, modeling *and* linear growth. In adults however, chronic inflammation will exclusively impact bone remodeling. These important physiological differences between children and adults need to be taken into account when interpreting clinical and research data on bone mass and considering therapeutic options to restore bone mass in the young.

A. 1. b. Bone metabolism in IBD—The pathophysiology of bone loss in IBD is complex. Bone modeling, remodeling and linear growth are inhibited in pediatric IBD. Children with IBD, especially Crohn disease, are frequently stunted at diagnosis and height deficits may become permanent [9]. At diagnosis, growth retardation is associated with

reduced bone metabolic activity. Both bone formation and bone resorption are decreased as reflected by the fact that biomarkers of bone formation and resorption are ~30-50% of normal [10]. Transiliac bone biopsies of newly diagnosed, untreated children with Crohn disease show signs of reduced trabecular bone turnover [11]. Although anti-inflammatory treatment and improved nutrition are associated with normalization of bone biomarkers, bone mineral content lags behind [10], and mechanical properties of bone may in fact worsen over time [12]. In addition, height Z-scores may not improve with conventional IBD therapy [9], and muscle mass deficits may also persist [1314], which can affect the accrual of bone mass. In IBD, disease factors that can affect growth and bone metabolism are malnutrition, delayed puberty, reduced physical activity, nutrient malabsorption and abnormal utilization, and persistent inflammation. Active inflammation may be the central mechanism responsible for alterations in normal bone metabolism. Intestinal inflammation can affect bone cell function in multiple ways. Serum of children with active Crohn disease contains factors that inhibit bone formation in vitro [15]. Activated T cells may shuttle inflammatory signals from gut to bone[16], and intestinal inflammation may induce an inflammatory response in the bone microenvironment [17]. Anti-inflammatory treatment with the tumor necrosis factor-α (TNF-α) antibody infliximab restores bone formation and linear growth in children with IBD [1819]. Recent evidence suggests that infliximab is also associated with increased muscle mass in children with Crohn disease, which should further stimulate bone mass accrual [18]. Collectively, these data suggest that adequate control of inflammation is both anti-catabolic and anabolic to bone.

Therefore, unlike post-menopausal osteoporosis where treatment with anti-resorptive agents is appropriate to slow down excessive bone resorption, in children with IBD, who are likely to have low bone formation and slow growth, it may be more appropriate and effective to adequately control inflammation, improve nutrition, and encourage physical activity, all of which should be anabolic to bone.

A. 1. c. Prevalence of suboptimal bone health and its consequences in children with IBD

A. Prevalence: Past studies have shown bone mass to be decreased in both adults [20, 21] and children [10, 12, 22, 23] with this disease. Children with IBD have significant bone mass deficits, even at diagnosis [10, 12, 24].

B. Peak Bone Mass: The majority of our adult bone mass is accumulated by the age of 18-20 yrs in boys and the age of 16 yrs in girls [25]. In healthy children, the period of most rapid bone mineral accrual is between the ages of 11-14 yrs in girls and 13-17 yrs in boys [26]. The average age at diagnosis of IBD in children is 12 yrs, with the majority of children diagnosed with IBD between the ages of 6 and 17 yrs [27] at a period when the bulk of their bone mass is acquired at the fastest rate. Although longitudinal studies of bone mass accrual and peak bone mass attainment in children with IBD, especially in comparison with healthy controls, are lacking, there is evidence from short-term studies that bone mass accrual is hampered in children with IBD, [10] and bone geometry and structure may not improve in time [12]. These findings lead to the reasonable hypothesis that without support, children with IBD and suboptimal BMD may not achieve full potential peak bone mass with grave consequences for later years.

C. Fractures: The finding of low BMD in a child or adolescent with IBD would be of direct relevance for the child and the clinician responsible for his/her care if it would mean that this child is at higher risk for fracture. Landmark studies in healthy children show that there is an inverse relationship between fracture risk and BMD similar to that in older adults. Specifically, a two-year prospective fracture study of healthy children by Clark et al.

demonstrated an approximate two-fold increase in fracture risk with each standard deviation (SD) decrease in areal BMD, and a more substantial increase in this risk with each SD decrease in volumetric BMD [28]. There are no studies of the relationship between fractures of any type and BMD in children with IBD specifically. However, fracture risk may be higher in children with IBD whose bone architecture (aside from BMD) may be negatively affected by factors such as systemic glucocorticoids and inflammation.

Is fracture incidence and prevalence higher in children with IBD? There is scarcity of data on this subject. The existing studies are case series, survey-based and retrospective only. A survey-based study compared the prevalence of fractures between pediatric patients with IBD and their siblings and found it to be similar [29]. However, a recent retrospective database-based study reported an increase in the overall fracture risk in children with IBD younger than 12 yrs, when compared with age and sex-matched controls [30]. In accordance, increased risk of fractures was found among children with juvenile rheumatoid arthritis, another chronic inflammatory childhood illness, when compared with healthy peers in a large population study [31].

An issue of rising concern is that of vertebral fractures and their true prevalence among children with IBD: Vertebral fractures are associated with chronic back pain, recurrent spinal fractures, loss of height, kyphosis and loss of functionality in adults and their occurrence is a major reason for quality of life deterioration in older subjects [32]. Vertebral fractures have been encountered in up to 22% of adults with IBD [33, 34]. Many of them were completely asymptomatic, and many were younger than 30 years [34]. Findings regarding the association between reduced BMD or glucocorticoid exposure and fracture risk, especially of the spine, are conflicting [33-35]. The incidence or spinal fractures in children with IBD is unknown. However, evidence is accumulating to support that there is reason for concern. A few case reports and series are published [3637]. One [36] included 5 cases of children with Crohn disease (CD) and terminal ileal involvement who had documented vertebral fractures, associated with persistent back pain. All had low BMD (Z-score < -2.3) and all were on glucocorticoids. Moreover, a recent retrospective database-based study reported an increased risk of vertebral fractures in children with CD compared to age and sex-matched controls [30]. The incidence of asymptomatic such fractures, the morbidity as a result of these fractures, the risk factors associated with their occurrence and their long term outcome are unknown in children with IBD. Clearly, systematic studies are needed to examine these issues.

A. 1. d. Risk factors for bone health compromise in children with IBD

1) Compromised linear growth: Longitudinal studies of bone mass accrual in healthy children have shown that it is positively related to linear growth [38]. A close relationship between height Z-score and BMD is well documented based on cross-sectional studies in young patients with IBD [39-41]. Although BMD Z-scores measured via dual-energy X-Ray absorptiometry (DXA) are underestimated in kids with low height Z-scores, bone mineralization deficits may persist after adjustments for size. A critically important factor which could be a common link between linear growth and bone mass accrual is the role of growth hormones. It is long known that growth hormone (GH), insulin growth factors I and II (IGF-I, IGF-II), and insulin growth factor binding proteins (IGFBPs) control growth, remodeling and mineralization of the skeleton in part via their direct actions on bone [42-45].

2) Lean mass deficits: Lean mass (muscle mass) is far more important for skeletal health than fat mass at least in pediatric populations. The mechanostat [1] and the “functional bone-muscle unit” [46] theories established that structural bone adaptation is driven by muscle contractions. Sarcopenia, a specific lean mass deficit, has been found to be prevalent among both adults and children with IBD [2239471213] Several investigators have documented a

relationship between muscle or lean mass deficits and bone mass or structure deficits in cross-sectional [3947] and longitudinal studies [12, 13] in children with IBD. In growing subjects, lean mass must be adjusted to body size, specifically height, in addition to age and gender. Formulas exist that calculate a lean mass Z-score based on the above adjustments (see A. 2. c). However, these require time and expertise not readily available to all clinicians in everyday practice. Weight and body mass index (BMI) are measurements routinely performed in clinical settings and are surrogate measures of lean mass. BMI is a measure of weight relative to height and major constituents of weight are fat and lean body mass. Indeed, many cross-sectional studies have linked higher BMD Z-scores with higher BMI Z-scores [10, 22, 23, 40, 48, 49] and higher weight Z-scores [41].

Based on the above, until lean mass Z-scores are widely available for use in children, weight and BMI Z-scores can be used as surrogate measures of lean mass, and their deficits should prompt physicians to examine bone health and investigate nutritional and inflammatory status.

3) Menstrual irregularity if female: Evidence of bone health compromise as a result of amenorrhea has been available from studying girls with anorexia nervosa and athletes [5051]. Although studies of the incidence and risk factors for amenorrhea are not known in girls with IBD, at least theoretically they are at risk for both primary and secondary amenorrhea due to disease-related factors. Both the attainment of menarche and continuation of regular menses appear to be highly dependent on nutritional status and body fat [52]. Inadequate body fat may reduce secretion of the adipocyte-derived hormone, leptin, which appears to modulate reproductive function in humans [52]. Nutritional status is often compromised in children and adolescents with IBD and reductions in body fat can be dramatic during acute phases of their illness. The central mechanism responsible for suboptimal bone mass accrual in girls with amenorrhea is not dependent on diagnosis. Identification of primary or secondary amenorrhea (as defined later) in girls with IBD should prompt referral, investigation of bone health and nutritional and inflammatory status.

4) Delayed puberty: Delayed puberty has been associated with decreased BMD later in life by landmark studies [5354]. Normal and timely pubertal progression is dependent on a well-balanced hypothalamic-pituitary-gonadal (HPG) axis. Leptin is known to play a critical role in the regulation of this axis and it is decreased in the setting of decreased body fat [52], condition which is not uncommonly encountered in children and adolescents with IBD. Recently, evidence pointing to a direct – independent of leptin - negative effect of inflammatory cytokines on the HPG axis has emerged [55]. Children and adolescents with IBD are at risk for delayed puberty based on the above. Although the incidence and risk factors for delayed puberty and its outcome in regard to peak bone mass achievement in children with IBD specifically have not been studied, given the above evidence, we recommend that pubertal status is examined regularly in every pediatric patient with IBD.

5) Prolonged use of systemic glucocorticoids: Several studies have examined the role of glucocorticoids in the bone health of children with IBD and the results have been conflicting. Of note is that most of the studies were retrospective. Some investigators found a negative relationship between cumulative glucocorticoid dose and BMD, [395657404158] where others did not [10, 12, 22, 48]. However, glucocorticoids are known to cause osteoblast cell dysfunction and premature apoptosis [596061], impaired intestinal absorption of calcium [62] and increased urinary calcium excretion [63]. Two recent studies confirmed the hypothesis that glucocorticoids negatively affect bone turnover in children with IBD: in one study, pediatric patients on glucocorticoids had decreased bone specific alkaline phosphatase levels (bone formation marker) [47] and in the other, both bone formation and resorption markers were decreased during glucocorticoid therapy, and were restored to normal values 1 month

after glucocorticoids cessation [64]. Although the minimum duration of glucocorticoid therapy that causes damage to bone architecture or hinders bone mass accrual in children is not known, several studies show that puberty (Tanner stages 2,3,4) is the most vulnerable period during which glucocorticoid exposure may lead to non-reversible bone loss [65]. However, in the case of children with IBD, the negative effect of glucocorticoids therapy on bone may be offset to a degree by their capacity to combat inflammation which in itself is detrimental for bone metabolism (see below). All above considered, we recommend evaluation of bone health status in children with IBD who receive 6 months or longer of systemic glucocorticoids at any time during their illness, and especially during their early and mid-pubertal years.

6) Severe inflammatory disease course, including persistently symptomatic disease, persistently elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and persistently decreased albumin level (< 3 g/dL): The effect of inflammation on bone health of children with IBD has been examined in many cross-sectional [5622574840414749] and a few longitudinal studies to date [1012]. Measures of inflammatory burden examined in the various studies varied from disease activity indices [56574841] to use of immunosuppressants [414956] and number of relapses and hospitalizations [4140]. A few studies examined albumin level and hematocrit as surrogate markers of disease severity [224112]. The majority of studies concluded that indeed inflammation exerts a negative effect on bone mass accrual or bone quality [4712491041224840]. The leading hypothesis - supported to date by findings *in vitro* and in animal models - is that in states of systemic inflammation, products of activated T-cells, such as inflammatory cytokines, directly and indirectly affect bone cells and cause a disruption in bone turnover [66]. TNF-α specifically, compromises the function of mature osteoblasts [67], inhibits osteoblast differentiation [68] and promotes osteoclast differentiation [69-71]. IL-6 decreases bone formation [72-74] and directly stimulates osteoclastogenesis [75]. As well, TNF-α and IL-6 stimulate osteoclastic activity through their effects on the common osteoclast activation pathway, consisting of the receptor activator for nuclear factor kB (RANK), its ligand (RANKL), and the decoy receptor of this ligand, osteoprotegerin (OPG) [76-78]. To date, the most direct evidence of such effects in children is the negative relationship between IL-6 serum levels and BMD Z-scores in two studies [10, 48]. An inflammatory marker or cytokine, or a specific constellation of such markers and cytokines, whose sustained elevation is related with bone damage, has not been identified. In the absence of this information, we recommend that elevations in indices of disease severity/clinical course, ESR, CRP, decreases in serum albumin level, and persistence of active disease on histological examination for at least 3 months are used as evidence of ongoing inflammation that should prompt examination of bone health status.

Gaps in knowledge: How does the inflamed intestine affect bone cell function? Newer therapies will emerge from an improved understanding of how intestinal inflammation subverts bone cell function. We need to improve our understanding of the effects of key cytokines such as TNF-α on bone cells, as this may identify new therapeutic targets to improve bone mass in patients with IBD.

Is fracture risk increased in children with IBD? Additional data are needed to reveal the true prevalence of fractures at susceptible sites, in children with IBD. By necessity, such a study would have to be prospective, multicenter, properly controlled and of sufficient duration to capture a sufficient number of events for a meaningful analysis.

Which young patients with IBD are at risk for not achieving their full potential peak bone mass based on longitudinal studies which include controls and parents' BMD?

What is the incidence, prevalence, morbidity, outcome, risk factors associated with vertebral fractures in children with IBD, both symptomatic and asymptomatic?

A. 2. SCREENING AND MONITORING SKELETAL HEALTH OF CHILDREN AND ADOLESCENTS WITH IBD

A. 2. a. BMD measurement modalities for children and adolescents with IBD

> "DXA is the preferred screening tool for children and adolescents with IBD and pediatric reference databases should be used to report BMD of a child or adolescent with IBD in comparison to healthy peers of the same age and gender as a Z-score"

Rate: Good-A*: Dual-energy x-ray absorptiometry (DXA) is the most commonly used densitometric technique for children throughout the world, preferred over other techniques because of its speed, precision, safety, low cost, and widespread availability. Several studies have evaluated bone health in children with IBD via DXA [10, 22, 23] which provides projectional, two-dimensional measurements. Peripheral quantitative computed tomography (pQCT), [12] is an assessment tool that provides more accurate, three-dimensional measurements, however, because of sparse availability, cost, and less well developed reference databases, its use is currently limited to research protocols in pediatrics.

DXA results should be analyzed with software containing pediatric reference dataset, and reported as Z-scores.

Of critical importance to clinicians is awareness of the reference dataset used, to be sure that it contains the appropriate age range and is based on similar DXA software and hardware. A common mistake in clinical assessment of BMD in children is comparison to an adult reference and computation of a T-score [79]. For children and adolescents it is necessary to use a BMD Z-score, a standard deviation score that compares a child's BMD to age- and gender-matched controls, rather than the T-score which compares the child's BMD to peak bone mass values (i.e., the BMD of a 20-year-old). In a young child, calculation of a T-score imparts erroneous interpretation of a DXA result which can cause anxiety for a family until they see a pediatric bone health specialist.

Excellent reference databases have been identified by an expert panel and are in use by DXA scanners, of each manufacturer. One such database, currently in use by most DXA scanners is the database developed by the Bone Mineral Density in Childhood Study which was funded by the US National Institutes of Health. The study has obtained longitudinal data on a multi-ethnic cohort of 1554 children in the US [80] and has made an enormous contribution to the densitometry field.

A. 2. b. Interpretation of DXA bone outcome measures

> "We recommend that in children with linear growth delay (height Z-score < -2.0 SD) DXA results are adjusted for size, especially if BMD is low (Z-score < -1.0 SD). Clinicians may consider consultation with a bone specialist to accomplish this in circumstances such as above".

Rate: Good-A: Childhood IBD is associated with malnutrition, malabsorption, delayed puberty, glucocorticoid therapy and increased production of inflammatory cytokines. Each of these may contribute to poor growth, impaired bone mass accrual, and alterations in lean mass and fat mass. Growth and body composition are important considerations in the interpretation of DXA measures of BMD in children and adolescents.

*For evidence rating system used, see end of report

DXA is a two-dimensional technique in which BMD is presented as the combined sum of cortical and trabecular bone mass within the projected bone area (in g/ cm^2). This BMD is not a measure of volumetric density (g/cm^3) since DXA does not provide information about bone depth. Bones of larger width and height are thicker. Since bone thickness is not factored into DXA results, reports of areal-BMD relative to age systematically underestimate BMD in children and adolescents with decreased height relative to age. Children with IBD often have faltering growth, often combined with delayed maturation. Accordingly, a low areal BMD for age Z-score in the context of short stature raises the question of the degree to which the low BMD status can be attributed to smaller bone size relative to age.

The magnitude of this effect was illustrated in a study comparing spinal areal BMD measurements obtained via DXA with spinal volumetric BMD measurements obtained via pQCT in children [81]. Among 400 children, 200 of whom were healthy and 200 of whom had a chronic disease, only 24% of those with a DXA areal BMD for age Z-score < -2.0 SD had a pQCT volumetric BMD for age Z-score < -2.0 SD. This over-diagnosis of skeletal deficits by DXA was most pronounced in children with chronic diseases and impaired growth.

The International Society of Clinical Densitometry Official Position for Skeletal Health Assessment in Children and Adolescents states that “In children with linear growth, spine and total body less head areal BMD results should be adjusted for absolute height or height age, or compared to pediatric reference data that provide age-, gender-, and height-specific Z-scores” [82]. Currently, pediatric reference data for determining height-specific Z-scores for spine or total body BMD are not available. A commonly used approach is to substitute skeletal age or “height age” (the age at which a child's height is the median height-for-age on the growth chart) for chronological age to adjust for short stature. DXA reports provide absolute height of patients, which can be used to extrapolate height for age Z-scores using the free of charge Center for Disease Control Epi Info calculator, 2000 version. A concern with the use of height-age is that short-for-age children will be compared to children of similar height who are younger and less physically mature. This discrepancy would be especially pronounced if a pubertal child is compared with pre-pubertal children through this adjustment. However, lacking the gold standard of reference databases which would provide a BMD Z-score for any given height at a given age, the use of height-age to adjust BMD in pre-pubertal children is an option. A recent study [83] proposed adjusting BMD Z-score for height for age Z-score and the authors provide the equations necessary. This technique can be used in both pubertal and pre-pubertal children.

In conclusion, substantial progress has been made addressing the confounding effects of bone size on DXA results in children with chronic disease. Greater recognition and consideration of the impact of growth failure on DXA results in children with IBD will lead to more accurate assessment of disease effects and therapies on bone mass accrual. Until normative databases which provide BMD Z-scores for each height measurement at a given age are incorporated in the DXA manufacturers’ software, we propose consulting a bone specialist when faced with low BMD Z-scores in children with delayed growth.

A. 2. c. DXA body composition data

> “Body composition measurements and specifically lean mass measurements would be helpful in order to provide targeted nutritional rehabilitation to pediatric patients with decreased muscle mass, especially in children with weight deficits and/or bone mass deficits. Interpretation of body composition measurements and their adjustment to body size requires expertise usually held by pediatric endocrinologists”

Rate: Poor - C: DXA measures the attenuation of two discrete energies as they pass through the body in order to differentiate between bone mineral content and soft tissue, which is subsequently differentiated into lean mass and fat mass [84].Total body DXA has evolved into an excellent method to quantify lean and fat mass precisely in children exposing them to minimal effective radiation doses. Cross-sectional studies found lean mass to be decreased in children with CD even at presentation [13, 85] and longitudinal studies showed that lean mass deficits may persist even after treatment [13, 14] when fat mass is mostly restored on follow up [13, 14]. Although the pathophysiology of lean mass deficits, referred to as "sarcopenia" in children with IBD is not clearly understood, inflammatory cytokines directly affecting myocytes, undernutrition and decreased physical activity may be contributing [14, 85]. All consequences and long term outcome of sarcopenia have not been investigated in children. However, one such consequence has been studied and appears to be decreased bone mass [13, 22]. The mechanism of this consequence lays on the close interaction between bone and muscle. Bone adapts its strength in response to the magnitude and direction of the forces to which it is subjected. Mechanical forces on the skeleton arise primarily from muscle contraction. This capacity of bone to respond to mechanical loading with increased bone size and strength is greatest during growth, especially during adolescence [86].

Consequently, body composition measurements and specifically lean mass measurements would be helpful in order to provide targeted nutritional rehabilitation to pediatric patients with decreased muscle mass, especially in children with weight deficits and/or bone mass deficits. Like bone mass, muscle mass should be adjusted for size. Reference data for body composition are available for Hologic DXA systems (Hologic, Inc. (Bedford, MA) Densitometers) based on data collected in the National Health and Nutrition Examination Survey between 1999 and 2004 [87]. Reference charts included in the above data detail lean mass relative to height, and provide lean mass index (lean mass / height^2) for children ages 8 years and older. Reference data for percent body fat are also included. Lunar DXA systems (GE Healthcare, Waukesha, WI) include software which provides body composition Z-scores for lean body mass for height following Crabtree et al [88].

A. 2. d. Bone mass screening and monitoring in children: The International Society for Clinical Densitometry Position Statement—The International Society for Clinical Densitometry, (ISCD) a not-for profit professional organization seeks to advance excellence in the assessment of skeletal health. The ISCD convened an international panel of pediatric experts in Montreal, Canada in May 2007 to examine scientific literature reviews by ad-hoc task forces and elaborate a position statement regarding the evaluation of bone mass in children. This document is available on-line at http://www.iscd.org and in print [89]. These guidelines have been adopted by other professional societies and are commonly used in clinical practice.

The ISCD Pediatric Position Statement advises that for a given patient suffering from a chronic illness, the clinician must consider the need for a BMD evaluation, including both the duration and severity of the chronic illness, and/or frequency and nature of fractures if any. Patients who have underlying diseases that affect the skeleton "should have spine and total body less head (TBLH) bone mineral content (BMC) and areal BMD measured via DXA at presentation, when technically feasible". Children and adolescents with IBD represent a "risk group" for low BMD because of skeletal losses associated with both CD and ulcerative colitis (UC).

According to this statement, all children with IBD who can comfortably lay on a cushioned table for 15-20 min should have a DXA scan. DXA should be performed in instruments loaded with updated pediatric software and interpreted by professionals familiar with

pediatric reference data after appropriate adjustments for height. The Position Statement warns that "therapeutic interventions should not be instituted on the basis of a single DXA measurement."

A. 2. e. Definition of suboptimal BMD in children and adolescents with IBD

"We recommend considering using a BMD Z-score < -1.0 SD as the threshold for "suboptimal BMD"

Rate: Poor-C: The ISCD expert panel [90] defined as "low" BMD for age, an areal BMD Z-score ≤ -2.0 SD, adjusted for age, gender and body size, as appropriate. This recommendation was based on a study of healthy children showing that there is an inverse relationship between fracture risk and BMD [28]. However, the two-year prospective fracture study of healthy children by Clark et al above, demonstrated a continuous increase in fracture risk as areal BMD decreases, and a more substantial increase in this risk as volumetric BMD decreases. Similar longitudinal studies to uncover such associations in children with IBD are lacking, but we have no reason to dispute the applicability of this finding to our patient population whose bone health may be further compromised by chronic administration of medications potentially hazardous for bone health (glucocorticoids), as well as the known effects of inflammation on bone metabolism.

We recommend using a BMD Z-score < -1.0 SD as the threshold for "suboptimal BMD", since according to the above study, the relative fracture risk doubles with each SD below the mean BMD in children of the same age and gender. As well, the use of a BMD Z-score < -1.0 SD as the "threshold" for suboptimal BMD will help identify patients who may benefit from closer monitoring of their progression of bone mass acquisition.

A. 2. f. Screening bone health in children with IBD

"We recommend considering obtaining a DXA scan of the spine and total body at presentation in children with the diagnosis of IBD when practical. We strongly recommend considering obtaining a DXA scan of the spine and total body at presentation or at any point in children with IBD and any of the following risk factors:

- **a.** suboptimal growth velocity or height Z-score < -2.0 SD or downward crossing of height percentile curves
- **b.** weight or BMI Z-score < -2.0 SD or downward crossing of weight or BMI percentiles curves
- **c.** secondary or primary amenorrhea if female
- **d.** delayed puberty
- **e.** severe inflammatory disease course, especially when associated with decreased albumin level (< 3 g/dL)"
- **f.** 6 months or longer of continuous use of systemic glucocorticoids.

In addition, we strongly recommend considering obtaining a DXA scan of the spine and total body if there is history of "clinically significant fractures". These are: fractures of the long bones of the lower extremities, spinal compression fractures, and two or more fractures of the long bones of the upper extremities"

Rate: Fair-B: Obtaining a DXA measurement of the BMD of children with IBD at diagnosis will help identify children whose BMD is suboptimal during periods of rapid skeletal growth and bone mass accrual. This measurement will serve as a baseline

measurement which clinicians can use for future reference. The awareness that a child or adolescent with IBD has suboptimal BMD could encourage clinicians to endorse general skeletal health support measures (i.e. optimization of vitamin D status and calcium intake, targeted exercise, improvement of nutritional status) early in the course of the disease. As well, this awareness could encourage clinicians to focus on alternative therapeutic approaches in order to avoid medications that might be harmful to skeletal development such as glucocorticoids, and consult professionals for primary or secondary amenorrhea, delayed growth, delayed puberty. These measures can give young patients with IBD the best possible opportunities (with current knowledge) to reach their genetically programmed growth potential and peak bone mass.

We realize that screening all children and adolescents with IBD at presentation may not be practical in some areas and under certain circumstances, for example when DXA technology is not available or pediatric software not installed in the equipment or if there are financial concerns. We then recommend focusing on screening pediatric patients with suboptimal linear growth and weight, menstrual irregularities, pubertal delay, greater inflammatory burden, prolonged glucocorticoid exposure and history of “clinically significant fractures”.

The type of fractures described in the recommendation above, represent “clinically significant fractures” in children, given the higher likelihood for hospitalization and surgery, as well as chronic pain and residual functional deficits associated with this type of fractures [90].

A. 2. g. Monitoring bone health in children with IBD

> “We recommend that clinicians consider obtaining DXA scans every 1-2 years in children and adolescents with IBD and total body or spine BMD Z-score ≤ -1.0 SD at any point”

Rate: Poor-C: In addition to potentially increased risk of fractures at BMD Z-scores < -1.0 SD as elaborated on in section A. 2. e, children with less than optimal BMD Z-score may be at risk for failure to reach their full potential peak bone mass. As previously noted, although longitudinal long-term studies of bone mineral accumulation in children with IBD are lacking, shorter term studies showed slower rates of bone accrual in this population. This leads to the reasonable hypothesis that without support, children with IBD and already suboptimal BMD, as above defined, may not achieve full potential peak bone mass with grave consequences for later years. We recommend DXA measurements of total body and spine BMD every 1-2 years in these patients. These measurements may help identify those patients whose BMD is declining during periods of rapid skeletal growth and bone mass accrual. This knowledge should encourage clinicians to endorse general skeletal health support measures, focus on alternate therapeutic approaches, and consult other professionals. Repeat DXA sooner than 6 months from a previous DXA is not recommended.

A. 2. h. Vertebral fractures—Vertebral fractures are considered “clinically significant” fractures. Although the incidence and prevalence, risk factors, morbidity and outcome of such fractures in children with IBD is unknown, evidence has been accumulating to support that they might be more common than previously thought, and contributing to reduced quality of life in the children who suffer them (see A. 1. c).

The recent position statement by ISCD regarding vertebral fracture assessment in adults recommends a densitometric vertebral fracture assessment in men and women on chronic glucocorticoid therapy (5 mg or more of prednisone daily for 3 or more months) as well as men with “low bone mass by densitometric criteria, and a chronic systemic disease, among others” [91], but not in children.

At this point, there is not enough evidence to support recommending vertebral fracture assessment with any modality in children with IBD without specific symptoms or previous such fractures.

> However, we recommend considering evaluating children with IBD for vertebral fracture if suggestive symptoms, such as persistent back pain are present, especially if these children also have low BMD as defined above (Z score <= -1.0 SD). Modalities which can be used to evaluate for such fractures include: radiography of the spine, magnetic resonance imaging, and densitometric spinal fracture assessment.

Rate: Poor-C

Gaps in knowledge: Are there modalities that measure bone health more objectively and comprehensively than DXA and what is their use in monitoring bone health in children with IBD?

Is there is a simple, universal method for adjusting BMD measurements for size?

What is the BMD "threshold" for "suboptimal" BMD in children and adolescents with IBD, based on objective longitudinal and outcome research?

What is the role of subclinical inflammation on BMD/bone health in children?

What is the minimum glucocorticoid exposure that causes bone health compromise in children?

Which is the most sensitive marker/combination of markers or modality for the detection of inflammation which would correspond well with or predict bone health compromise?

PART B. INTERVENTIONS AND PRACTISES FOR MAINTAINING AND IMPROVING BONE HEALTH IN CHILDREN AND ADOLESCENTS WITH IBD

B. 1. Assessment of Growth, Puberty, and Menstrual Function in Children and Adolescents with IBD

> "We recommend monitoring linear growth and growth velocity, pubertal development and menstrual function regularly in children or adolescents with IBD. It would be reasonable to seek consultation from an endocrinologist in a child or adolescent with IBD who has evidence of delayed puberty or menstruation abnormalities as defined below."

Rate: Poor-C—As elaborated on in section A.1.d. linear growth deficits, pubertal delay and menstrual irregularity represent risk factors for suboptimal bone health in children. Therefore, it is important to monitor growth, puberty progression and menstrual status in children and adolescents. Below are practical considerations, definitions and timing for referral for the clinical pediatric gastroenterologist.

B. 1. a. Growth: Close examination of height plotted on a growth chart is extremely important and concern should be raised in the child or adolescent with a height Z-score of -2 SD or less, as this would suggest that the child or adolescent's height is significantly below that of age- and gender-matched peers. Consideration of the child's genetic potential is important, using the parent's heights as a guide and using accepted formulas to calculate the midparental or target height (calculated from parents' heights) [92, 93]. A child whose growth curve is tracking significantly below his/her genetic potential is a cause for concern. Beyond

genetics, it should be recognized by clinicians that a normal growth velocity for a pre-pubertal child is ~5 cm/year. The peak pubertal growth velocity is 8.3 cm/yr in girls, and 9.5 cm/yr in boys. [94]. A growth velocity substantially less than these thresholds raises concern for growth delay or arrest. Lastly, growth potential as indicated via bone age x-ray assessment should be considered in the evaluation of short stature.

B. 1. b. Delayed Puberty: In Table 1 we tabulated in chronological sequence the stages of normal pubertal development for females and males, noting the average age at which each characteristic presents or event occurs, the time range for such presentation or occurrence, and the age by which no appearance of the characteristic or occurrence of the event should raise concern. Note that the highlighted characteristics or events are the most significant [9495].

Delayed puberty is defined as no evidence of the development of secondary sex characteristics by the age of 13 years in a girl and 14 years in a boy. [94]. If either the pace or sequence of puberty is noted to be abnormal, consideration should be given to the involvement of a pediatric endocrinologist and further investigation of bone health, nutritional and inflammatory status. Prompt intervention with sex steroid replacement may have beneficial effects on long-term bone health.

B. 1. c. Menstruation: Menarche, or the first menstrual period, typically begins 3.3 years after the onset of the growth spurt or approximately 2 years after breast budding [94]. The normal age for menarche ranges from 9-15 years. Primary amenorrhea has conventionally been defined as no menses by the age of 16 years. However, more recent data suggest that the age of 15 years is more accurate and evidenced- based. [96] Within the first year after menarche, girls should establish a regular 20-45 day cycle. Significant variations should be monitored closely and significant aberrations merit evaluation. As was discussed in section A.1.d., nutritional status compromise and decrease in body fat can disrupt hormonal secretion and lead to delayed menarche, a key milestone in pubertal development for girls. Therefore, attention to appropriate dietary intake and appropriate weight gain in the young adolescent with IBD and avoidance of weight loss in the older adolescent is paramount.

B. 2. Screening, monitoring and maintaining optimal vitamin D status in children with IBD

B. 2. a. Vitamin D and skeletal health—Vitamin D is a steroid hormone produced in the skin when the skin is exposed to adequate solar ultraviolet B radiation (UVB) [97]. 1,25-dihydroxyvitamin D ($1,25(OH)_2 D_3$) is vitamin D's active metabolite [98] while 25-hydroxyvitamin D (25OHD) is the most abundant metabolite in the human body and it is indicative of overall vitamin D status [99]. In addition to maintaining calcium and phosphorus homeostasis [100-102] vitamin D promotes both bone formation and resorption with its positive effect on osteoblasts [103, 104] and osteoclasts [105, 106], therefore, this hormone is very important during periods of rapid bone growth or modeling. Notably, bone formation is significantly decreased in children with IBD when compared with their healthy peers [10, 107].

Although BMD and vitamin D status were not related according to cross-sectional studies in children with IBD [10, 108], longitudinal studies of the effect of vitamin D status on bone health in this population have not been reported to date. However, several studies in healthy children showed a positive effect of vitamin D on bone health [109]. Additionally, a recent longitudinal study in newly diagnosed adults with IBD found that higher 25OHD levels were positively correlated with both baseline BMD and BMD gains after 2 years [110]

B. 2. b. Vitamin D status in children and adolescents with IBD—Many investigators consider serum concentration of 25OHD above 32 ng/mL as the optimal

vitamin D level in adults, given that this is the minimum level at which maximal suppression of parathyroid hormone [111-114] and maximal efficiency of calcium absorption from the intestine are observed [112]. Such studies are lacking in children, however, given the evidence of the positive effect of higher vitamin D levels on bone health in healthy children and adults with IBD and its anabolic properties especially in view of decreased bone formation rates encountered in children with IBD we recommend that the level of 32 ng/mL is considered as the minimum level of sufficiency for children and adolescents with IBD. In our support, the Cystic Fibrosis Foundation has adopted this level as indicating optimal vitamin D status in all patients with cystic fibrosis (CF) in a consensus statement that set guidelines for bone health in CF [115]. Suboptimal bone health is a major complication of CF for reasons overlapping with reasons for suboptimal bone health in children with IBD, such as inflammation and undernutrition [115].

The prevalence of suboptimal vitamin D status in children with IBD has been the focus of a few studies [108116]. When a cut-off level of 15 ng/mL is used, suboptimal vitamin D status has been reported among 16% to 34% of children with IBD. Vitamin D levels were found to be lower in children with IBD than in their healthy peers [117]. Malabsorption and protein-losing enteropathy secondary to intestinal inflammation, decreased exposure to sunlight, and decreased vitamin D intake are potential mechanisms of hypovitaminosis D in children with IBD. Indeed, in addition to dark skin complexion and winter season (vitamin D is not made through cutaneous synthesis in northern latitudes (32 degrees N) from November through February [118]), other disease-specific risk factors were identified in children with IBD. These were: upper gastrointestinal system (UGI) involvement (in children with CD), more severe disease, and early stage of the disease, low albumin level, lower BMI and weight Z-score [10827, 11626].

B. 2. c. Screening and monitoring of vitamin D status

> "We recommend that the level of 32 ng/mL is considered as the minimum level of sufficiency for children and adolescents with IBD. We recommend that consideration be given to monitoring vitamin D levels at least yearly, at the end of the winter-beginning of spring, especially in populations with dark skin complexion (i.e. Hispanics, African-Americans). It would be reasonable to obtain a 25OHD level in children with IBD and: active disease, low albumin level (< 3 g/dL), and evidence of nutritional compromise".

Rate: Poor-C: Rationale: See B. 2. a and B. 2. b.

B. 2. d. Treatment of hypovitaminosis D

> "Our recommendation is that it is reasonable to use *cumulative* doses of at least 400,000 international units (IU) if 25OHD level is < 20 ng/mL. For levels > 20 ng/mL, but lower than 32 ng/mL a *cumulative* dose of at least 250,000 IU would be reasonable"

Rate: Poor-C: The American Academy of Pediatrics recently recommended treating children with 25OHD level < 20 ng/mL with cumulative vitamin D doses between 140,000 IU to 600,000 IU given over a period of 8 to 12 weeks [119, 120]. Factors such as protein losing enteropathy and malabsorption due to intestinal inflammation may lead to treatment failures with regimens towards the lower end of the proposed doses in children with IBD. Lacking clinical trials of the efficacy of any regimen in the treatment of hypovitaminosis D in children with IBD, we propose the use of cumulative doses of at least 400,000 IU if 25OHD level is < 20 ng/mL and at least 250,000 IU if 25OHD is > 20 ng/mL, but lower than 32 ng/mL. In our experience compliance with daily regimens is low in adolescents, especially

those burdened with several other daily medications for their chronic illness. Therefore, we recommend weekly dosing with 50,000 IU if possible.

Literature suggests that vitamin D_3 (cholecalciferol) is superior to vitamin D_2 (ergocalciferol) in raising vitamin D levels [121, 122]. However, lacking studies comparing the two in children with IBD we could not recommend one form over the other. Such study is nearing completion at Children's Hospital Boston.

Restoration of vitamin D stores, especially if hypovitaminosis D is accompanied by secondary hyperparathyroidism, could lead to sudden hypocalcemia, resulting from suppression of parathyroid hormone and bone remineralization occurring after vitamin D stores are replete. This phenomenon was frequently encountered after parathyroidectomy for primary hyperparathyroidism, and is referred to as “hungry bone syndrome” [123]. To avoid this serious complication we recommend that adequate calcium intake is secured simultaneously with vitamin D repletion regimens above (see Table in B. 3.)

B. 2. e. Maintenance of optimal vitamin D status

> “We recommend considering advising daily vitamin D intake of 800-1,000 IU for children and adolescents with IBD”.

Rate: Poor-C: The National Institute of Medicine (NIM) updated the DRI (dietary reference intake) for both calcium and vitamin D in November of 2010 (http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx). The NIM recommends daily intake of 600 IU of vitamin D for healthy individuals 1 to 30 yo as “this intake is adequate to keep vitamin D levels above 20 ng/mL in most individuals”. However, higher supplementation doses may be needed in children with chronic conditions that predispose them to chronic malabsorption, and decreased sunlight exposure. Importantly, the NIM raised the tolerable upper limit of intake from 2,000 IU per day to 3,000 IU for 4-8 yo and 4,000 IU for any individual older than 9 yrs, confirming that no adverse effects are likely to occur up to that intake. The minimum vitamin D supplementation dose recommended for all children with cystic fibrosis (CF) by the CF Foundation is 800 IU per day [124]. Although no studies of the efficacy of any dose of vitamin D supplementation in keeping 25OHD level > 32 ng/mL in children with IBD have been reported to date, given the increased risk for hypovitaminosis D in children with IBD (see B. 2. b) we would recommend intake of 800-1,000 IU per day of vitamin D in children with IBD and optimal vitamin D levels. Note that such study is currently under way at Children's Hospital Boston

B. 3. CALCIUM INTAKE IN CHILDREN AND ADOLESCENTS WITH IBD

> “We recommend considering advising daily intake of 1,000 to 1,600 mg of elemental calcium in children (> 4 yo) and adolescents with IBD”

Rate: Poor-C—The 2010 National Institute of Medicine Daily Recommended Intakes (DRI) and Tolerable Upper Limits (TUL) for calcium and vitamin D, respectively, are summarized in Table 2. It is well established that the average calcium intake in healthy children falls far below these recommendations, especially during adolescence [125, 126]. Daily calcium intake is likely even lower in children with IBD, due to secondary lactose intolerance. Randomized trials of calcium supplementation in healthy children demonstrated that the positive effect of calcium on BMD requires a total calcium intake between 1200 to 1600 mg/day. [127-131] Studies in children and adults have demonstrated that physical activity has a beneficial bone effect only at higher calcium intake levels [132-134]. Daily doses of

1000-1200 mg of calcium have been used in trials in healthy children without adverse effects [130, 131, 133].

Subjects with CD involving the small bowel are at increased risk for calcium oxalate kidney stones. Normally dietary calcium binds with oxalate in the intestine to form a complex that is poorly absorbed. In individuals with small bowel disease, fat malabsorption results in increased binding of fatty acids with calcium to form insoluble soaps, thereby increasing the soluble oxalate available for absorption.[135] Calcium supplementation results in binding available soluble intestinal oxalate thereby decreasing urinary oxalate without increasing urinary calcium above normal levels; therefore, calcium is recommended to prevent enteric hyperoxaluria [136].

Calcium intake also modifies the bone response to physical activity.[137] A review of 17 physical activity trials in adults concluded that physical activity has beneficial effects on BMD at high calcium intakes, but no effect at calcium intakes less than 1000 mg/day.[134] Pre-pubertal and early-pubertal girls demonstrated greater gains in bone mass at loaded sites when they combined exercise with calcium supplementation [132].

Treatment with systemic glucocorticoids affects body calcium balance negatively. Systemic glucocorticoids are known to inhibit calcium absorption in the gut and stimulate tubular calcium excretion in the kidneys [138]. The net result is hypercalciuria and decrease in the calcium stores. Under such circumstances, systemic hypocalcemia rarely becomes evident, due to the development of secondary hyperparathyroidism. If vitamin D insufficiency or deficiency is also present, calcium loss in the intestine and kidney continues unopposed, since vitamin D's classic actions include enhancement of calcium absorption in the proximal intestine and the distal nephron [100-102]. It is advised that clinicians are mindful of the body calcium balance when administering systemic glucocorticoids to their young patients with IBD. Establishing vitamin D sufficiency and adequate calcium intake in children with IBD on glucocorticoids will help defray secondary hyperparathyroidism and bone resorption, as well as play a protective role against hypercalciuria.

B. 4. Nutritional support in children and adolescents with IBD

> "We recommend consideration of exclusive enteral nutrition alone, or supplemental enteral nutrition in addition to conventional therapy during the acute inflammatory phase and consideration of supplemental enteral nutrition during remission in children and adolescents with IBD and delayed linear growth"

Rate: Poor - C—Exclusive enteral nutrition has been shown to result in mucosal healing of inflammatory lesions in patients with IBD, most likely mediated by its effect on pro-inflammatory cytokines [139, 140]. A recent meta-analysis concluded that despite the lack of large well-controlled studies, nutritional therapy is comparable to glucocorticoids in inducing remission and superior in improving height velocity [141]. Elemental and polymeric formulas were found equally effective in inducing remission. No studies have examined the impact of exclusive enteral nutrition upon BMD in children with IBD. It is hypothesized that control of inflammation and improvements in weight, height and lean mass sustained during exclusive enteral therapy [142] will have a positive impact upon bone density as well. As a first step in confirming this hypothesis, a recent study found that bone formation and resorption markers – both affected at diagnosis - normalized after treatment with exclusive enteral nutrition in children with CD [143]. Systematic studies are needed to support this hypothesis and compare the skeletal benefits of exclusive enteral nutrition to those of several anti-inflammatory agents used for the treatment of IBD.

The role of supplemental enteral nutrition in improving bone health in the setting of either disease under remission or active disease in children with IBD has not been studied. Small prospective studies [144145146] and one retrospective study [147] found that supplemental enteral nutrition improves linear growth in children with IBD. Deficits in linear growth are closely related to bone mineral deficits [87] and improvements in linear growth were associated with lean mass increases and bone mineral improvement in various pediatric populations [148149]. Thus, supplemental enteral nutrition could improve BMD in children with IBD through linear growth and lean mass increase. The studies mentioned above used various regimens of supplementation. Most used the nasogastric or gastric-tube route, and nightly administration. Frequency of supplementation varied from intermittent (1 out of every 4 months) to continuous (4 to 5 days/week continuously). The amount of supplementary calories provided also varied from 50-60% of the total daily caloric requirement for age to 25% increase from the caloric intake prior to supplementation. The investigators used elemental of semi-elemental formulas. Based on the above, for the purpose of supplemental nutrition, we would recommend the use of elemental or semielemental formulas to provide 25-50% caloric increase, administered in a fashion that would achieve best patient compliance.

B. 5. Exercise in children and adolescents with IBD

> "It may be helpful for children and adolescents with IBD to follow an exercise program consisting of resistance training (muscle-building) activity twice weekly in addition to high-impact weight-bearing activity"

Rate: Poor-C—Children with IBD, due to their disease burden, may be less likely to engage in physical activity, compared to healthy children. Numerous studies have documented the beneficial effect of physical activity and biomechanical loading on bone geometry in healthy children [150-155]. Bone adapts its strength in response to the magnitude and direction of the forces to which it is subjected. This capacity of bone to respond to mechanical loading with increased bone size and strength is greatest during growth, especially during adolescence [86]. Physical activity affects the skeleton via two distinct mechanisms which function as osteogenic stimuli: (1) "muscle pull" which involves the force of contracting muscles upon their bony attachments and (2) weight-bearing exercise which results in the mechanical loading of the bone with compressive forces.

A physical intervention trial in adults with CD utilizing a home-based program of low-impact dynamic muscle conditioning exercises did not show a statistically significant difference in BMD of the lumbar spine and hip between cases and controls; however, analyses limited to those subjects achieving 100% adherence to the program did show a significant increase in trochanteric BMD [156]. Based on evidence in adults, a program consisting of resistance training (muscle-building) activity twice weekly in addition to high-impact weight-bearing activity may result in positive impacts on skeletal health in children with IBD. An intervention of low magnitude mechanical stimulation is currently underway in pediatric patients with CD.

B. 6. The role of biologics

In addition to its pivotal role in the pathogenesis of intestinal inflammation in CD, tumor necrosis factor- α (TNF-α) has a direct, detrimental effect on bone cells. *In vitro* studies have demonstrated that TNF-α inhibits bone formation by osteoblasts and promotes bone resorption by osteoclasts [157-159]. Consistent with the hypothesis that TNF-α contributes to bone deficits in CD, recent studies in adults have demonstrated significant increases in bone formation markers and reductions in bone resorption markers following anti-TNF-α therapy with infliximab [160-163]. The REACH study of infliximab induction and maintenance therapy

in pediatric CD also demonstrated significant increases in bone formation and resorption during the 10 week induction period, but with increases in formation far greater than those observed in adults [164]. Importantly, none of these studies related changes in bone markers to subsequent changes in bone mass or structure. One study of adults with CD found significant improvements in BMD measured via DXA, one year after treatment with infliximab [165]. One prospective study of 19 (17 received infliximab) adults with spondyloarthropathy demonstrated significant increases in lean mass, BMD, and IGF-1 and a decrease in bone resorption markers after 12 months of anti-TNF-α therapy. A study of changes in bone and muscle mass during infliximab therapy in pediatric CD is currently underway. At this juncture, anti-TNF-α therapy for bone deficits in pediatric IBD is not indicated.

B. 7. Bisphosphonates

Bisphosphonates are anti-resorptive agents that inactivate or inhibit the formation of osteoclasts, the cells responsible for bone break-down [166]. Bisphosphonates have been used in children with osteogenesis imperfecta, rheumatoid arthritis, and other forms of secondary osteoporosis [167-170]. Recent systematic reviews of the literature and meta-analyses reveal the fact that our cumulative experience with these agents in children is in part empirical and in part based on limited or low quality studies. These studies appear to support the efficacy of bisphosphonates in increasing BMD, but are inadequate to prove any effect on clinically meaningful outcomes such as reduction in the risk of fractures. As well, long term adverse effects of bisphosphonates in children have not been adequately studied. These include over-suppression of modeling and remodeling which could theoretically lead to the formation of dense bone of suboptimal quality, and thus more prone to fractures, and the potential for consequences to fetal skeletal development, since many of these agents have an estimated half life of several years. In addition, the target duration of use and optimal dose for each agent have not been defined as of yet [167-170]. At this point, it would be wise to limit the use of bisphosphonates to children with low BMD and significantly reduced quality of life second to fragility fractures, or in the context of well-designed clinical trials. Our opinion is that it is best that bisphosphonates are administered under the direction and direct supervision of a pediatric bone health expert, usually a pediatric endocrinologist.

Gaps in knowledge—Is there a relationship between bone health and vitamin D status in children with IBD based on systematic longitudinal studies? What is the vitamin D level that benefits bone health in these children based on large clinical trials?

Does exclusive enteral nutrition and enteral supplementation benefit bone health based on clinical trials?

What is the exercise regimen (s) that would prevent bone health compromise and improve bone health in children with IBD?

Would changing therapeutic approach (IBD therapy) be beneficial in children with IBD and compromised bone health, and which approach would be most beneficial (i.e. early introduction of biologics vs. conventional therapy vs. enteral nutrition or supplementation)?

Is there a role for “bone-active” medications such as calcitonin and bisphosphonates in children with IBD and who would benefit?

SUMMARY OF RECOMMENDATIONS: Children's bone health is negatively affected by inflammatory bowel disease (IBD). Inflammation decreases the rate of bone formation, process important for growing bones. Bone mineral density (BMD) lower than that of their healthy peers is evidence of suboptimal bone health in children with IBD. However, other

consequences such as increased fracture risk, especially of the spine, and decreased peak bone mass for life are feared.

Risk factors for compromised bone health in children with IBD are: linear growth delays, lean mass deficits, pubertal delays, severe inflammatory course and prolonged use of systemic glucocorticoids.

Recommendations regarding screening

1. DXA is the preferred method for measuring BMD in children with IBD and the result should be reported in Z-scores, adjusted for age and gender. Total body minus head and spine are the sites most accurately and consistently representing bone health status
2. In children with growth delays (height Z-score < -2.0 SD) and BMD Z-score < -1.0 SD, BMD should be adjusted for size after consultation with a bone specialist, to avoid underestimation of BMD.
3. We strongly recommend considering obtaining a DXA of total body minus head and spine in all children with IBD and the following risk factors:

    . growth delays (height Z-score < -2.0 SD, decreasing height Z-score)

    . BMI Z-score < -2.0 SD or decreasing BMI Z-score

    . pubertal delays *

    . secondary or primary amenorrhea (females) *

    . severe inflammatory course *

    . prolonged use of glucocorticoids *

    . history of clinically significant fractures (including vertebral fractures) *

Recommendation regarding monitoring: We recommend that clinicians consider obtaining follow up BMD measurements every 1-2 years in children with IBD and BMD Z-score of total body minus head or spine < -1.0 SD.

Low BMD: It may be helpful to consider total body minus head or spine BMD Z-score < 1.0 SD (adjusted for size) as “low” in terms of applying measures supportive to bone health and increased vigilance.

Measures specific to the finding of BMD Z-score < -1.0 SD

1. Consider treating inflammation with steroid-sparing techniques, including exclusive enteral nutrition in children who in addition have delayed linear growth (height Z-score < -2.0 SD).
2. Consider supplemental enteral nutrition in children who in addition have delayed linear growth (height Z-score < -2.0 SD), regardless of inflammation state or other treatments.

*details in full clinical report

Measures applicable to children with IBD regardless of bone health status

1. It is reasonable to monitor regularly linear growth, pubertal progression and menstrual regularity and consider consulting a specialist when pubertal delay or menstrual irregularity is noted.
2. Give consideration to monitoring vitamin D status yearly in late winter or early spring, treat hypovitaminosis D and consider recommending intake of 800 to 1,000 IU of vitamin D per day to maintain optimal vitamin D status.
3. Consider recommending intake of 1,000 to 1,600 mg of elemental calcium per day, according to age.
4. Consider recommending high impact weight bearing activity and resistance exercises 2-3 times per week.
5. Consider recommending supplemental enteral nutrition in children with linear growth delay (height Z-score < -2.0 SD).

Biologics: Until studies connect the use of biologics with favorable bone health outcomes in children with IBD, we cannot recommend their use solely for this purpose at this juncture.

Bisphosphonates: Bisphosphonates may play a role in the improvement of bone health in children with significant morbidity from compromised bone health, but their use should be left to the hands of bone experts at this point.

EVIDENCE RATING: We based the rating of this clinical report's recommendations on the system utilized by the Expert Panel of the International Society for Clinical Densitometry (ISCD) pediatric position statement in 2007 [82].

Our rating system – which is tailored after the ISCD rating system - includes the following criteria:

a. Quality of evidence as: 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.

b. Strength of the recommendation: A, B or 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.

QUALIFYING STATEMENT/DISCLAIMER

· Further controlled clinical studies may be needed to clarify aspects of this clinical report. This clinical report may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice.

· This clinical report is intended to be an educational device to provide information that may assist pediatric gastroenterologists in providing care to patients. This clinical report is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead a gastroenterologist to take a course of action that varies from this clinical report.

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TABLE 1

Timing of normal pubertal development and reasons for concern

	ONSET Average age in yrs (range)	CONCERN
FEMALES		
Breast development	**10 (7-13)**	Not present by the age of 13 yrs
Pubic hair	10.5 (7-14)	
Growth spurt (peak)	12	
Menarche	**12.5 (9-15)**	Not present by the age of 15 yrs
MALES		
Testicular enlargement	**11 (9-13.5)**	Not present by the age of 14-15
Pubic hair	12 (10-15)	
Penile enlargement	**12.5 (11-14.5)**	Not present by the age of 14-15
Growth spurt (peak)	14	

TABLE 2

Institute of Medicine 2,010 recommendations for calcium and vitamin D intake

	Calcium (mg/d)		Vitamin D (IU/d)	
Age	**DRI**	**TUL**	**DRI**	**TUL**
1-3 yr	700	2,500	600	2,500
4-8 yr	1,000	2,500	600	3,000
9-18 yr	1,300	3,000	600	4,000
19-30 yr	1,000	2,500	600	4,000

DRI: Daily recommended intake

TUL: Tolerable upper limit