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Pathological fractures in paediatric patients with inflammatory bowel disease

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Abstract

Paediatric inflammatory bowel disease (IBD), especially Crohn's disease (CD) is commonly associated with poor skeletal health, related to direct effects of chronic inflammation, prolonged use of glucocorticoid (GC), poor nutrition, delayed puberty and low muscle mass. Low bone mineral density is commonly reported, although the prevalence of long bone fractures may not be increased in these patients. Emerging evidence however suggests that there maybe an increased risk of vertebral fractures (VF) in this group. VF presenting at diagnosis of paediatric CD, prior to any GC exposure, have been reported, highlighting the deleterious effect of inflammation on skeletal health. This paper reviews the published literature on pathophysiology of skeletal morbidity and fractures in paediatric IBD, illustrated with a new case report of multiple VFs in a prepubertal girl with CD, soon after diagnosis, who received minimal amounts of oral GC. Optimising control of disease, addressing vitamin D deficiency, encouraging physical activity, ensuring normal growth and pubertal progression are paramount to management of bone health in these patients. Despite the lack of evidence, there may be a place for bisphosphonate treatment, especially in the presence of symptomatic pathological fractures but this requires close monitoring by clinicians with expertise in paediatric bone health.

Conclusion: Chronic inflammation mediated by pro-inflammatory cytokines may have adverse effects on skeletal health in paediatric patients with IBD. The risk of vertebral fractures may be increased, even without exposure to glucocorticoid. Clinical monitoring of these patients requires careful attention to the various factors that impact on bone health.

Introduction

An important extra-intestinal manifestation of paediatric inflammatory bowel disease (IBD) is poor bone health which can lead to pathological fractures. Abnormal bone health is commoner in paediatric patients with Crohn's disease (CD) than those with ulcerative colitis (UC) [10; 33].

This clinical review aims to provide an up to date summary of published information of skeletal health in paediatric IBD, in particular concentrating on fracture risk. A literature review was conducted using a PubMed search in May 2013 using the following keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, bone, fracture, vertebral fracture, bone mineral density, bone mineral content. Non English articles were excluded. Relevant articles were obtained and information were synthesised into the literature review of this article by the authors. This current review is divided into three sections:

1- Literature review of the pathophysiology of skeletal morbidity and fracture risk in paediatric IBD, including a summary of all published cases of symptomatic vertebral fracture (VF) in children and adolescents with IBD
2- Instructive case report of a pre-pubertal girl with CD and multiple VF with minimal GC exposure. Informed consent was acquired from the parents for anonymous publication of the child's clinical course and x rays as part of an instructive case.
3- A proposed pathway of clinical monitoring of bone health and management of skeletal morbidities in paediatric patients with IBD.

SECTION ONE: LITERATURE REVIEW

1. Patho-physiology of skeletal morbidity in IBD

Abnormal bone mass, bone geometry, bone metabolism and mineralisation in children and adolescents with IBD occur as a consequence of numerous factors. These include direct impact of the disease process mediated by pro-inflammatory cytokines, prolonged use of high dose glucocorticoid (GC), reduction of lean mass, poor nutrition, calcium, vitamin D deficiency, poor growth and delayed puberty associated with a state of relative hormone insufficiency (sex steroid) and resistance (growth hormone and insulin like growth factor 1) [11; 76; 94; 101]. Clearly all those factors are interlinked, although it is apparent that the inflammatory process mediated by pro-inflammatory cytokines is the central modulating factor. Pathological fractures in paediatric patients with IBD prior to GC exposure [85] or in those treated with minimal amount of GC [29] point to the crucial role of inflammation itself on bone health [80; 92; 96].

There are two important potential clinical consequences of poor bone health in children and adolescents with chronic inflammation. Firstly, poor bone health could lead to increased childhood fracture risk. However, fracture prevalence studies in these paediatric patients are still scarce. It is possible that there may not be an increased risk of long bone fractures but emerging evidence suggests an increased risk of VF which may be subclinical [44; 47]. To date, there are nine other published reports of symptomatic VF in children with IBD [17; 29; 52; 73; 85]. The clinical characteristics of these nine patients and a new patient included in this review are summarised in Table 1.

Secondly, chronic inflammation during the growing years impairs bone accrual, leading to reduction in peak bone mass by the end of adolescence and therefore significantly increased fracture risk in later life. During puberty approximately 40-50% of total bone mass is accrued, contributing to peak bone mass functioning as a “bone bank” for life [51]. Cortical thickness increases, along with increased trabecular mineralization, under the influence of sex hormone [71]. Given that paediatric IBD most frequently presents during late childhood or early adolescence, uncontrolled disease during those years may lead to reduction in both

cortical and trabecular quality and peak bone mass and therefore increased lifetime fracture risk [9; 82].

Research studies suggest that paediatric patients with UC have a lesser degree of abnormality in bone mass and metabolism [79]. Of all the published cases of symptomatic VFs in children and adolescents with IBD, only one is from a child with UC, a seven year old girl who had multiple lumbar VFs despite treatment with only three 2 month cycles of high dose GC [79]. There appears to be a female preponderance in published case reports of children with IBD and VFs. Seven of the nine previously published cases are girls. This contrasts with results from a murine model of colitis where significant trabecular bone loss, present mostly in vertebrae, was observed in males but not females [43].

2. What is the evidence for skeletal health abnormalities in paediatric patients with IBD?

• Evidence from bone densitometry studies

Numerous studies have evaluated the effects of chronic inflammation on the growing skeleton in paediatric patients with IBD. These have mostly utilized the non invasive imaging modality of dual energy absorptiometry (DXA). Interpretation of DXA derived bone mineral content (BMC) and bone mineral density (BMD) is subject to potential misinterpretation, as these measurements are influenced by body size [30; 34]. In a group of children and adolescents where growth retardation and pubertal delay is commonly seen, interpreting DXA BMC and BMD matched only for age and gender is inadequate and is likely to over-estimate the proportion with “low” BMD. Adjustments for size using height [38], bone area [2], bone age [38; 39] and lean mass [11; 19] reduce the likelihood of diagnosing low bone mass, but the various methods of size correction have not been adequately validated with a “gold” standard of assessment of bone mass [31].

Given that cortical bone development is reduced with active chronic disease, adjunctive bone assessment is now possible. Peripheral quantitative CT (pQCT) allows for assessment of trabecular and cortical bone, by providing volumetric three dimensional

assessment of the structural and geometric properties (bone mineral density, bone size) of the appendicular skeleton, not possible using DXA [48]. In addition, it also allows for measurement of muscle cross sectional area as a surrogate for total muscle mass, which allows for interpretation of the muscle-bone unit.

(a) DXA studies in paediatric patients with IBD

DXA studies in children and adolescents with IBD have documented variable degrees of deficit in bone mass. The International Society for Clinical Densitometry defines BMD z score adjusted for age, gender and body size ≤ -2.0 SD as "low" BMD [3; 65]. However, a recent expert consensus recommends using a BMD z score < -1.0 SD as the definition of "suboptimal" BMD in children and adolescents with IBD [58], even though pubertal delay is frequently not taken into account in these estimations.

DXA in paediatric patients with IBD at diagnosis prior to GC exposure

Several studies show variable degrees of mild to moderate deficit in DXA measured BMD in paediatric patients with IBD at diagnosis. Severity of disease at presentation and duration of symptoms prior to diagnosis may explain some of the differences. However, interpretation can be limited by variability in reporting methodology. In 60 newly diagnosed children and adolescents with IBD (39 CD), DXA height corrected lumbar spine (LS) BMD z score was moderately reduced (z score -1.4 SD), worse in those with CD [27]. In an older study, BMD z score at LS was mildly reduced (z score -0.8 SD) for CD but normal for UC (z score -0.1SD) [92]. By contrast, in a small study with 23 paediatric patients with CD, BMD z score adjusted for height and bone age was no different from controls at LS and total body (TB), although there was mild reduction of LS BMD z score adjusted for bone age (z score -0.77SD) [77].

Longitudinal DXA in paediatric patients with IBD from diagnosis

Following diagnosis and management of disease status, TB and LS BMD z score, adjusted for height, did not improve in those with CD whilst there was improvement for those with UC[79]. Interestingly, there was no relationship between change in BMD with paediatric

Crohn's disease activity index, GC exposure, body mass index, puberty or vitamin D in this study.

DXA and fracture occurrence in paediatric patients with IBD

In healthy children of the same age and gender, relative fracture risk doubles with each SD below the mean BMD[12; 13]. It is unclear if this also applies for children and adolescents with chronic disease. Overall, BMD z scores were significantly low in published cases of VF in paediatric patients with IBD (median BMD Z score -3.5) but less marked reduction in BMD would be expected had the values been adjusted for size, given that those patients were significantly short (Table 1: patients 5-6, 8-10).

There is some recent preliminary evidence from retrospective studies to suggest that size adjusted DXA measurements may differentiate children with chronic disease with fractures from those without fractures [18; 100]. Volumetric adjustment, bone mineral apparent density (BMAD), has the highest odds ratio for vertebral fractures in children with chronic disease [18]. Lower BMD adjusted for lean mass has also been found to be associated with fractures in children with chronic disease, especially long bone fractures [18; 100]. Currently, there is no clear fracture threshold based on unadjusted or adjusted DXA parameters in children with chronic disease. This implicates several other factors that may influence the occurrence of fracture in these children. These may include abnormal bone shape and geometry, abnormal bone mineralisation and rate of bone mass accrual. Therefore, clinical decisions regarding management of bone health should not be based on one single "abnormal" DXA BMD measurement.

(b) pQCT studies in paediatric patients with IBD

pQCT in paediatric patients with IBD at diagnosis prior to GC exposure

Studies from children and adolescents with CD at diagnosis show that trabecular BMD z score is significantly reduced (approximately -1.5 SD), whereas cortical BMD is preserved (approximately 0 SD). Although no deficit in cortical BMD was observed, abnormalities in bone geometry exist, in that cortical area was reduced (smaller bones) with

reduced periosteal circumference but increased endosteal circumference (thinner bones), with consequent increased stress –strain index and fracture risk [24; 88].

Longitudinal pQCT in paediatric patients with IBD from diagnosis

Longitudinal studies in paediatric patients with CD after diagnosis suggest inadequate improvement in trabecular BMD, despite improvement in disease activity. Cortical BMD showed initial improvement but then subsequently declined, related both to disease activity and GC dose. With long term follow-up, the abnormal bone geometry persists [24; 88].

• Evidence from markers of bone metabolism studies

In children and adolescents with IBD as opposed to adults, both bone formation and resorption are reduced, with an expected greater degree of reduction in markers of bone formation [79; 89]. Bone biomarkers, such as alkaline phosphatase and collagen type 1 C terminal propeptide largely reflect growth [81; 91] and are not helpful in the clinical setting in these patients .

• Evidence of clinical fractures

Whilst pathological fractures are reported in paediatric IBD, two studies suggest no increase in fracture prevalence in childhood and adolescence as a group [44; 64]. In a questionnaire study of 132 (73 CD) children and adolescence with IBD and 131 siblings as controls, no increase in fracture occurrence was reported. Those findings were replicated an American study using a database of 1221 (733 CD) children and adolescence with IBD and 3287 healthy controls. A sub-analysis however showed that children under the age of twelve years had an odds ratio (OR) of 2.2 (95% CI 1.2-3.8) for all fractures. In that study, importantly, there was a trend towards increased odds for VF as a group, OR 2.7 (95% 0.7-1.8) [44].

In a recent study, with 80 IBD patients (26 CD), median age 14.9 years (range 5-20) and 80 age, gender matched healthy controls, VF diagnosed from images obtained from DXA

scans was seen in nine out of 80 (11%) of patients and two out of 80 (3%) of healthy controls. Interestingly, reported fracture occurrence at peripheral sites was similar in patients and controls, highlighting the importance of assessment for VF in these children and adolescents. As opposed to the female predominance in published cases of symptomatic VF, eight out of 9 (89%) of the patients in this study were males. Disease severity, LS BMD, cumulative GC dose, vitamin D level and use of the anti-tumour necrosis factor (TNF) inhibitor infliximab were not associated with VF in that study [47]. By contrast, in a recent study of VF in adults with IBD with mean age of 37.4 years, VF diagnosed from anteroposterior and lateral x rays was seen in 38.2% of patients and 13.7% of controls [93]. In a multicentre study of 134 children with chronic inflammatory rheumatic conditions within 30 days of commencing GC, VF was seen in nine out of 134(7%) patients of that cohort [41]. Currently, there is little data on fracture history of adults with paediatric onset IBD. The odds ratio for sustaining a fracture in adulthood for paediatric onset IBD is 1.6 (95% CI 1.4- 1.8).

3. Contributors to poor bone health in children with IBD

(a) The role of glucocorticoid (GC)

Oral GC are generally used for induction of remission in paediatric patients with UC. They are also used in children and adolescents with CD although exclusive enteral nutrition may be considered as first line for induction of remission in those with mild-moderate CD. GC can affect bone health via several mechanisms. GC has direct effects on reduction of osteoblastogenesis, whilst promoting apoptosis of osteoblasts and osteocytes, leading to decreased bone formation [97]. GC may also increase bone resorption by increasing the life span of osteoclasts [40]. GC also promotes renal and gastrointestinal calcium loss, thus affecting bone remodelling and increase osteoclastic activity due to secondary hyperparathyroidism [36]. They affect to a greater degree trabecular bone, the predominant bone in vertebrae [83; 87].

Clinical studies in childrenand adolescents with IBD have failed to show a consistent link between GC and BMD. However, they are limited by minimal numbers and reported

assessments do not always include the important aspects of volumetric bone density and pubertal status and progress. . Some investigators have found a negative relationship between cumulative GC dose and BMD [10; 50; 95] whereas others have not [24; 33; 57; 79; 88]. However, most previous case reports of VF in IBD include children and adolescents treated with prolonged and / or high doses of GC. The largest series of VF in paediatric IBD (Table 1: patient 3, 5-8) included five female patients (median age 14.5 yrs) treated with GC for prolonged periods [73]. Some published cases were treated for a shorter duration with GC (Table 1; patient 4, 10) [17; 29]. The minimum duration and dose of GC therapy that may cause damage to bones in paediatric patients with IBD is currently unknown. Conversely, the negative effects of GC on bone may be offset by their capacity to improve inflammation, which in itself adversely affects bone health.

Enteral nutrition may be used for induction of remission in CD [20; 25] and have several possible advantages. Children and adolescents treated with enteral nutrition have better growth velocity than those treated with GC [56; 66; 86], with corresponding improvement in systemic growth factors of insulin like growth factor 1 (IGF1) and insulin growth factor binding protein 3 (IGFBP3) [6]. Improvement in IGF1 and IGFBP3 occur prior to nutritional reconstitution, suggesting a direct effect in reduction of inflammation. In a recent prospective study, enteral nutrition also led to reduction of a marker of bone breakdown and increased levels of a marker of bone formation[99]. It is however unclear if fracture risk is reduced in cohorts of children and adolescents managed with enteral nutrition compared with GC.

(b) The role of pro-inflammatory cytokines

Evidence from experimental studies in primary cultures of rat osteoblasts and foetal rat parietal bones, where serum from children with CD at diagnosis was added, suggests that osteoblastic function, terminal differentiation, bone formation and matrix mineralisation are all affected [80; 92]. Incubation of foetal rat parietal bones exposed to serum of paediatric patients with CD with an antibody against IL6 prevents the change in osteoblast and bone

morphology in that model [42]. TNFα affects differentiation and function of osteoblasts and promotes osteoclast differentiation [1; 32; 46] whilst both TNFα and IL6 promote osteoclast activity[49; 75].Chronic inflammation in paediatric IBD may also increase renal phosphate excretion and inhibit renal 25-hydroxyvitamin D3 1α hydroxylase via increased level of fibroblast growth factor 23 (FGF23) [26; 90].

Acute inflammation may increase locally active GC or local GC sensitivity. Osteoblasts generate active glucocorticoid through expression of 11β hydroxysteroid dehydrogenase type 1 (11βHSD1) which converts inactive GC (cortisone and prednisone) to their active counterparts (cortisol and prednisolone). 11βHSD1 activity is increased by pro-inflammatory cytokines and GC [15; 16; 45]. The concentration of dexamethasone and prednisolone with lethal effects on lymphocytes from the child with UC and VF was 30% and 63% lower compared with controls, suggesting increased GC sensitivity [52].

No children or adolescents with IBD and VF reported in the literature were treated with newer immunosuppressants or biologic therapy (Table 1). Anti TNFα agents (infliximab and adalimumab) are considered in patients with severe fistulising disease and in the presence of resistance to conventional immunosuppressants [28; 102]. Data from the REACH study, which included 112 children with CD, showed that use of infliximab led to significant improvement in bone specific alkaline phosphatase and N-terminal propeptide of type 1 collagen and bone formation biomarkers [84]. Some adult studies of patients with CD treated with infliximab have shown improvement in BMD assessed by DXA [8; 55; 63] but it is unclear if this translates to reduction in fracture risk.

(c) The role of delayed puberty and poor linear growth

Delayed puberty and inadequate pubertal growth spurt are common in adolescentd with IBD [4; 54]. Both GC and pro-inflammatory cytokines can also lead to a functional degree of relative resistance to GH and IGF1 [67; 101]and can also impact on gonadal function via effects on the pituitary, hypothalamus and gonads. GH and IGF1 regulate growth of bones throughout childhood. In girls during puberty, oestrogen inhibits periosteal

apposition of bone while stimulating endocortical bone formation, with consequent narrowing of the medullary cavity. Testosterone enlarges bone size by apposition on the periosteal surface [23; 37; 70; 72]. Whilst low leptin levels, which have been shown to regulate the hypothalamic-pituitary-gonadal axis, due to low fat stores, may explain delayed puberty in IBD, recent animal studies suggest that inflammation itself plays a larger role [21; 22].

Whilst delayed puberty can impact on bone health in these adolescents, significantly delayed puberty has only been reported in two paediatric patients with IBD and VF (See Table 1- Patient 5 and 10). Addressing delayed puberty in these patients is however important to provide adequate bone accrual.

(d) The role of vitamin D deficiency

Current studies do not show an obvious relationship between vitamin D levels and bone densitometry results in paediatric IBD [59; 79]. There are also no studies addressing the risk of fracture in these children in relationship to vitamin D levels. Vitamin D levels were found to be lower in patients with IBD than healthy controls. Using a cut off of 37 nmol/L, suboptimal vitamin D levels were reported in between 16-34% of children and adolescents with IBD in spite of vitamin D supplementation [60; 61; 74]. A recent randomized trial in paediatric IBD suggests that larger doses of either vitamin D2 or vitamin D3 are effective for treatment of vitamin D deficiency in this group of patients [62]. An open label trial of 1000 mg calcium supplements and 50,000 units of Vitamin D2 monthly given orally in 39 children and adolescents with IBD failed to show improvement in DXA LS BMD [7]. Therefore, there are still numerous unanswered questions about the optimal method and dose of replacing vitamin D in paediatric IBD.

(e) The role of low muscle mass

The structural integrity of bone is influenced by weight bearing and muscle load. As muscle mass and strength increases, bone increases in mass, strength and dimension [69]. Both GC and inflammatory cytokines can have adverse effects on muscle cells through

increasing the expression of myostatin, a negative regulator of muscle mass [53], increasing protein degradation [14] and inhibiting skeletal muscle differentiation [35]. Longitudinal clinical studies in paediatric CD suggest that in spite of treatment following diagnosis, deficits in lean mass persist [78]. A recent study showed that physical activity and muscle strength were reduced in paediatric CD despite inactive disease [98], which may partly account for the failure of bone accrual even with treatment.

SECTION TWO: INSTRUCTIVE CASE

A 6 year 9 months old pre-pubertal girl presented with a one year history of upper lip swelling, loose stools and abdominal pain. Height was 126.3 cm (height z score +0.9 SD, premorbid height z score 3 years previously +2.3 SD), weight 18.5 kg (weight z score -1.3 SD, premorbid weight z score 3 years previously +0.8 SD). Investigations revealed hypochromic, microcytic anaemia: haemoglobin (Hb) 76 g/L (normal range (NR) 115-155), MCV 69 fl (77-95), MCH 21.1 pg (25-33) with abnormal iron studies: iron 1 µmol/L (9-30), transferrin 1.5 g/L (2.1-4.3) and iron binding capacity 37.7 µmol/L (44-80), thrombocytosis with platelets of 491 x10e9/L (150-400), raised white cell count 21.7 x10e9/L (4.5-13.5) and hypoalbuminaemia 18 g/L (33-47). Faecal calprotectin was significantly elevated at 545.8 µg/g (19.5-50), highly suggestive of significant intestinal inflammation. Vitamin D was < 22nmol/L (50-160) at diagnosis, which might not be unusual given the history of severe CD and that the child is of South Asian origin. A stoss dose of 150,000 units of vitamin D was given orally. Gastroscopy and colonoscopy identified anal fissures, severe rectosigmoid ulceration, scattered colonic aphthous ulcers and an ileitis. Histopathology showed granulomatous inflammation with an active gastritis, focal duodenitis, terminal ileal ulceration and an active chronic colitis consistent with Crohn's disease. Unfortunately during the diagnostic procedure, a rectosigmoid perforation occurred. Laparoscopy, peritoneal washout and repair of perforation were immediately performed, together with a. defunctioning ilesotomy.

Her clinical course was complicated by problems of fluid balance, nutrition, pain control and sepsis, with an inpatient stay for a total of 3 months. She was initially treated with total parenteral nutrition and subsequently maintained on semi elemental feeds with Nutrini Extra (Nutricia N Ryde, NSW). GC treatment was given for a total of 31 days- initially with methylprednisolone intravenously for a total of 8 days (25 mg twice daily for 5 days and 25 mg daily for 3 days) and subsequently a weaning course of oral prednisolone for a total of 23 days, commencing at 20 mg daily. Total GC exposure for the 31 days was 2.5 mg/kg/day

Prednisolone equivalent. Mesalazine was commenced when the patient was fully enterally fed but was discontinued after 2 weeks due to intolerance.

Severe incapacitating back pain was reported 4 months post diagnosis at an outpatient appointment, when the child had to be carried by her parents. Xray confirmed extensive vertebral fractures from T7-L4 with the most severe involvement at T11 with the loss of 25% of anterior vertebral height at that level (Figure 1). Investigations performed at the time showed total calcium 2.41 mmol/L (2.10-2.60), phosphate 1.72 mmol/L (1.10-1.80), 25 hydroxy vitamin D 55 nmol/L (50-160), PTH 3.6 pmol/L (1.3-6.8). Disease activity markers were relatively unremarkable: ESR 9 mm/hr (0-6), faecal calprotectin 25.3 µg/g (19.5- 50), Hb 125 g/L (115-155), platelets 522 x10e9/L (150-400), WCC 11.4 x10e9/L (4.5-13.5) and albumin 32 g/L (33-47). The patient was not taking any GC, background immunosuppressant or alternative medications at that time. Bone age was 7 years (chronological age was 7 years 1 month). Evaluation with DXA showed that volumetric adjustment for bone size, bone mineral apparent density (BMAD) Z scores were significantly low: -4.7 SD (total body), -2.2 SD (neck of femur) and -4.3 (lumbar spine). Taking into account the patient's size, height age adjusted bone mineral density (BMD) Z scores were also significantly low, especially at lumbar spine at -4.0 SD. In view of the extensive symptomatic vertebral fractures, bisphosphonate, as zoledronic acid 0.04 mg/kg/dose was commenced, with immediate and total pain relief within a week, and return of independent mobility. Infusions were repeated four monthly. Background immunosuppressant was commenced using azathioprine.

SECTION THREE: CLINICAL MONITORING AND MANAGEMENT

Bone health monitoring in paediatric IBD

Expert consensus recommends that a DXA scan be considered in all children and adolescents with IBD close to time of diagnosis and in the presence of risk factors like suboptimal linear growth, weight loss, secondary or primary amenorrhoea, delayed puberty, severe inflammatory disease , after 6 months or longer of continuous use of systemic GC and those with a history of clinically significant fractures (fractures of long bones of the lower extremities, two or more fractures of the upper extremities and/or vertebral compression fractures) [58]. It is crucial that DXA results are analysed with software containing paediatric data sets and reported as size adjusted z scores. Repeat DXA scans should be performed using the same machine to allow for comparison.

We additionally recommend a low threshold for obtaining lateral spine x rays in all children with IBD regardless of GC exposure, especially if there is evidence of back pain. Consideration of spine x rays should be made for all patients with severe CD regardless of the presence of symptoms (eg those requiring hospitalisations, PCDAI > 50 at diagnosis), within the first 6-8 weeks following diagnosis. Another possible alternative to spine x ray is assessment of images from DXA scans, if equipment permits assessment of lateral spine.

Regular assessment of linear growth and pubertal development gives the clinician an excellent guide to the general health of the patient IBD. Pubertal assessment should be performed in every child and adolescent with IBD at least every 6-12 months. Calcium and vitamin D status should be assessed every 6 months. Severe vitamin D deficiency can be present at diagnosis as highlighted by our instructive case.

Management of abnormal skeletal health and fracture in paediatric IBD

Bone health in the presence of chronic inflammatory disease should be addressed by optimization of disease management with reduction of cytokines, attention to calcium and vitamin D intake, induction of puberty and maintenance of pubertal progress where necessary. As the skeletal abnormality in children with IBD is driven by the inflammatory process, the

most important management strategy is careful evaluation for disease status and optimization of disease control. In the presence of “sub-optimal” BMD or pathological fractures, escalation of medical therapy like the introduction of immunomodulator in our instructive case or anti TNF therapy may be appropriate.

Given the importance of puberty for bone mass accrual, it is crucial that delayed puberty or failure to progress through puberty is appropriately addressed. If there is evidence of delayed puberty (defined as < 4 mL testes in boys by 14 years and no breast development in girls by 13 years), referral to a paediatric endocrinologist for evaluation of the possible benefit of pubertal induction with sex steroid should be considered. Whilst sex steroid can lead to improvement in bone mass, to date, there are no published studies of the efficacy of pubertal induction on improving bone health in paediatric IBD. Therefore, such decisions require careful thought. .In our clinical experiencewhilst a short course of sex steroids for 6 months might be adequate to induce puberty in a normal adolescent , in the presence of active IBD, sex steroid supplementation may be required until full sexual maturity is achieved, as pubertal progress may be intermittent or pubertal arrest may occur in the presence of chronically active disease.

If there is evidence for symptomatic pathological fractures in IBD, bisphosphonate treatment is indicated [5; 58]. Bisphosphonate has a dramatic effect on pain control, as seen in our instructive case. However, there are still numerous controversies regarding the choice, dose and duration of treatment with bisphosphonate. The only clinical indication for the use of bisphosphonates in paediatric IBD is in the presence of symptomatic pathological fractures with low BMD. Bisphosphonates treatment should only be initiated and monitored by a paediatric endocrinologist with expertise in bone health.

There maybe a place to consider the use of bisphosphonates in the absence of symptomatic pathological fractures in paediatric IBD with evidence of low bone mass, but they should ideally only be considered in the context of well designed therapeutic clinical trials. These situations include the detection of asymptomatic VF or “low” BMD (eg size corrected BMD z score < -2.0) together with failure to gain bone mass at an age appropriate

rate or ongoing bone loss despite optimization of disease control, vitamin D, calcium status and pubertal induction if appropriate. We however stress that it is uncommon to encounter the latter situation. A preliminary trial of bisphosphonate with a single dose of zoledronic acid (0.066 mg/kg/day) in a small study in thirteen adolescents with CD (7 zoledronic acid, 6 placebo) with low bone mass but no fractures demonstrated a significant increase in volumetric LS BMD z score up to 12 months [68], although it is unclear if this translates to reduction in fracture risk. Therefore, "prophylactic" use of bisphosphonates is currently not recommended.

CONCLUSION

Chronic inflammation has an adverse effect on skeletal health in paediatric patients with IBD by multiple mechanisms. Not only is bone density affected in these children and adolescents , but abnormal bone geometry may also predispose to increased fracture risk. Whilst current data do not suggest an increased risk of long bone fractures, emerging data suggest that these patients maybe at increased risk of VFs. It is currently unclear if there is a role for routine screening of VF in a subset of these children and adolescents the role of prophylactic bone protective agents. It is however imperative that clinicians have a low threshold for suspecting pathological fractures in these patients even in the absence of exposure to GC. Aggressive control of inflammation using GC sparing agents, careful attention to nutrition, calcium, vitamin D status, growth, puberty and exercise are paramount in preventing the catastrophic consequences of VF in these paediatric .

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REFERENCES

1. Abu-Amer Y, Ross FP, Edwards J, Teitelbaum SL (1997) Lipopolysaccharide-stimulated osteoclastogenesis is mediated by tumor necrosis factor via its P55 receptor. J Clin Invest 100:1557-1565

2. Ahmed SF, Russell S, Rashid R, Beattie TJ, Murphy AV, Ramage IJ, Maxwell H (2004) Bone mineral assessment in children with inflammatory bowel disease: evaluation by age or bone area. J Pediatr Gastroenterol Nutr 38:276-280

3. Baim S, Leonard MB, Bianchi ML, Hans DB, Kalkwarf HJ, Langman CB, Rauch F (2008) Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom 11:6-21

4. Ballinger AB, Savage MO, Sanderson IR (2003) Delayed puberty associated with inflammatory bowel disease. Pediatr Res 53:205-210

5. Batch JA, Couper JJ, Rodda C, Cowell CT, Zacharin M (2003) Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. Journal of paediatrics and child health 39:88-92

6. Beattie RM, Camacho-Hubner C, Wacharasindhu S, Cotterill AM, Walker-Smith JA, Savage MO (1998) Responsiveness of IGF-I and IGFBP-3 to therapeutic intervention in children and adolescents with Crohn's disease. Clin Endocrinol (Oxf) 49:483-489

7. Benchimol EI, Ward LM, Gallagher JC, Rauch F, Barrowman N, Warren J, Beedle S, Mack DR (2007) Effect of calcium and vitamin D supplementation on bone mineral density in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 45:538-545

8. Bernstein M, Irwin S, Greenberg GR (2005) Maintenance infliximab treatment is associated with improved bone mineral density in Crohn's disease. Am J Gastroenterol 100:2031-2035

9. Bonjour JP, Chevalley T, Ferrari S, Rizzoli R (2009) The importance and relevance of peak bone mass in the prevalence of osteoporosis. Salud publica de Mexico 51 Suppl 1:S5-17

10. Boot AM, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM (1998) Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 42:188-194

11. Burnham JM, Shults J, Semeao E, Foster B, Zemel BS, Stallings VA, Leonard MB (2004) Whole body BMC in pediatric Crohn disease: independent effects of altered growth, maturation, and body composition. J Bone Miner Res 19:1961-1968

12. Clark EM, Ness AR, Bishop NJ, Tobias JH (2006) Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res 21:1489-1495

13. Clark EM, Tobias JH, Ness AR (2006) Association between bone density and fractures in children: a systematic review and meta-analysis. Pediatrics 117:e291-297

14. Clowes GH, Jr., George BC, Villee CA, Jr., Saravis CA Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. N Engl J Med 308:545-552

15. Cooper MS, Bujalska I, Rabbitt E, Walker EA, Bland R, Sheppard MC, Hewison M, Stewart PM (2001) Modulation of 11beta-hydroxysteroid dehydrogenase isozymes by proinflammatory cytokines in osteoblasts: an autocrine switch from glucocorticoid inactivation to activation. J Bone Miner Res 16:1037-1044

16. Cooper MS, Rabbitt EH, Goddard PE, Bartlett WA, Hewison M, Stewart PM (2002) Osteoblastic 11beta-hydroxysteroid dehydrogenase type 1 activity increases with age and glucocorticoid exposure. J Bone Miner Res 17:979-986

17. Cowan FJ, Parker DR, Jenkins HR (1995) Osteopenia in Crohn's disease. Arch Dis Child 73:255-256

18. Crabtree NJ, Hogler W, Cooper MS, Shaw NJ (2013) Diagnostic evaluation of bone densitometric size adjustment techniques in children with and without low trauma fractures. Osteoporos Int 24:2015-2024

19. Crabtree NJ, Kibirige MS, Fordham JN, Banks LM, Muntoni F, Chinn D, Boivin CM, Shaw NJ (2004) The relationship between lean body mass and bone mineral content in paediatric health and disease. Bone 35:965-972

20. Critch J, Day AS, Otley A, King-Moore C, Teitelbaum JE, Shashidhar H (2012) Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. J Pediatr Gastroenterol Nutr 54:298-305

21. Deboer MD, Li Y (2011) Puberty is delayed in male mice with dextran sodium sulfate colitis out of proportion to changes in food intake, body weight, and serum levels of leptin. Pediatr Res 69:34-39

22. DeBoer MD, Li Y, Cohn S (2010) Colitis causes delay in puberty in female mice out of proportion to changes in leptin and corticosterone. J Gastroenterol 45:277-284

23. Duan Y, Turner CH, Kim BT, Seeman E (2001) Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. J Bone Miner Res 16:2267-2275

24. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, Herskovitz RM, Howard KM, Leonard MB (2009) Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology 136:123-130

25. Dziechciarz P, Horvath A, Shamir R, Szajewska H (2007) Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther 26:795-806

26. El-Hodhod MA, Hamdy AM, Abbas AA, Moftah SG, Ramadan AA (2012) Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease. BMC gastroenterology 12:44

27. El-Matary W, Sikora S, Spady D (2011) Bone mineral density, vitamin D, and disease activity in children newly diagnosed with inflammatory bowel disease. Dig Dis Sci 56:825-829

28. Feagan BG, Lemann M, Befrits R, Connell W, D'Haens G, Ghosh S, Michetti P, Ochsenkuhn T, Panaccione R, Schreiber S, Silverberg M, Sorrentino D, van der

Woude CJ, Vermeire S, Rutgeerts P (2012) Recommendations for the treatment of Crohn's disease with tumor necrosis factor antagonists: an expert consensus report. Inflamm Bowel Dis 18:152-160

29. Ferreira R, Almeida S (2010) Crohn's disease in a child: unusual presentation with severe osteoporosis. BioDrugs 24 Suppl 1:31-33

30. Fewtrell MS (2003) Bone densitometry in children assessed by dual x ray absorptiometry: uses and pitfalls. Arch Dis Child 88:795-798

31. Fewtrell MS, Gordon I, Biassoni L, Cole TJ (2005) Dual X-ray absorptiometry (DXA) of the lumbar spine in a clinical paediatric setting: does the method of size-adjustment matter? Bone 37:413-419

32. Gilbert LC, Rubin J, Nanes MS (2005) The p55 TNF receptor mediates TNF inhibition of osteoblast differentiation independently of apoptosis. Am J Physiol Endocrinol Metab 288:E1011-1018

33. Gokhale R, Favus MJ, Karrison T, Sutton MM, Rich B, Kirschner BS (1998) Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterology 114:902-911

34. Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, Lorenc RS, Tosi LL, Ward KA, Ward LM, Kalkwarf HJ (2008) Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom 11:43-58

35. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS, Jr. (2000) NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. Science 289:2363-2366

36. Hahn TJ, Halstead LR, Teitelbaum SL, Hahn BH (1979) Altered mineral metabolism in glucocorticoid-induced osteopenia. Effect of 25-hydroxyvitamin D administration. J Clin Invest 64:655-665

37. Henry YM, Fatayerji D, Eastell R (2004) Attainment of peak bone mass at the lumbar spine, femoral neck and radius in men and women: relative contributions of bone size and volumetric bone mineral density. Osteoporos Int 15:263-273

38. Herzog D, Bishop N, Glorieux F, Seidman EG Interpretation of bone mineral density values in pediatric Crohn's disease. Inflamm Bowel Dis 4:261-267

39. Hill RJ, Brookes DS, Lewindon PJ, Withers GD, Ee LC, Connor FL, Cleghorn GJ, Davies PS (2009) Bone health in children with inflammatory bowel disease: adjusting for bone age. J Pediatr Gastroenterol Nutr 48:538-543

40. Hofbauer LC, Gori F, Riggs BL, Lacey DL, Dunstan CR, Spelsberg TC, Khosla S (1999) Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology 140:4382-4389

41. Huber AM, Gaboury I, Cabral DA, Lang B, Ni A, Stephure D, Taback S, Dent P, Ellsworth J, LeBlanc C, Saint-Cyr C, Scuccimarri R, Hay J, Lentle B, Matzinger M, Shenouda N, Moher D, Rauch F, Siminoski K, Ward LM, Canadian Steroid-Associated Osteoporosis in the Pediatric Population C (2010) Prevalent vertebral fractures among children initiating glucocorticoid therapy for the treatment of rheumatic disorders. Arthritis Care Res (Hoboken) 62:516-526

42. Hyams JS, Wyzga N, Kreutzer DL, Justinich CJ, Gronowicz GA (1997) Alterations in bone metabolism in children with inflammatory bowel disease: an in vitro study. J Pediatr Gastroenterol Nutr 24:289-295

43. Irwin R, Lee T, Young VB, Parameswaran N, McCabe LR (2013) Colitis-induced bone loss is gender dependent and associated with increased inflammation. Inflamm Bowel Dis 19:1586-1597

44. Kappelman MD, Galanko JA, Porter CQ, Sandler RS (2011) Risk of diagnosed fractures in children with inflammatory bowel diseases. Inflamm Bowel Dis 17:1125-1130

45. Kaur K, Hardy R, Ahasan MM, Eijken M, van Leeuwen JP, Filer A, Thomas AM, Raza K, Buckley CD, Stewart PM, Rabbitt EH, Hewison M, Cooper MS (2010) Synergistic

induction of local glucocorticoid generation by inflammatory cytokines and glucocorticoids: implications for inflammation associated bone loss. Ann Rheum Dis 69:1185-1190

46. Kobayashi K, Takahashi N, Jimi E, Udagawa N, Takami M, Kotake S, Nakagawa N, Kinosaki M, Yamaguchi K, Shima N, Yasuda H, Morinaga T, Higashio K, Martin TJ, Suda T (2000) Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. The Journal of experimental medicine 191:275-286
47. Laakso S, Valta H, Verkasalo M, Toiviainen-Salo S, Viljakainen H, Makitie O (2012) Impaired bone health in inflammatory bowel disease: a case-control study in 80 pediatric patients. Calcif Tissue Int 91:121-130
48. Leonard MB, Shults J, Elliott DM, Stallings VA, Zemel BS (2004) Interpretation of whole body dual energy X-ray absorptiometry measures in children: comparison with peripheral quantitative computed tomography. Bone 34:1044-1052
49. Liu XH, Kirschenbaum A, Yao S, Levine AC (2005) Cross-talk between the interleukin-6 and prostaglandin E(2) signaling systems results in enhancement of osteoclastogenesis through effects on the osteoprotegerin/receptor activator of nuclear factor-{kappa}B (RANK) ligand/RANK system. Endocrinology 146:1991-1998
50. Lopes LH, Sdepanian VL, Szejnfeld VL, de Morais MB, Fagundes-Neto U (2008) Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease. Dig Dis Sci 53:2746-2753
51. Lu PW, Briody JN, Ogle GD, Morley K, Humphries IR, Allen J, Howman-Giles R, Sillence D, Cowell CT (1994) Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross-sectional and longitudinal study. J Bone Miner Res 9:1451-1458
52. Lucarelli S, Borrelli O, Paganelli M, Capocaccia P, Frediani T, Ferri F, Cucchiara S (2006) Vertebral fractures and increased sensitivity to corticosteroids in a child with

ulcerative colitis: successful use of pamidronate. J Pediatr Gastroenterol Nutr 43:533-535

53. Ma K, Mallidis C, Bhasin S, Mahabadi V, Artaza J, Gonzalez-Cadavid N, Arias J, Salehian B (2003) Glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. Am J Physiol Endocrinol Metab 285:E363-371

54. Mason A, Malik S, Russell RK, Bishop J, McGrogan P, Ahmed SF (2011) Impact of inflammatory bowel disease on pubertal growth. Horm Res Paediatr 76:293-299

55. Mauro M, Radovic V, Armstrong D (2007) Improvement of lumbar bone mass after infliximab therapy in Crohn's disease patients. Can J Gastroenterol 21:637-642

56. Newby EA, Sawczenko A, Thomas AG, Wilson D (2005) Interventions for growth failure in childhood Crohn's disease. Cochrane Database Syst Rev:CD003873

57. Paganelli M, Albanese C, Borrelli O, Civitelli F, Canitano N, Viola F, Passariello R, Cucchiara S (2007) Inflammation is the main determinant of low bone mineral density in pediatric inflammatory bowel disease. Inflamm Bowel Dis 13:416-423

58. Pappa H, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C (2011) Skeletal health of children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 53:11-25

59. Pappa HM, Gordon CM, Saslowsky TM, Zholudev A, Horr B, Shih MC, Grand RJ (2006) Vitamin D status in children and young adults with inflammatory bowel disease. Pediatrics 118:1950-1961

60. Pappa HM, Grand RJ, Gordon CM (2006) Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis 12:1162-1174

61. Pappa HM, Langereis EJ, Grand RJ, Gordon CM (2011) Prevalence and risk factors for hypovitaminosis D in young patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 53:361-364

62. Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, Quinn N, Lawton RC, Varvaris M, Van Straaten S, Gordon CM (2012) Treatment of vitamin D insufficiency in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing three regimens. J Clin Endocrinol Metab 97:2134-2142

63. Pazianas M, Rhim AD, Weinberg AM, Su C, Lichtenstein GR (2006) The effect of anti-TNF-alpha therapy on spinal bone mineral density in patients with Crohn's disease. Ann N Y Acad Sci 1068:543-556

64. Persad R, Jaffer I, Issenman RM (2006) The prevalence of long bone fractures in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 43:597-602

65. Rauch F, Plotkin H, DiMeglio L, Engelbert RH, Henderson RC, Munns C, Wenkert D, Zeitler P (2008) Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2007 Pediatric Official Positions. J Clin Densitom 11:22-28

66. Sanderson IR, Udeen S, Davies PS, Savage MO, Walker-Smith JA (1987) Remission induced by an elemental diet in small bowel Crohn's disease. Arch Dis Child 62:123-127

67. Sarzi-Puttini P, Atzeni F, Scholmerich J, Cutolo M, Straub RH (2006) Anti-TNF antibody treatment improves glucocorticoid induced insulin-like growth factor 1 (IGF1) resistance without influencing myoglobin and IGF1 binding proteins 1 and 3. Ann Rheum Dis 65:301-305

68. Sbrocchi AM, Forget S, Laforte D, Azouz EM, Rodd C (2010) Zoledronic acid for the treatment of osteopenia in pediatric Crohn's disease. Pediatr Int 52:754-761

69. Schoenau E (2005) From mechanostat theory to development of the "Functional Muscle-Bone-Unit". Journal of musculoskeletal & neuronal interactions 5:232-238

70. Schoenau E, Neu CM, Mokov E, Wassmer G, Manz F (2000) Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. J Clin Endocrinol Metab 85:1095-1098

71. Schoenau E, Neu CM, Rauch F, Manz F (2002) Gender-specific pubertal changes in volumetric cortical bone mineral density at the proximal radius. Bone 31:110-113

72. Seeman E (2001) Clinical review 137: Sexual dimorphism in skeletal size, density, and strength. J Clin Endocrinol Metab 86:4576-4584

73. Semeao EJ, Stallings VA, Peck SN, Piccoli DA (1997) Vertebral compression fractures in pediatric patients with Crohn's disease. Gastroenterology 112:1710-1713

74. Sentongo TA, Semaeo EJ, Stettler N, Piccoli DA, Stallings VA, Zemel BS (2002) Vitamin D status in children, adolescents, and young adults with Crohn disease. Am J Clin Nutr 76:1077-1081

75. Siggelkow H, Eidner T, Lehmann G, Viereck V, Raddatz D, Munzel U, Hein G, Hufner M (2003) Cytokines, osteoprotegerin, and RANKL in vitro and histomorphometric indices of bone turnover in patients with different bone diseases. J Bone Miner Res 18:529-538

76. Sylvester FA (2001) Bone abnormalities in gastrointestinal and hepatic disease. Rev Endocr Metab Disord 2:75-80

77. Sylvester FA, Davis PM, Wyzga N, Hyams JS, Lerer T (2006) Are activated T cells regulators of bone metabolism in children with Crohn disease? J Pediatr 148:461-466

78. Sylvester FA, Leopold S, Lincoln M, Hyams JS, Griffiths AM, Lerer T (2009) A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. Clin Gastroenterol Hepatol 7:452-455

79. Sylvester FA, Wyzga N, Hyams JS, Davis PM, Lerer T, Vance K, Hawker G, Griffiths AM (2007) Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. Inflamm Bowel Dis 13:42-50

80. Sylvester FA, Wyzga N, Hyams JS, Gronowicz GA (2002) Effect of Crohn's disease on bone metabolism in vitro: a role for interleukin-6. J Bone Miner Res 17:695-702

81. Szulc P, Seeman E, Delmas PD (2000) Biochemical measurements of bone turnover in children and adolescents. Osteoporos Int 11:281-294

82. Taes Y, Lapauw B, Griet V, De Bacquer D, Goemaere S, Zmierczak H, Kaufman JM (2010) Prevalent fractures are related to cortical bone geometry in young healthy men at age of peak bone mass. J Bone Miner Res 25:1433-1440

83. Terpstra AM, Kalkwarf HJ, Shults J, Zemel BS, Wetzsteon RJ, Foster BJ, Strife CF, Foerster DL, Leonard MB (2012) Bone density and cortical structure after pediatric renal transplantation. J Am Soc Nephrol 23:715-726

84. Thayu M, Leonard MB, Hyams JS, Crandall WV, Kugathasan S, Otley AR, Olson A, Johanns J, Marano CW, Heuschkel RB, Veereman-Wauters G, Griffiths AM, Baldassano RN, Reach Study G (2008) Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. Clin Gastroenterol Hepatol 6:1378-1384

85. Thearle M, Horlick M, Bilezikian JP, Levy J, Gertner JM, Levine LS, Harbison M, Berdon W, Oberfield SE (2000) Osteoporosis: an unusual presentation of childhood Crohn's disease. J Clin Endocrinol Metab 85:2122-2126

86. Thomas AG, Taylor F, Miller V (1993) Dietary intake and nutritional treatment in childhood Crohn's disease. J Pediatr Gastroenterol Nutr 17:75-81

87. Tsampalieros A, Gupta P, Denburg MR, Shults J, Zemel BS, Mostoufi-Moab S, Wetzsteon RJ, Herskovitz RM, Whitehead KM, Leonard MB (2013) Glucocorticoid effects on changes in bone mineral density and cortical structure in childhood nephrotic syndrome. J Bone Miner Res 28:480-488

88. Tsampalieros A, Lam CK, Spencer JC, Thayu M, Shults J, Zemel BS, Herskovitz RM, Baldassano RN, Leonard MB (2013) Long Term Inflammation and Glucocorticoid Therapy Impair Skeletal Modeling during Growth in Childhood Crohn Disease. J Clin Endocrinol Metab

89. Tuchman S, Thayu M, Shults J, Zemel BS, Burnham JM, Leonard MB (2008) Interpretation of biomarkers of bone metabolism in children: impact of growth velocity and body size in healthy children and chronic disease. J Pediatr 153:484-490

90. Uno JK, Kolek OI, Hines ER, Xu H, Timmermann BN, Kiela PR, Ghishan FK (2006) The role of tumor necrosis factor alpha in down-regulation of osteoblast Phex gene expression in experimental murine colitis. Gastroenterology 131:497-509

91. van Coeverden SC, Netelenbos JC, de Ridder CM, Roos JC, Popp-Snijders C, Delemarre-van de Waal HA (2002) Bone metabolism markers and bone mass in healthy pubertal boys and girls. Clin Endocrinol (Oxf) 57:107-116

92. Varghese S, Wyzga N, Griffiths AM, Sylvester FA (2002) Effects of serum from children with newly diagnosed Crohn disease on primary cultures of rat osteoblasts. J Pediatr Gastroenterol Nutr 35:641-648

93. Vazquez MA, Lopez E, Montoya MJ, Giner M, Perez-Temprano R, Perez-Cano R (2012) Vertebral fractures in patients with inflammatory bowel disease compared with a healthy population: a prospective case-control study. BMC gastroenterology 12:47

94. Viswanathan A, Sylvester FA (2008) Chronic pediatric inflammatory diseases: effects on bone. Rev Endocr Metab Disord 9:107-122

95. Walther F, Fusch C, Radke M, Beckert S, Findeisen A (2006) Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. J Pediatr Gastroenterol Nutr 43:42-51

96. Ward LM, Rauch F, Matzinger MA, Benchimol EI, Boland M, Mack DR (2010) Iliac bone histomorphometry in children with newly diagnosed inflammatory bowel disease. Osteoporos Int 21:331-337

97. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC (1998) Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest 102:274-282

98. Werkstetter KJ, Ullrich J, Schatz SB, Prell C, Koletzko B, Koletzko S (2012) Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. J Crohns Colitis 6:665-673

99. Whitten KE, Leach ST, Bohane TD, Woodhead HJ, Day AS (2010) Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. J Gastroenterol 45:399-405

100. Wong SC, Khanna S, Rashid R, Ahmed SF (2008) Auditing bone densitometry and fractures in children with chronic disease. Arch Dis Child 93:705-707

101. Wong SC, Smyth A, McNeill E, Galloway PJ, Hassan K, McGrogan P, Ahmed SF (2010) The growth hormone insulin-like growth factor 1 axis in children and adolescents with inflammatory bowel disease and growth retardation. Clin Endocrinol (Oxf) 73:220-228

102. Yang LS, Alex G, Catto-Smith AG (2012) The use of biologic agents in pediatric inflammatory bowel disease. Current opinion in pediatrics 24:609-614

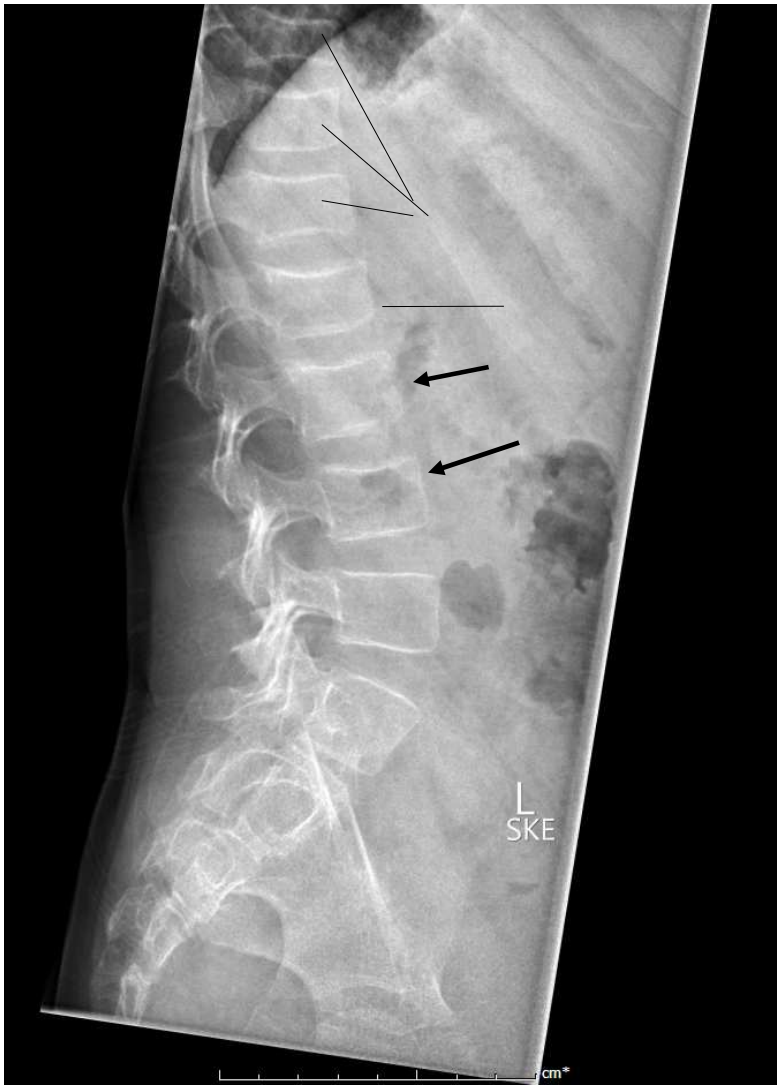

Figure 1: Lateral spine x rays at presentation demonstrating extensive vertebral collapse

Thoraco-lumbar spine x-ray : Fracture L1,2,3, 4, T10, 11,12

Patient	Age	Gender	Diagnosis	Duration disease	Steroid treatment	Duration of steroids	Other medication and nutritional support	Height	Puberty	Vertebral fractures	Bone mineral density	References
1	7yrs	F	UC	1.1 yrs	Methylprednisolone 2 mg/kg/day Total of 3 previous 2 months course of treatment	6 months	Azathioprine, sulphasalazine	ND	B1	Multiple lumbar	LS -3.5 SD (unadjusted)	Lucarelli et al [52]
2	7 yrs	F	CD	0.3 yts	Methylprednisolone for 8 days, Prednisolone for 23 days; total 2.5 mg/kg/day Prednisolone equivalent	31 days	-	+0.9 SD	B1	T10-L4	LS -4.0 SD (height adjusted)	Current case
3	10.6 yrs	F	CD	1.7 yrs	Prednisolone 0.42 mg/kg/day	ND	Mesalazine, 6- mercaptupurine, TPN	-0.1 SD	B1	T5-T7, T9, L1-L2	LS -2.3 SD (unadjusted)	Semeao et al [73]
4	11 yrs	F	CD	0.08 yrs	Prednisolone 2 mg/kg	28 days	Mesalazine, azathioprine	ND	ND	ND	-3.0 SD (no detail of site and if adjusted for size)	Ferreira et al [15]
5	13 yrs	F	CD	1.0 yrs	Prednisolone 1.2 mg/kg/day	ND	Metronidazole, 6- mercaptopurine, mesalazine	-3.3 SD	B1	T8-T9, L1, L5	LS -4.3 SD (unadjusted)	Semeao et al [73]
6	14.5 yrs	F	CD	5.0 yrs	Prednisolone 0.5 mg/kg/day	ND	Mesalazine, 6- mercaptopurine, cyclosporine	-3.7 SD	B3	T9, T11-T12, L1-L5	LS -5.1 (unadjusted)	Semeao et al [73]
7	14.6 yrs	F	CD	0.4 yrs	Prednisolone 0,96 mg/kg/day	ND	Metronidazole, mesalazine, 6-mercaptopurine	+0.2 SD	B4	T10-T12	LS -3.4 SD (unadjusted)	Semeao et al [73]
8	16.8 yrs	F	CD	4.6 yrs	Prednisolone 0.6 mg/kg/day	ND	Metronidazole, mesalazine, 6-mercaptopurine, cyclosporine	-2.4 SD	B5	T7, T11- T12, L1	LS -3.5 SD (unadjusted)	Semeao et al [73]
9	12 yrs	M	CD	At diagnosis	Nil	Nil	Nil	-2.8 SD	Prepubertal	T8-T11, L1- L5	LS -5.2 SD (adjusted for bone area, height, weight, puberty)	Thearle et al [85]
10	16 yrs	M	CD	0.3 yrs	Prednisolone 2mg/kg initially; 0.5 mg/kg alternate day at diagnosis of VF	3 months	Nil	-4.7 SD	G1, 4 ml testes (Early puberty)	T12, L1, L2	LS -4.8 SD (adjusted for bone age)	Cowan et al [17]

Summary of published cases of paediatric vertebral fractures in inflammatory bowel disease

UC: ulcerative colitis, CD: crohn's disease, ND: no details, LS: lumbar spine, SD: standard deviation, VF: vertebral fracture, B: breast stage, G: genitalia stage