Pathological fractures in paediatric patients with inflammatory bowel disease

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1 **Abstract**

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

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

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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.

1 SECTION ONE: LITERATURE REVIEW

2 1. Patho-physiology of skeletal morbidity in IBD

3 Abnormal bone mass, bone geometry, bone metabolism and mineralisation in
 4 children and adolescents with IBD occur as a consequence of numerous factors. These
 5 include direct impact of the disease process mediated by pro-inflammatory cytokines,
 6 prolonged use of high dose glucocorticoid (GC), reduction of lean mass, poor nutrition,
 7 calcium, vitamin D deficiency, poor growth and delayed puberty associated with a state of
 8 relative hormone insufficiency (sex steroid) and resistance (growth hormone and insulin like
 9 growth factor 1) [11; 76; 94; 101]. Clearly all those factors are interlinked, although it is
 10 apparent that the inflammatory process mediated by pro-inflammatory cytokines is the central
 11 modulating factor. Pathological fractures in paediatric patients with IBD prior to GC exposure
 12 [85] or in those treated with minimal amount of GC [29] point to the crucial role of
 13 inflammation itself on bone health [80; 92; 96].

14 There are two important potential clinical consequences of poor bone health in
 15 children and adolescents with chronic inflammation. Firstly, poor bone health could lead to
 16 increased childhood fracture risk. However, fracture prevalence studies in these paediatric
 17 patients are still scarce. It is possible that there may not be an increased risk of long bone
 18 fractures but emerging evidence suggests an increased risk of VF which may be subclinical
 19 [44; 47]. To date, there are nine other published reports of symptomatic VF in children with
 20 IBD [17; 29; 52; 73; 85]. The clinical characteristics of these nine patients and a new patient
 21 included in this review are summarised in Table 1.

22 Secondly, chronic inflammation during the growing years impairs bone accrual,
 23 leading to reduction in peak bone mass by the end of adolescence and therefore significantly
 24 increased fracture risk in later life. During puberty approximately 40-50% of total bone mass
 25 is accrued, contributing to peak bone mass functioning as a “bone bank” for life [51]. Cortical
 26 thickness increases, along with increased trabecular mineralization, under the influence of sex
 27 hormone [71]. Given that paediatric IBD most frequently presents during late childhood or
 28 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 -0.1 SD) [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 -0.77 SD) [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 children and 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]. TNF α affects differentiation and function of osteoblasts and promotes osteoclast differentiation [1; 32; 46] whilst both TNF α and IL6 promote osteoclast activity[49; 75]. Chronic inflammation in paediatric IBD may also increase renal phosphate excretion and inhibit renal 25-hydroxyvitamin D3 1 α 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 11 β hydroxysteroid dehydrogenase type 1 (11 β HSD1) which converts inactive GC (cortisone and prednisone) to their active counterparts (cortisol and prednisolone). 11 β HSD1 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 TNF α 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 adolescent 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

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

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

11 ***(d) The role of vitamin D deficiency***

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

25 ***(e) The role of low muscle mass***

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

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

1 **SECTION TWO: INSTRUCTIVE CASE**

2 A 6 year 9 months old pre-pubertal girl presented with a one year history of upper lip
 3 swelling, loose stools and abdominal pain. Height was 126.3 cm (height z score +0.9 SD,
 4 premorbid height z score 3 years previously +2.3 SD), weight 18.5 kg (weight z score -1.3
 5 SD, premorbid weight z score 3 years previously +0.8 SD). Investigations revealed
 6 hypochromic, microcytic anaemia: haemoglobin (Hb) 76 g/L (normal range (NR) 115-155),
 7 MCV 69 fl (77-95), MCH 21.1 pg (25-33) with abnormal iron studies: iron 1 $\mu\text{mol/L}$ (9-30),
 8 transferrin 1.5 g/L (2.1-4.3) and iron binding capacity 37.7 $\mu\text{mol/L}$ (44-80), thrombocytosis
 9 with platelets of 491 $\times 10^9/\text{L}$ (150-400), raised white cell count 21.7 $\times 10^9/\text{L}$ (4.5-13.5) and
 10 hypoalbuminaemia 18 g/L (33-47). Faecal calprotectin was significantly elevated at 545.8
 11 $\mu\text{g/g}$ (19.5-50), highly suggestive of significant intestinal inflammation. Vitamin D was <
 12 22nmol/L (50-160) at diagnosis, which might not be unusual given the history of severe CD
 13 and that the child is of South Asian origin. A stoss dose of 150,000 units of vitamin D was
 14 given orally. Gastroscopy and colonoscopy identified anal fissures, severe rectosigmoid
 15 ulceration, scattered colonic aphthous ulcers and an ileitis. Histopathology showed
 16 granulomatous inflammation with an active gastritis, focal duodenitis, terminal ileal
 17 ulceration and an active chronic colitis consistent with Crohn's disease. Unfortunately during
 18 the diagnostic procedure, a rectosigmoid perforation occurred. Laparoscopy, peritoneal
 19 washout and repair of perforation were immediately performed, together with a
 20 defunctioning ileostomy.

21 Her clinical course was complicated by problems of fluid balance, nutrition, pain
 22 control and sepsis, with an inpatient stay for a total of 3 months. She was initially treated with
 23 total parenteral nutrition and subsequently maintained on semi elemental feeds with Nutrin
 24 Extra (Nutricia N Ryde, NSW). GC treatment was given for a total of 31 days- initially with
 25 methylprednisolone intravenously for a total of 8 days (25 mg twice daily for 5 days and 25
 26 mg daily for 3 days) and subsequently a weaning course of oral prednisolone for a total of 23
 27 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 x10⁹/L (150-400), WCC 11.4 x10⁹/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.

1 **SECTION THREE: CLINICAL MONITORING AND MANAGEMENT**

2 **Bone health monitoring in paediatric IBD**

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

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

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

23

24 **Management of abnormal skeletal health and fracture in paediatric IBD**

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

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

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

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

24 There maybe a place to consider the use of bisphosphonates in the absence of
25 symptomatic pathological fractures in paediatric IBD with evidence of low bone mass, but
26 they should ideally only be considered in the context of well designed therapeutic clinical
27 trials. These situations include the detection of asymptomatic VF or “low” BMD (eg size
28 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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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- mercaptopurine, 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

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Pathological fractures in paediatric patients with inflammatory bowel disease

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