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ORIGINAL PAPER

Impaired Bone Health in Inflammatory Bowel Disease: A Case–Control Study in 80 Pediatric Patients

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Abstract Previous studies have indicated that children with inflammatory bowel disease (IBD) may not achieve optimal bone mass. We evaluated the skeletal characteristics in children and adolescents with IBD. This cross-sectional cohort study comprised 80 IBD patients (median age 14.9 years, range 5–20) with a median disease duration of 3.4 years; 51 had ulcerative colitis, 26 Crohn disease, and 3 unspecified colitis. Eighty age- and gender-matched healthy subjects served as controls. Areal bone mineral density (aBMD), body composition, and vertebral fractures (VFs) were assessed by DXA. Bone age (BA) was determined for IBD patients. Findings were correlated with disease- and treatment-related parameters and biochemistry. IBD patients had lower BA-adjusted lumbar spine and whole-body aBMD ($p < 0.001$ for both) and whole-body BMC adjusted for height ($p = 0.02$) than controls. Lean mass and fat mass *Z* scores did not differ between the groups, but IBD patients had lower whole-body BMC relative to muscle mass ($p = 0.006$). Despite vitamin D supplementation in 48 %, vitamin D deficiency was common. In IBD cumulative weight-adjusted prednisolone dose >150 mg/kg for the preceding 3 years increased the risk for low whole-body aBMD (OR = 5.5, 95 % CI 1.3–23.3, $p = 0.02$). VFs were found in 11 % of patients and in 3 % of controls ($p = 0.02$). IBD in childhood was associated with low aBMD and reduced bone mass accrual relative to muscle mass; the risk for subclinical VFs may be increased. These observations warrant careful follow-up and active preventive measures.

Keywords Children · Adolescents · Ulcerative colitis · Crohn disease · Bone density · Fracture · Vitamin D deficiency

Current evidence of impaired bone health in children and adolescents with inflammatory bowel disease (IBD) encourages clinicians to screen and monitor bone health in pediatric IBD patients [1]. Inflammation with increased production of cytokines, growth failure, delayed puberty, malabsorption, decreased physical activity, and the use of glucocorticoids (GCs) are risk factors for suboptimal bone health in pediatric patients with Crohn disease (CD) or ulcerative colitis (UC).

Previous studies have shown that children with IBD may not achieve their optimal peak bone mass. Low bone mineral density (BMD) is increasingly reported in children with CD and UC [2, 3]. Studies on children with IBD at the time of diagnosis have demonstrated altered bone metabolism and geometry attributable to the underlying inflammatory, nutritional, and hormonal factors. Children with CD have decreased trabecular volumetric BMD, decreased cortical bone strength, and substantial muscle deficits at diagnosis [4]. Transilial bone biopsies in newly diagnosed IBD children have shown a mild cortical bone deficit and low turnover of trabecular bone [5]. Despite improvements in trabecular volumetric BMD and muscle mass, substantial musculoskeletal deficits persist after the onset of

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IBD treatment [4, 6]. A study on biomarkers of bone metabolism has associated CD with suppressed bone formation and increased bone resorption [7]. However, the clinical consequences and long-term outcome of suboptimal bone health remain largely unknown.

Limited data are available on the fracture risk in pediatric IBD patients with decreased bone mass [8]. An epidemiological study on 1,242 children with CD or UC and 3,287 healthy age- and gender-matched controls revealed no increase in fracture risk. However, a subanalysis in children younger than 12 years demonstrated a significant positive association between IBD and fractures. Importantly, the study showed a trend toward increased prevalence of vertebral fractures (VFs), a significant indicator of osteoporosis-related bone fragility in the pediatric age group [9]. VFs have been reported in children with CD [10], and they are not uncommon in young adults with CD [11]. However, only few studies on children with IBD have searched for subclinical VFs [5, 12].

In addition to impaired bone mass accrual, children with IBD are at risk for growth failure and delayed pubertal maturation. At diagnosis, CD is associated with lower height and body mass index (BMI) for age [13, 14]. Follow-up studies have found no catch-up in height [6, 14, 15]. Low BMD may reflect retarded skeletal development due to growth failure and delayed maturation. Previous reports have demonstrated improved BMD *Z* scores when values are adjusted for bone age (BA) instead of chronological age (CA) [16, 17].

The aim of our study was to evaluate the prevalence of impaired bone health and fractures in children and adolescents with IBD in comparison to healthy peers and to identify clinical and treatment-related determinants of compromised bone health. We analyzed anthropometric data, BMD, and body composition in relation to both CA and BA.

Materials and Methods

Patients and Controls

This cross-sectional cohort study involved 80 (43 girls) children and adolescents with IBD, diagnosed according to the Lennard-Jones criteria [18]. All patients were treated and enrolled into this study at the Outpatient Clinic for Pediatric Gastroenterology at the Children's Hospital, Helsinki University Central Hospital. This hospital is a tertiary center for pediatric gastroenterology patients, with ~150 patients with IBD at the time of the study between June 2004 and December 2005. Inclusion criteria were age between 4 and 20 years at the time of study enrollment and IBD diagnosed at least 3 months prior to the date of enrollment. In order to avoid any selection bias, consecutive patients visiting the outpatient clinic were recruited for the study. Subjects were ineligible if they had other medical conditions unrelated to IBD that could potentially affect growth or bone mineral accrual. The study protocol was approved by the Ethics Committee, Children's Hospital, Helsinki University Central Hospital, and University of Helsinki. Written informed consent was obtained from all participants and/or their guardians.

Altogether 80 age- and gender-matched control subjects were selected from a cohort of 186 healthy preliminary and secondary school students in Helsinki. The characteristics of the cohort have been previously published [19].

Patients and controls were assessed similarly: anthropometry, BMD, and body composition measurements with dual-energy X-ray absorptiometry (DXA) and a fasting blood sample and urine sample were obtained from all subjects.

Clinical Data Collection

Medical records of the patients were reviewed for disease and treatment characteristics. Disease duration was calculated from the date of the first diagnostic gastroenterological endoscopy. For each patient, weight-adjusted (dose per body weight) cumulative doses of orally administered prednisolone equivalents were calculated for 3 years preceding the study. Also, other drugs used either for treatment prior to the study protocol or at the time of the study were carefully registered. The patients and controls and/or their parents filled out questionnaires on the study subject's fracture history; fracture localization and mechanism of injury were recorded. Fractures were classified as low- or high-energy traumas; fractures resulting from falls from standing height or less were regarded as low-energy fractures. Dietary intakes of Ca were obtained from a 3-day dietary recall for 49 (61 %) IBD patients and using a food-frequency questionnaire for 60 (75 %) controls. The average daily intake of Ca was calculated using the Finnish National Food Composition Database (Fineli®, version 2001), which is maintained by the Nutrition Unit, National Institute of Health and Welfare (Helsinki, Finland). The calculated total intake of Ca included intake from supplements.

All patients were clinically assessed by a pediatric gastroenterologist. Disease activity was scored using the pediatric Crohn's disease activity index (PCDAI) for children with CD [20] and the pediatric ulcerative colitis activity index (PUCAI) for children with UC [21]. A patient was classified as having (1) "moderate–severe disease" at examination if PCDAI was $\geq$30 or PUCAI was $\geq$35; (2) "mild disease" if PCDAI was $\geq$10 and $<$30 or PUCAI was $\geq$10 and $<$35; and (3) "inactive disease" if PCDAI was $<$10 or PUCAI was $<$10 [20, 21]. Pubertal status was determined clinically according to Tanner [22]

in IBD patients. For healthy controls, pubertal stage was determined as either pre-, mid-, or postpubertal based on gonadotropin and sex steroid concentrations by a pediatric endocrinologist (O. M.).

Growth Assessment

Height was measured with a Harpenden stadiometer (Holtain, Crosswell, Crymych, UK) and weight in thin underwear by an electric scale. Height SD score (height *Z* score) was defined as a deviation of height, in SD units, from the mean height for age and sex; weight was expressed as a height-adjusted value, as a percentage of the mean ratio in a normal population of the same gender and height, according to the Finnish standards [23, 24]. BMI was calculated as weight in kilograms divided by square of height in meters, and BMI *Z* scores were determined by British reference values [25].

Imaging Studies

BA was determined for patients from a plain radiograph of the left hand according to Greulich and Pyle [26] by a pediatric endocrinologist (O. M.), and it was considered delayed or advanced when BA differed from the patient's CA by more than 1 year; the BA-adjusted BMD values were used in these cases. BA films were not available for controls.

Bone mineral content (BMC, g) and areal BMD (aBMD, g/cm^2) of the lumbar spine (L1–L4), total hip, and whole body were measured with DXA (Hologic Discovery A, pediatric software, version 12.4; Hologic, Waltham, MA). aBMD values were transformed into *Z* scores and compared with age- and gender-adjusted reference data for U.S. Caucasian children. We calculated *Z* scores for BMC using the least mean square algorithm with age- and gender-adjusted reference data for nonblack children aged 7–17 years [27] and BMC *Z* scores for height *Z* score according to both CA and BA [28]. The same DXA device was used to assess body composition; both lean mass (LM) and fat mass (FM) were registered. We calculated *Z* scores for LM for height and percent FM for age using the least mean square algorithm [29].

To detect VFs of the thoracic and lumbar spine, vertebral fracture assessment (VFA) images were obtained with the same DXA equipment from all patients and controls. Compression fractures were graded using a pediatric method in which abnormal changes were classified as mild (grade 2a, 20–49 % anterior height reduction) or severe (grade 2b, ≥50 % anterior height reduction) wedge deformities or mild (grade 3a, vertebral middle and/or posterior height reduction 20–29 %) or severe (grade 3b, vertebral middle and/or posterior height reduction ≥30 %) compression deformities [30]. VFA images were assessed independently by a pediatric radiologist (S. T.-S.) and a pediatric endocrinologist (O. M.); discrepancies between the readers were resolved by consensus.

Biochemistry

Blood hemoglobin, hematocrit, and erythrocyte sedimentation rate were measured from IBD patients and plasma Ca, phosphate, alkaline phosphatase, and albumin from both patients and controls by standard methods. Serum 25-hydroxyvitamin D (S-25[OH]D) was assessed by high-performance liquid chromatography (HPLC), and plasma fasting parathyroid hormone was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE 2000, DPD; Diagnostic Products, Los Angeles, CA); the reference range was 8–73 ng/L. Urine was analyzed for Ca/creatine ratio (U-Ca/U-Crea).

Statistical Analyses

The *t* test was used when comparing clinical and biochemical characteristics between the IBD and control groups and between the CD and UC groups. For nonnormally distributed parameters the Mann-Whitney nonparametric *U* test was used. Differences in categorical variables were tested using Pearson's χ^2 test. Differences between CA-adjusted and BA-adjusted parameters were tested with a paired samples *t* test. The strength of the relationship between lumbar spine aBMD *Z* score and the clinical measurements was estimated by Kendall's rank correlation in the IBD and control groups. The relationship between low aBMD *Z* score and cumulative weight-adjusted prednisolone dose of >150 mg/kg as well as possible factors associated with VFs in patients together were estimated using logistic regression. $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 17.0 statistical package for Mac (SPSS, Inc., Chicago, IL).

Results

Study Cohort

The study cohort included 80 IBD patients (43 girls) who were between 5 and 20 years of age. Characteristics of the patients are shown in Table 1. UC had been diagnosed in 49 (61 %), CD in 28 (35 %), and unspecified colitis in three subjects at a median age of 10.4 years. At the time of study assessment, the median age of the subjects was 14.9 years. BA was delayed in 27 (34 %) and advanced in 12 (15 %) subjects. Altogether 65 (81 %) patients had been

Table 1 Characteristics of the 80 patients with inflammatory bowel disease

Characteristic	*n* (%) or median (range)
Gender (boy/girl)	37 (46 %)/43 (54 %)
Diagnosis (ulcerative colitis/Crohn disease/unspecified colitis)	49 (61 %)/28 (35 %)/3 (4 %)
Age at diagnosis (years)	10.4 (2.1–15.4)
Duration of disease (years)	3.4 (0.3–14.5)
Age at examination (years)	14.9 (5.1–20.1)
BA (years)	13.9 (3.3–19.0)
Delayed BA	27 (34 %)
Advanced BA	12 (15%)
Lifetime surgery (IBD-related)	8 (10 %)
Disease activity at study visit (inactive/mild/moderate–severe)	52 (65 %)/22 (27 %)/6 (8 %)
Medication	
5-ASA (lifetime/current)	80 (100 %)/58 (73 %)
Sulfasalazine (lifetime/current)	9 (11 %)/3 (4 %)
Azathioprine (lifetime/current)	18 (23 %)/14 (18 %)
Infliximab (lifetime/current)	9 (11 %)/4 (5 %)
Oral glucocorticoids (lifetime/current)	65 (81 %)/24 (30 %)
Cumulative weight-adjusted prednisolone dose during preceding 3 years (mg/kg)	94 (13–393)
Duration of glucocorticoid treatment during the preceding 3 years (days)	295 (24–912)
Biochemistry	
ESR (mm/h)	11 (3–53)
Plasma albumin (g/L)	41 (30–50)
Hemoglobin (g/L)	131 (103–162)
HCT (%)	39 (32–48)

BA bone age, *IBD* inflammatory bowel disease, *5-ASA* 5-aminosalicylic acid, *ESR* erythrocyte sedimentation rate, *HCT* hematocrit

on systemic GC treatment, and the cumulative weight-adjusted prednisolone dose during the preceding 3 years ranged from 13 to 393 mg/kg. At the time of the study, most of the patients (65 %) had inactive disease and 10 (12.5 %) were not on any medication.

Bone Health in IBD Patients Compared to Healthy Controls

Anthropometric data, bone health, and biochemical parameters of IBD patients and healthy controls are shown in Table 2. Pubertal development was appropriate for CA in all control subjects. Half of the age- and gender-matched control subjects were postpubertal, while only 24 % of patients had ended their pubertal development ($p < 0.001$, Table 2). At the time of study assessment, no difference in height *Z* scores, weight-for-height percentages, or BMI *Z* scores was observed between the groups when the values of patients were corrected for BA. Based on *Z* scores relative to CA, IBD patients had lower height *Z* scores than controls (Table 2).

aBMD *Z* scores adjusted for both CA and BA in IBD patients are shown in comparison to healthy peers in Fig. 1. BA-adjusted aBMD *Z* scores of lumbar spine, whole body, and total hip were all significantly higher than CA-adjusted scores. However, even the BA-adjusted lumbar spine (IBD vs. control, median [range] –0.6 [–3.4 to +1.9] vs. +0.1 [–1.5 to +2.6], $p < 0.001$) and whole-body aBMD (–0.3 [–3.0 to +2.3] vs. +0.1 [–1.0 to +2.4], $p < 0.001$) *Z* scores were significantly lower in the patients, whereas BA-adjusted total-hip aBMD *Z* scores did not differ between the patients and controls (–0.1 [–2.8 to +2.4] vs. 0.0 [–1.9 to +2.4], $p = 0.06$) (Fig. 1). Low BA-adjusted lumbar spine aBMD (< –1.0 *Z* score) was detected in 29 (36 %) and low whole-body BMD in 18 (23 %) patients, whereas low whole-body aBMD was observed in zero and low lumbar spine aBMD in three (4 %) control subjects ($p < 0.001$ for both). Whole-body BMC *Z* scores adjusted for both CA and BA are shown in Table 3. IBD patients had significantly lower whole-body BMC *Z* scores than control children even if the *Z* scores were adjusted for height *Z* scores (Table 3). LM and FM *Z* scores did not differ between the groups (Fig. 1). However, whole-body BMC in relation to total LM was significantly lower in IBD patients (IBD vs. control, 0.050 [0.039–0.068] vs. 0.051 [0.041–0.071] g/g, $p = 0.006$) indicating lower bone mineral accrual in relation to muscle mass.

Table 2 Anthropometry, biochemical parameters, and vitamin D status in 80 patients with IBD and 80 healthy controls

Median (range) or *n* (%)	IBD patients ($n = 80$)	Controls ($n = 80$)	*p*
Age (years)*	14.9 (5.1–20.1)	14.4 (7.4–18.8)	0.5
Pubertal status (prepubertal/pubertal/postpubertal)	23 (29 %)/38 (47 %)/19 (24 %)	25 (31 %)/15 (19 %)/40 (50 %)	<0.001
Height CA *Z* score	–0.1 (–3.0 to 2.5)	0.5 (–2.3 to 3.2)	0.009
Height BA *Z* score	0.3 (–2.7 to 4.2)		0.2
Weight-for-height (%)	105 (87–156)	105 (84–192)	0.9
BMI CA *Z* score	0.1 (–1.9 to 2.5)	0.1 (–1.8 to 3.4)	0.1
BMI BA *Z* score	0.0 (–1.7 to 2.7)		0.4
P-Ca (mM)	2.35 (2.07–2.58)	2.33 (2.12–2.48)	0.05
P-Pi (mM)	1.32 (0.91–1.77)	1.37 (0.83–1.69)	0.2
P-ALP (U/L)*	165 (46–381)	202 (39–438)	0.3
P-PTH (ng/L)	40 (14–112)	38 (3–136)	0.4
U-Ca/U-Crea (mM/mM)*	0.22 (0.01–1.1)	0.15 (0.02–0.68)	0.002
S-25(OH)D (nM)	49 (16–102)	43 (17–82)	0.02
Vitamin D supplementation in use	38 (48)	17 (21)	<0.001
S-25(OH)D < 37.5 nM	24 (30)	28 (37)	0.4

The *p* values were taken from the independent samples *t* test or Pearson's χ^2 test, except for variables marked with an asterisk, which were analyzed with the Mann–Whitney *U* test

IBD inflammatory bowel disease, *CA* chronological age, *BA* bone age, *P* plasma, *Ca* calcium, *Pi* phosphate, *ALP* alkaline phosphatase, *PTH* parathyroid hormone, *Crea* creatine, *S-25(OH)D* serum 25-hydroxyvitamin D

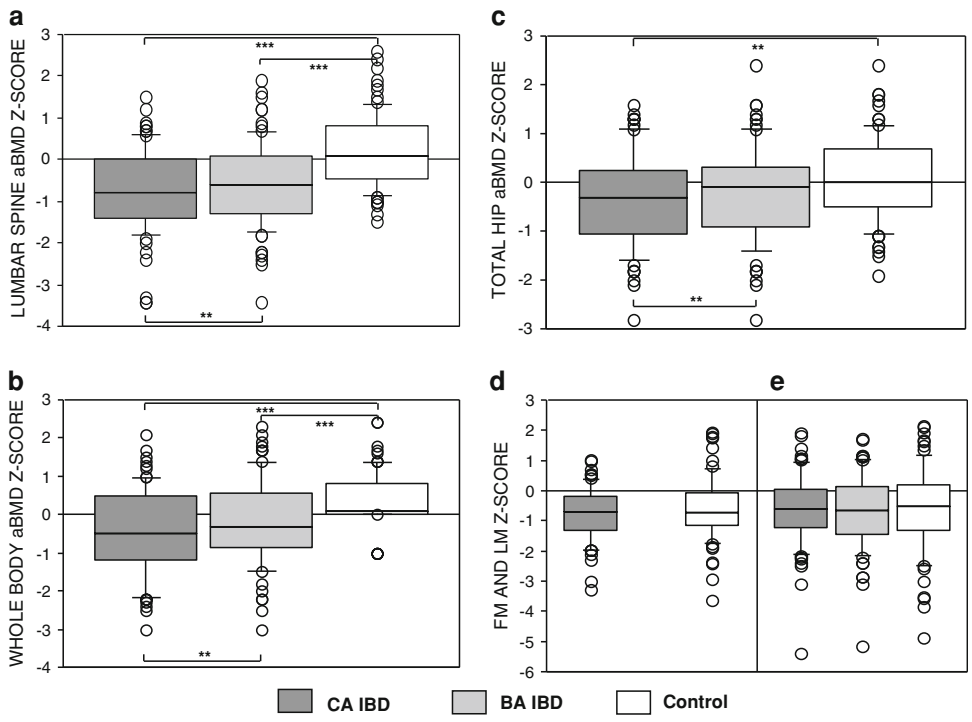

Fig. 1 Lumbar spine (**a**), whole-body (**b**), and total-hip (**c**) aBMD *Z* scores and total fat mass (**e**) *Z* scores adjusted for calendar age (*CA*, *dark gray bars*) and bone age (*BA*, *light gray bars*) in the 80 pediatric patients with IBD and in their age- and gender-matched control subjects (*white bars*). Total lean mass for height *Z* scores (**d**) in the IBD patients (*dark gray bars*) and in control subjects (*white bars*). The bottom of each *box* indicates the first, the *cross line* the second (median), and the top the third quartile of the variables. Whiskers extend to the 5th and 95th percentiles. Outliers are shown as *open circles*. $^{**}p < 0.01$, $^{***}p < 0.001$

In healthy control subjects, the lumbar spine aBMD *Z* score correlated with the LM *Z* score ($\tau = 0.29$, $p < 0.001$), whereas no correlation with FM *Z* score or S-25(OH)D level ($p = 0.2$ and $p = 0.9$, respectively) was observed. In IBD patients, the BA-adjusted lumbar spine aBMD *Z* score did not correlate with the LM *Z* score, the FM *Z* score, S-25(OH)D level, or cumulative weight-adjusted prednisolone dose in the preceding 3 years (Kendall's τ, $p = 0.4$, $p = 0.4$, $p = 0.8$, $p = 0.05$). Cumulative weight-adjusted prednisolone dose had a positive correlation with FM *Z* score ($\tau = 0.20$, $p = 0.04$) and U-Ca/U-Crea ratio ($\tau = 0.23$, $p = 0.02$). A cumulative weight-adjusted

Table 3 Parameters of bone mineral content in 80 patients with IBD and 80 healthy controls

Median (range)	IBD patients	Controls	*p*
Whole-body BMC (g)	1,832 (670–2,925)	1,943 (798–3,103)	0.07
Subtotal BMC (g)	1,462 (456–2,425)	1,585 (537–2,606)	0.1
Whole-body BMC CA *Z* score	–0.16 (–3.41 to 2.17)	0.96 (–1.13 to 3.94)	<0.001
Whole-body BMC BA *Z* score	0.38 (–2.64 to 2.70)		0.002[a]
Whole-body BMC CA Ht-*Z* score[b]	0.32 (–1.50 to 2.17)	0.55 (–0.93 to 3.02)	0.03
Whole-body BMC BA Ht-*Z* score[c]	0.38 (–1.50 to 2.17)		0.02[a]

The *p* values were taken from the independent samples *t* test

IBD inflammatory bowel disease, *BMC* bone mineral content, *CA* calendar age, *BA* bone age, *HtZ* height *Z* score

[a] BA *Z* score in patients in comparison to CA *Z* score in controls

[b] *n* IBD patients vs. controls, 50 versus 66

[c] *n* IBD patients vs. controls, 58 versus 66

prednisolone dose >150 mg/kg during the preceding 3 years increased the risk of low BA-adjusted aBMD in both the lumbar spine (< –1.0 *Z* score, odds ratio [OR] = 5.1, 95 % confidence interval [CI] 1.2–21.6, $p = 0.03$) and the whole body (OR = 5.5, 95 % CI 1.3–23.3, $p = 0.02$).

Although IBD patients received more often daily vitamin D supplementation and their S-25(OH)D levels were higher than in controls, 30 % of them were vitamin D–deficient (S-25[OH]D <37.5 nM) (Table 2). All control subjects were studied in the winter (October–March), whereas 39 (49 %) of IBD subjects were assessed in the summer. When we restricted the analysis to subjects examined in the winter, the statistically significant difference between IBD subjects and controls disappeared (IBD, $n = 41$ vs. control, $n = 76$; S-25[OH]D 43 [17–97] vs. 42.5 [17–82] nM, $p = 0.2$) and the prevalence of vitamin D deficiency (37 %) was equal in both groups. Dietary intake of Ca was lower in IBD patients (IBD, $n = 49$ vs. control, $n = 60$; 1,010 [256–2,820] vs. 1,490 [573–2,940] mg/day, $p < 0.001$), whereas total intake of Ca did not differ between the groups (1,400 [577–2,820] vs. 1,500 [573–2,940], $p = 0.1$) and met the dietary recommendation in most of the subjects.

Differences Between UC and CD Patients

Disease history, anthropometric data, aBMD, and body composition parameters of UC ($n = 49$) and CD ($n = 28$) patients separately are shown in Table 4. Gender distribution, age at diagnosis, duration of the disease, and disease activity at study assessment did not differ significantly between these groups. Although the median cumulative weight-adjusted prednisolone dose and duration of GC treatment for the preceding 3 years were higher in UC patients, the differences were not statistically significant. There was a trend for higher prevalence of delayed BA in CD patients. Height *Z* score, BMI *Z* score, and lumbar spine and total-hip aBMD *Z* scores did not differ between the UC and CD groups irrespective of CA or BA adjustment (Table 4 and data not shown). The whole-body aBMD *Z* score was lower in CD patients only relative to CA (CD vs. UC, –0.8 [–3.0 to +0.9] vs. –0.3 [–2.2 to +1.7], $p = 0.04$) and not to BA (Table 4). However, the FM *Z* score was lower in CD patients regardless of CA or BA adjustment (Table 4 and data not shown). BA-adjusted aBMD *Z* scores were significantly higher than CA-adjusted Z scores both in the UC group (BA vs. CA, median, lumbar spine, –0.6 vs. –0.8, $p = 0.005$; whole-body, –0.2 vs. –0.3, $p = 0.008$) and in the CD group (lumbar spine, –0.4 vs. –1.0, $p = 0.03$; whole-body, –0.4 vs. –0.8, $p = 0.005$).

Fracture History and VFs

No difference between the IBD and control groups was found in the history of peripheral fractures. Altogether 12 peripheral fractures were reported in 9 (11 %) IBD patients and 28 fractures in 16 (20 %) control subjects ($p = 0.2$). One fracture in both the IBD and control groups resulted from a high-energy injury and the other fractures, from a low-energy injury. Four vertebral compression fractures had been diagnosed in one male patient 6 months after the diagnosis of CD at the age of 13 years. VFA images of the spine were available for 79 IBD patients and 79 control subjects. Abnormal vertebral morphology was detected in 11 % ($n = 9$) of IBD patients and 3 % ($n = 2$) of controls ($p = 0.02$). Twenty vertebrae in IBD patients were fractured; 16 (80 %) of them occurred in the thoracic and 4 (20 %) in the lumbar region. Six (30 %) of the fractures were graded as mild anterior wedge deformity (2a) and 14 (70 %) as mild compression deformity (3a). Eight (89 %) IBD patients with VF were boys ($p = 0.03$). Abnormal vertebral morphology was not associated with diagnosis of CD (3 [33 %] patients with VF vs. 24 [34 %] patients with normal

Table 4 Comparisons of 49 pediatric patients with ulcerative colitis to 28 pediatric patients with Crohn disease

Characteristics Median (range) or *n* (%)	Ulcerative colitis ($n = 49$)	Crohn disease ($n = 28$)	*p*
Female gender	26 (53 %)	16 (57 %)	0.7
Age at diagnosis (years)*	10.5 (2.2–15.3)	11.2 (2.1–15.4)	0.6
Duration of disease (years)*	3.4 (0.3–14.5)	3.7 (0.5–14.1)	0.6
Disease activity at study visit (inactive/mild/moderate–severe)	33 (67 %)/13 (27 %)/3 (6 %)	16 (57 %)/9(32 %)/3 (11 %)	0.6
Cumulative weight-adjusted prednisolone dose during the preceding 3 years (mg/kg)*	100 (13–313)	81 (19–393)	0.2
Duration of GC treatment during preceding 3 years (days)*	342 (50–851)	188 (24–912)	0.8
Age at examination (years)*	14.7 (5.1–19.2)	15.3 (8.7–20.1)	0.3
BA (years)	14.0 (3.3–19.0)	14.2 (7.8–19.0)	0.2
Delayed BA/appropriate BA/advanced BA	14 (29 %)/30 (60 %)/5 (19 %)	13 (46 %)/10 (36 %)/5 (18 %)	0.1
Pubertal status (prepubertal/pubertal/postpubertal)	15 (31 %)/24 (49 %)/10 (20 %)	5 (18 %)/14 (50 %)/9 (32 %)	0.2
Height BA *Z* score	0.1 (–2.7 to 4.2)	0.5 (–2.4 to 2.5)	0.9
BMI BA *Z* score	0.1 (–1.6 to 2.0)	–0.1 (–1.7 to 2.7)	0.5
Lumbar spine aBMD BA *Z* score	–0.6 (–2.5 to 1.6)	–0.4 (–3.4 to 1.9)	>0.9
Total-hip aBMD BA *Z* score	–0.1 (–1.8 to 2.4)	–0.5 (–2.8 to 1.3)	0.4
Whole-body aBMD BA *Z* score	–0.2 (–2.2 to 2.3)	–0.4 (–3.0 to 1.8)	0.2
Lean mass *Z* score	–0.8 (–3.3 to 1.0)	–0.7 (–2.3 to 1.0)	0.6
Fat mass BA *Z* score	–0.5 (–2.4 to 1.7)	–0.9 (–5.2 to 1.7)	0.02

The *p* values were taken from the independent samples *t* test or Pearson's χ^2 test, except for variables marked with asterisk, which were analyzed with the Mann–Whitney *U* test

GC glucocorticoid, *BA* bone age, *BMI* body mass index, *aBMD* areal bone mineral density

vertebral morphology, $p > 0.99$), mild to severe state of disease (3 [33 %] vs. 24 [34 %], $p > 0.99$), low lumbar spine aBMD (3 [33 %] vs. 25 [36 %], $p > 0.99$), cumulative weight-adjusted prednisolone dose >150 mg/kg during the preceding 3 years (1 [25 %] vs. 8 [17 %], $p > 0.99$), vitamin D deficiency (3 [33 %] vs. 21 [30 %], $p > 0.99$), or use of infliximab (1 [11 %] vs. 8 [11 %], $p > 0.99$). When these factors were modeled together in a logistic regression model for VF, none of them became significant ($p > 0.8$).

Discussion

Our cross-sectional cohort demonstrated lower lumbar spine and whole-body aBMD *Z* scores in children and adolescents with IBD in comparison to their healthy peers even when pubertal delay was taken into account by BA adjustment. Low BA-adjusted aBMD was observed in 23–36 % of patients, depending on the site of measurement. Although the frequency of previous fractures did not differ between IBD patients and controls, abnormal vertebral morphology was observed more often in children and adolescents with IBD as a potential clinical consequence of impaired bone health.

Although most of the patients had inactive disease, their bone health was still impaired. The results on lower aBMD in pediatric IBD patients are in concordance with previous studies demonstrating persistently impaired BMD after diagnosis of the disease [6, 14, 31, 32]. One-third of the patients had delayed BA, and BA-adjusted aBMD *Z* scores were significantly higher than CA-adjusted values, which emphasizes the importance of correcting the BMD values for delayed pubertal maturation when analyzing DXA results in both CD and UC patients. Most previous studies that have evaluated BA of pediatric IBD patients have reported significant delay of BA, with a mean difference of 0.5–1.2 years to CA [6, 16, 17, 32–34]. Two studies on IBD patients found no difference between BA and CA [3, 5]. Sylvester et al. [31] reported no significant difference between BMD *Z* scores calculated for BA or height age in a cohort of 76 IBD patients; the difference in the mean of CA and BA was 1 year in 58 CD patients. Altogether, only a few studies have corrected BMD *Z* scores of IBD adolescents for delayed BA. Gokhale et al. [16] found that only girls with CD had significantly lower BMD than their healthy sibling controls when BMD *Z* scores were calculated for BA. Hill et al. [17] reported significantly higher whole-body and lumbar spine BA-adjusted aBMD *Z* scores than CA-adjusted scores for 32 CD patients, whereas the CA and BA aBMD *Z* scores were not significantly different for 12 UC patients. In contrast to these studies, our study with more UC patients demonstrated higher BA aBMD *Z* scores in both CD and UC groups in comparison to CA aBMD *Z* scores. However, the BA and height *Z*-score adjustments did not completely normalize the

Z scores, and the IBD patients' BMD and BMC remained significantly lower than those of controls. We did not detect any significant difference in BA-adjusted aBMD *Z* scores between CD and UC patients, whereas some previous studies have suggested that low BMD is more evident in CD patients than UC patients [16, 31]. Our findings thus show impaired bone mass accrual in patients with IBD and confirm that the low BMD values are not solely due to short stature or delayed skeletal maturation.

Peripheral fractures were as frequent in IBD patients as in controls. However, abnormal vertebral morphology was observed more often in IBD patients. In patients, we were able to associate abnormal vertebral morphology only with male gender and not with any disease- or treatment-related parameter. Thoracic VFs were more common than lumbar VFs, as shown in previous studies on chronically ill pediatric patients with increased risk for osteoporosis [35, 36]. Semeao et al. [10] reported on five female pediatric patients (age range 10.6–16.8 years) with CD who had developed VFs (15 thoracic, 7 lumbar). All had markedly decreased BMD. One had VF only 4 months after onset of CD, while in the others the time since diagnosis ranged 1–4 years. The largest epidemiological study on fracture risk of pediatric IBD patients thus far has shown no increased risk of diagnosed fractures but a strong trend toward increased VFs in pediatric IBD patients, particularly those with CD. Kappelman et al. [9] discussed their power (1,242 patients with IBD, 737 CD) not to be adequate to detect a significant association owing to the rarity of VFs. Two studies with small numbers of patients found no subclinical VFs by X-ray images [5, 12]. Although VFA images are not as accurate for detecting VF as X-ray images [37], they offer a practical and safe tool for screening vertebral deformities. Our patients and controls were assessed similarly, and therefore, the difference in VFs is unlikely to be due to methodological issues but rather reflects compromised bone strength in IBD.

Cumulative weight-adjusted prednisolone dose was associated positively with U-Ca/U-Crea ratio, which was higher in IBD patients than in healthy control subjects. This finding is in line with the fact that GCs increase urinary Ca excretion [38]. A cumulative weight-adjusted dose of prednisolone of 150 mg/kg for the preceding 3 years was associated with increased risk for low BA-adjusted aBMD *Z* score for both the lumbar spine and whole body. This shows the deleterious effect of high GC dose on bone health. In previous studies on pediatric IBD patients, cumulative GC dose has been associated with reduced aBMD in one [16], while others have found no association between GC treatment and bone parameters or bone mineral accrual rate [3, 6, 14, 31, 32, 34]. Longitudinal assessment of bone structure in CD patients with peripheral quantitative computed tomography has associated GCs with increases in cortical volumetric BMD [4]. Several studies have demonstrated a negative association between cumulative GC dose and height *Z* score [2, 15, 34, 39]. Greater increases in FM *Z* scores have been associated with cumulative CG exposure [15]. Cumulative weight-adjusted prednisolone dose of the preceding 3 years was associated positively with FM *Z* scores in our IBD patients. CD patients had lower FM *Z* scores than UC patients. Our small cross-sectional cohort of both UC and CD patients did not demonstrate differences in LM *Z* scores in comparison to healthy peers, as opposed to previous reports on body composition in IBD patients [4, 6, 15, 34, 39]. The positive association between LM *Z* score and lumbar spine aBMD *Z* score was found only in our control group and not in the IBD group.

Although nearly half of the IBD patients were on vitamin D supplementation, 30 % of them were vitamin D–deficient. The prevalence of vitamin D deficiency did not differ from that of their healthy peers living in the same district of Helsinki (60°N). Pappa et al. [40, 41] reported a 5.8–34.6 % prevalence of vitamin D deficiency in pediatric IBD patients treated in a tertiary-care center in Boston (42°N). Since IBD subjects are at increased risk of compromised bone health, it is important to ensure adequate vitamin D supplementation, regardless of the season and latitude, to accomplish S-25(OH)D concentrations above 50 nmol/L. The optimal S-25(OH)D may be even greater and the needed vitamin D dose may be significantly higher than presently recommended in most countries; these remain to be determined in future studies.

Our study has limitations that may explain some of our findings. The power of the study was limited to exclude all negative results, and we were not able to test differences in smaller subgroups divided by, e.g., gender or pubertal stage. Furthermore, due to limited data collection, we were not able to estimate the effects of physical activity or dietary factors on bone health. Ideally, we should have included all IBD patients treated at our clinic but had to limit the study to 80 patients. In order to avoid selection bias, we recruited consecutive patients fulfilling the inclusion criteria. It is possible that the limited size of our cohort prevented us from identifying some factors that are relevant to bone health in larger cohorts. Assessment of pubertal maturation differed between patients and controls. However, the BMD comparisons between patients and controls were not based on pubertal staging, and therefore, this limitation is unlikely to have an effect on our findings. The cross-sectional study setting did not offer the possibility to test causalities between impaired bone health and the IBD itself or treatments. Longitudinal studies with sufficient follow-up time beyond adolescence are needed to clarify the risk and significance of reduced peak bone mass in pediatric IBD patients. Screening of subclinical VFs

with X-ray images is needed to estimate the real risk of VFs in pediatric IBD patients [37].

In conclusion, our study shows that children and adolescents with UC or CD have an increased risk for impaired bone health in comparison to their healthy peers. IBD patients had lower lumbar spine and total-body aBMD *Z* scores, even after adjustment of the DXA results for BA. A high weight-adjusted dose of prednisolone was associated with increased risk for low BA-adjusted aBMD. The results of VFA images suggest a higher risk for subclinical VFs in pediatric IBD patients. These observations warrant careful follow-up and emphasize the need for more active preventive measures, including adequate vitamin D supplementation, in children and adolescents with IBD.

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