Young Adult Male Patients With Childhood-onset IBD Have Increased Risks of Compromised Cortical and Trabecular Bone Microstructures

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Background: Young adults with childhood-onset inflammatory bowel disease (IBD) have increased risks of low areal bone mineral density and low skeletal muscle mass. Volumetric BMD (vBMD), bone geometry and microstructures, in addition to possible associations with skeletal muscle index (SMI) and physical exercise have been scarcely studied in this patient group.

Patients and methods: In total, 49 young adult male patients with childhood-onset IBD and 245 age- and height-matched young adult male controls were scanned with high-resolution peripheral quantitative computed tomography. Bone geometry, vBMD, and bone microstructures were calculated as median values and compared between the patients and controls. Multivariable linear regression analyses were performed to determine the independent associations among IBD diagnosis, SMI (kg/m^2), and physical exercise.

Results: The group of young adult patients had, in comparison with the controls, significantly smaller median cortical area (126.1 mm^2 vs 151.1 mm^2, P < .001), lower median total vBMD (296.7 mg/cm^3 vs 336.7 mg/cm^3, P < .001), and lower median cortical vBMD (854.4 mg/cm^3 vs 878.5 mg/cm^3, P < .001). Furthermore, the patients compared with the controls had lower median trabecular volume fraction (16.8% vs 18.2%, P < .001) and thinner median trabeculae (0.084 mm vs 0.089 mm, *P* < .001). The differences between the patients with IBD and controls persisted in multivariable analyses that included adjustments for SMI and physical exercise.

Conclusions: Young adult men with childhood-onset IBD are at increased risk of having reduced bone quality in both the cortical and trabecular bone structures compared with normative matched controls.

Lay Summary

Young adult men with childhood-onset IBD appear to have deficits in both cortical and trabecular bone microstructures, measured with high resolution peripheral computed tomography, compared with age- and height-matched young adult male controls.

Introduction

Patients with inflammatory bowel disease (IBD) are at high risk of low areal bone mineral density (aBMD).[1–13] This risk has been reported for children,[1–4] young adults with childhood-onset IBD,[6–8] and adults.[9–13] Most of the data regarding the bone health of patients with IBD are derived from dual x-ray absorptiometry (DXA) measurements. Dual x-ray absorptiometry is considered the gold standard for assessing aBMD in clinical practice. There is a strong association between low aBMD and increased risk of fracture in the adult population.[14,15] However, the DXA method suffers from the limitation that it does not provide information about the 3D bone structure (volumetric BMD [vBMD]), bone geometry, or bone microstructure characteristics. These bone structures encompass the dense outer cortical layer and the honeycomb-like trabecular structure of the medullary cavity.

In recent years, high-resolution peripheral quantitative computed tomography (HR-pQCT) has become available with a spatial resolution of 82 μm. In addition to allowing more accurate measurements of bone geometry and vBMD, HR-pQCT can measure the cortical and trabecular bone microstructures that make up the structural architecture of bone. These estimations of the structural architecture provide additional important clinical information. For instance,

Key Messages

What is already known?

Young adults with childhood-onset IBD have an increased risk of low areal bone mineral density.

What is new here?

We show that in young men, childhood-onset IBD is associated with a deficit in both cortical and trabecular bone.

How can this study help patient care?

With this in mind, preventive and supportive measures could be taken in childhood and young adulthood to promote better bone health in the patient's future.

a few studies have revealed that HR-pQCT-derived bone parameters, such as cortical area and mass, predict fractures in older men—independently of aBMD.[16,17]

To our knowledge, only 2 HR-pQCT studies have been conducted with patients who have IBD, and those studies have reported somewhat conflicting results. Pepe and colleagues examined adolescents and young adults (mean age 23 years; range, 12-33 years) with IBD and found deficits in their trabecular microstructures without significant changes in their cortical structures.[18] However in a study of adults with IBD (median age 44 years; interquartile range [IQR], 31-54 years), Haschka and colleagues described deficits primarily in the cortical microstructures. In addition, they reported deficits in trabecular structures only in patients with Crohn's disease.[19]

A large proportion of patients with IBD have a low skeletal muscle index (SMI; ie, the weight of lean mass in the arms and legs divided by the height squared, kg/m²)[20] and engage in physical exercise only to a limited extent.[21] Deficits in SMI[20] and lack of physical exercise[22] are associated with compromised BMD in young adult patients with childhood-onset IBD. Previously published studies involving HR-pQCT analyses have not studied how SMI and physical exercise are associated with the bone microstructure deficits seen in patients with IBD.

This study aimed to investigate the extent of microstructural alterations in young adult males with IBD and the association between these changes and the patient's SMI and the amount of physical exercise. A cohort of 49 young adult male patients, all with childhood-onset of IBD, was scanned with HR-pQCT and compared with 249 normative controls, matched for age, gender, and height (ratio of 1:5).

Subjects and Methods

Study Participants

The present study is part of our prospective longitudinal project concerned with BMD and body composition in patients with childhood-onset IBD. Initially, from 2003 to 2005, 144 patients (93 boys and 51 girls) were included, representing the entire spectrum of IBD, from the greater Gothenburg area, Sweden.[2] In the first follow-up (2005-2007), a total of 126 patients (81 males and 45 females) participated. The current study is a part of the second follow-up (2012-2015) conducted in early adulthood, in which 49 men (age range, 18-27 years) were included. In this study

the term "early adulthood" refers to the age period of 18 to 27 years.

In the current study, 49 male patients with childhood-onset IBD were included at the time of the second follow-up. For comparison, we had access to a large contemporary control group of males who were randomly selected from the same region and who participated in the GOOD study, a previously collected large and population-based cohort study.[23] Five male control subjects from the GOOD study were matched to each male patient with IBD based on propensity score for both age and height. In total, 829 control subjects were available for age- and height-specific matching. A patient to control subject ratio of 1:5 was chosen to ensure appropriate power and minimal variation of the matching variables. Females with childhood-onset IBD were not included in this study because we did not have access to a female control cohort.

Anthropometric, DXA, and body composition measurements for both the patients with childhood-onset IBD and the control subjects have previously been published as part of a larger cohort[6,20] and are summarized in Table 1. Dual x-ray absorptiometry scans were used for estimation of areal BMD (g/cm²), bone mineral content (BMC, g) in the whole body, lumbar spine (L1–L4), total hip, and SMI. The DXA measurements were all performed at the Sahlgrenska University Hospital in Gothenburg (Sweden) with a Lunar Prodigy DXA (GE Medical Systems Lunar) in both patients and controls.

The disease-specific characteristics of the patient group has also been published previously[6,20] and include IBD subcategory (ulcerative colitis, $n = 32$ [65.3%]; Crohn's disease, $n = 17$ [34.7%]); median (IQR) age at disease onset 12.3 (9.7-13.8) years; and median (IQR) disease duration of 11.1 (9.5-13.6) years. Disease extension was classified according to the Montreal classification.[24] The patients with ulcerative colitis had disease extension as follows: E1, $n = 0$ (0%); E2, $n = 1$ (3%); and E3, $n = 31$ (97%). The corresponding data on disease localization in patients with Crohn's disease were L1, $n = 3$ (18%); L2, $n = 3$ (18%); L3, $n = 11$ (65%); and L4, $n = 5$ (30%). The following classifications of disease behavior were noted: B1, $n = 11$ (65%); B2, $n = 5$ (29%); B3, $n = 1$ (6%); and perianal disease, $n = 2$ (12%). Surgical intervention was reported in 14 patients (28.6%), including 9 patients with ulcerative colitis, all of whom underwent colectomy, and 5 patients with Crohn's disease, in whom small bowel surgery was performed.

All patients were treated over time according to current international guidelines from diagnosis to the time of bone microstructure measurement in young adulthood.[25,26] A total of 32 (65.3%) patients had no disease symptoms at the time of the bone microstructure measurement. Current treatment regimens were as follows: prednisolone, $n = 2$ (4%); 5-aminosalicylic acid (5-ASA), $n = 13$ (26.5%); azathioprine, $n = 18$ (36.7%); antitumor necrosis factor (TNF)-α inhibitor, $n = 2$ (4.1%); methotrexate, $n = 1$ (2.0%); and no treatment, $n = 12$ (22.4%). The pharmacologic treatment of patients with childhood-onset IBD in our catchment area, as in the rest of Sweden, has followed the treatment principles stated in the National Care Program for IBD prepared on behalf of the Swedish Paediatric Society and the Swedish Society of Gastroenterology. The following pharmacologic treatments were prescribed from the time of diagnosis to the time of second follow-up: prednisolone, $n = 47$ (95.9%); 5-ASA, $n = 49$ (100%); azathioprine $n = 38$ (77.6%); and

Table 1. Anthropometrics and DXA measurements in young adult males with childhood-onset inflammatory bowel disease compared with controls.

	Patients With IBD ($n = 49$)	Age- and Height-Matched Controls ($n = 245$)	Difference (%)	P
Age (years)	23.3 (21.6-25.2)	23.7 (23.5-24.3)	−1.7	.110
Height (cm)	178.3 (174.4-181.6)	178.3 (173.4-185)	0	.441
Weight (kg)	70.9 (63.3-79)	74.3 (67.9-82.3)	−4.6	.095
BMI (kg/m^2)	22.5 (20.8-24.4)	23.1 (21.2-25.1)	−2.5	.152
SMI (kg/m^2)	8.0 (7.3-8.7)	8.3 (7.7-9)	−3.6	.050
Physical exercise (hours/week)	1.0 (0-4)	1.4 (0-4)	−27.3	.408
Total body BMD (g/cm^2)	1.2 (1.1-1.3)	1.3 (1.2-1.3)	−6.3	<.001
Total body BMC (kg)	2.8 (2.6-3.4)	3.2 (2.9-3.5)	−10.6	<.001
Lumbar spine BMD (g/cm^2)	1.1 (1-1.2)	1.2 (1.1-1.3)	−7.8	<.001
L2L4 BMD (g/cm^2)	1.1 (1.0-1.2)	1.2 (1.1-1.3)	−11.8	<.001
L2L4 BMC (g)	51.3 (45.6-59.4)	58.2 (52.6-66.9)	−6.8	<.001
Femoral neck BMD (g/cm^2)	1.0 (0.9-1.1)	1.1 (1-1.2)	−5.7	.001
Femoral neck BMC (g)	5.4 (4.8-6.3)	6.0 (5.3-6.8)	−8.7	.002
Total hip BMD (g/cm^2)	1.0 (0.9-1.1)	1.1 (1-1.2)	−5.7	<.001

All values are presented as median (IQR). Difference between groups were tested with Mann-Whitney U test.
Abbreviations: BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; IBD, inflammatory bowel disease; SMI, skeletal muscle index

TNF-α inhibitor as biologic therapy, n = 11 (22.4%). No biologic therapies other than TNF-α inhibitors were used in these patients. Physical exercise was defined as regular training and registered as hours per week, averaged for the entire previous year. Physical exercise data were used in regression analyses. Our research group recently published data regarding physical exercise habits in young adults with childhood-onset IBD.[22]

We performed an analysis comparing the disease-specific characteristics of patients who participated in the second follow-up (participants, n = 49) with those of patients who did not choose to participate further in the study after the first follow-up (nonparticipants, n = 35). The following parameters did not differ significantly between the participants and nonparticipants: median age at diagnosis; median age; median disease duration; disease subcategory (ulcerative colitis vs Crohn's disease); surgical treatment; current corticosteroid use; current azathioprine use; and median BMD Z-scores.

High-resolution Peripheral Quantitative Computed Tomography

Measurements of bone geometry and microstructure (schematic illustration in Figure 1) with HR-pQCT were performed for all the study participants at the ultradistal tibia, ipsilateral to the nondominant arm, with the same Xtreme computed tomography (CT) scanner (Scanco Medical AG, Brüttisellen, Switzerland) using the manufacturer's standard in vivo protocol, as previously described.[27] A reference line was manually placed at the tibia's articular plateau with regular x-ray imaging guidance. The first CT slice was taken 22.5 mm distal to the reference line, and 104 parallel images were taken (82-μm voxel size) in total, depicting a 9.02-mm 3D representation of the bone. Images were acquired over 2.8 minutes, and the effective dose was 3 μSv per measurement. Image quality was assessed, and the measurements were repeated until the quality was sufficient. A standard analysis was performed according to an earlier described protocol.[28]

From the measurements, the following parameters were recorded: volumetric density (mg/cm^3); cortical cross-sectional area (mm^2); cortical volumetric BMD (mg/cm^3); cortical thickness (mm); periosteal circumference (mm); trabecular cross-sectional area (mm^2); trabecular bone volume fraction (%); trabecular number (mm^{-1}); trabecular thickness (mm); and trabecular separation (mm). The same 2 operators performed all the measurements and graded all the images for quality (score 1-5) using recommendations from the manufacturer.[29]

Statistics

Statistical analyses were performed with the SPSS version 26 software (IBM Corp., Armonk, NY). Propensity score matching was performed with an R package plugin for SPSS. Continuous variables are presented as median (IQR). Categorical variables are presented as number (%). The differences between categorical and continuous variables between the 2 groups were tested with the Fisher exact test or the Mann-Whitney U test, respectively. Each multivariable linear regression analysis had one HR-pQCT measurement outcome as the dependent variable. Covariates were diagnosis of IBD, SMI (kg/m^2), and physical exercise (hours/week). All tests were 2-tailed and conducted, assuming a significance level of 0.05.

Ethics

Informed written consent was obtained from all young adult patients with childhood-onset IBD and controls. The study was approved by the Regional Ethical Review Committee of the University of Gothenburg (Sweden; application numbers: for the IBD cohort 182-02 and 117-11; and the GOOD study cohort S600-02 and 017-08).

Results

In the present study, 49 young adult male patients with childhood-onset IBD and 245 age- and height-matched young

Cortical bone/
Cortical thickness

Trabecular bone
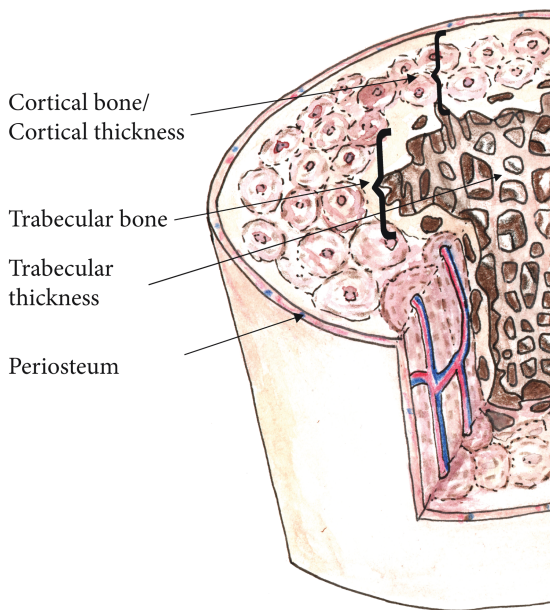
Trabecular
thickness

Periosteum

Figure 1. Illustration of bone showing basic trabecular and cortical microstructures.

adult male controls were scanned with high-resolution peripheral quantitative computed tomography. A schematic illustration of the basic bone microstructures is illustrated in Figure 1.

Dual x-ray absorptiometry and anthropometric measurements have previously been published,[6,20] and these results are described for the young adult male patients in Table 1. The median age of the patients was 23.3 years (IQR, 21.6-25.2) and 23.7 years (23.5-24.3) in controls. Out of the patients, 32 (65%) had ulcerative colitis, and 17 (35%) had Crohn's disease.

Bone Geometry and Microstructure Measurements in Young Adult Men With Childhood-onset IBD

The patient group with IBD had a median 16.5% smaller cortical area than the controls ($P < .001$). However, the patients and controls had similar total tibial and trabecular areas (Table 2). The median total vBMD was 12% lower in the patients with IBD than in the controls ($P < .001$), whereas the median cortical vBMD was 3% lower in the patients than in the controls ($P < .001$; Table 2).

The HR-pQCT measurements of bone microstructure revealed that the patients with IBD had 16.5% thinner median cortical layer than the controls ($P < .001$), but the periosteal circumference was similar in the patients and controls. Furthermore, the patient group had 7.7% lower median trabecular volume fraction than the controls ($P < .001$), whereas a 5.6% median reduction of the trabecular thickness was observed in the patients compared with the controls ($P < .001$). The patients showed a 7.0% greater median trabecular separation than the controls ($P = .036$). However, the number of trabeculae did not differ significantly between the groups (Table 2).

In order to evaluate differences in microstructure parameters between the 2 major IBD subcategories, 32 patients with ulcerative colitis and 17 with Crohn's disease were compared with 160 and 85 matched controls, respectively. The 2 IBD

subcategories had similar deficits in bone geometry and bone microstructures compared with the matched controls—with 2 exceptions (Table 3). Median cortical BMD was significantly lower in the patients with ulcerative colitis (3.3% lower, $P < .001$) but not in the patients with Crohn's disease (1.7% lower, $P = .175$) in comparison with each respective control group. Furthermore, the median trabecular separation was significantly higher in the patients with Crohn's disease (7.4% higher, $P = .048$) but not in the patients with ulcerative colitis (6.3% higher, $P = .217$) compared with the respective controls.

Predictors of Bone Microstructure Deficiencies in Young Adult Men With Childhood-onset IBD

To determine whether having childhood-onset IBD per se was independently associated with the observed deficits in bone geometry and microstructure or dependent on differences in skeletal muscle index or physical exercise amount, we performed a multiple linear regression analysis for each HR-pQCT measurement variable (Table 4). Each analysis was adjusted for the SMI and the amount of physical exercise. A diagnosis of IBD was independently associated with a smaller cortical area but not with the total bone area or trabecular area (Table 4). Furthermore, IBD was independently associated with lower total vBMD, cortical vBMD, trabecular volume fraction and trabecular thickness, and thinner cortices (Table 4). However, we found no clear association between IBD diagnosis and the extent of trabecular separation, trabecular number, or periosteal circumference (Table 4).

Further, in these linear regression analyses, we found in both patients and controls that SMI was positively independently associated with the total, cortical, and trabecular area, as well as with total vBMD, but not with the cortical vBMD. Skeletal muscle index was also positively independently associated with all the measured cortical and trabecular bone microstructure parameters (Table 4). Furthermore, we found that physical exercise in hours/week in both diagnostic groups was not independently associated with bone geometric, vBMD, or microstructural measurements (Table 4). However, when performing the same analyses without adjusting for SMI, physical exercise was independently associated with higher cortical thickness but not with other microstructural measurements.

Discussion

In this study, young adult male patients with childhood-onset IBD were examined with HR-pQCT to evaluate their bone geometry and bone microstructure. For comparison, we used age- and height-matched young adult male controls from the same region. Our results reveal that young adult male patients with childhood-onset IBD display deficits in both the cortical and trabecular microstructures of the tibia.

Young men with childhood-onset IBD had a 12% lower 3D median vBMD than controls. In accordance, 2 recently published studies including both male and female patients, one with middle-aged participants and the other with young adults, showed that vBMD was lower in adults with IBD than in controls.[18,19] The most striking deficit in our patients was the combination of a median of 17% thinner cortical layer and 6% thinner trabeculae compared with the controls. In contrast, previous studies using HR-pQCT for patients with

Table 2. Bone geometry and microstructure in young adult males with childhood-onset inflammatory bowel disease compared with controls.

	Patients With IBD (n = 49)	Age- and Height-Matched Controls (n = 245)	Difference (%)	P
Bone Geometry				
HR-pQCT Total area (mm^2)	844.8 (761.7-957.6)	849.7 (741.8-956.8)	−0.6	.697
HR-pQCT Cortical area (mm^2)	126.1 (110.9-147.1)	151.1 (131.9-171.9)	−16.5	<.001
HR-pQCT Trabecular area (mm^2)	706.9 (632.4-848)	692.3 (591.9-813.4)	2.1	.179
Volumetric Bone Mineral Density				
HR-pQCT vBMD (mg/cm^3)	296.7 (282.5-322.9)	336.7 (309.7-368.2)	−11.9	<.001
HR-pQCT Cortical BMD (mg/cm^3)	854.4 (821-878.5)	878.5 (858.2-901.2)	−2.7	<.001
Bone Microstructure				
HR-pQCT Cortical thickness (mm)	1.110 (0.975-1.275)	1.330 (1.155-1.515)	−16.5	<.001
HR-pQCT Periosteal circumference (mm)	113.4 (107.9-121.0)	114.0 (107.0-121.5)	−0.5	.914
HR-pQCT Trabecular volumefraction (%)	16.8 (15.4-18.1)	18.2 (16.5-19.8)	−7.7	<.001
HR-pQCT Trabecular number (mm^{-1})	1.96 (1.75-2.27)	2.03 (1.83-2.255)	−3.4	.156
HR-pQCT Trabecular thickness (mm)	0.084 (0.076-0.089)	0.089 (0.083-0.096)	−5.6	<.001
HR-pQCT Trabecular separation (mm)	0.429 (0.364-0.488)	0.401 (0.357-0.451)	7.0	.036

IBD, Inflammatory bowel disease; XCT, Xtreme CT (High-resolution peripheral quantitative computed tomography); vBMD, volumetric bone mineral density. All values are presented as median (IQR). Difference between groups were tested with Mann–Whitney *U* test.

Table 3. Bone characteristics analyzed both with DXA and HR-pQCT, in young adult males with ulcerative colitis or Crohn's disease, compared with age- and height-matched controls.

	Ulcerative Colitis (*n* = 32)	Age-Height Matched Controls (*n* = 160)	P	Crohn's Disease (*n* = 17)	Age-Height Matched Controls (*n* = 85)	P
Bone Geometry						
HR-pQCT Total area (mm^2)	883.2 (807.2-963.2)	861.0 (744.0-965.5)	0.365	813.4 (709.3-940.2)	836.4 (736.8-944.6)	.539
HR-pQCT Cortical area (mm^2)	125.2 (113.3-150.2)	151.5 (134.2-172.8)	<0.001	129.2 (108.5-145.7)	150.0 (125.4-168.9)	.001
HR-pQCT Trabecular area (mm^2)	732.8 (680.2-863.3)	701.8 (590.9-817.2)	0.097	666.0 (600.9-810.6)	686.6 (592.0-803.7)	.971
Volumetric Bone Mineral Density						
HR-pQCT vBMD (mg/cm^3)	297.8 (278.2-325.2)	335.9 (307.4-369.9)	<0.001	296.7 (284.9-317.8)	343.5 (310.6-363.5)	<.001
HR-pQCT Cortical BMD (mg/cm^3)	850.3 (824.8-865.2)	879.7 (862.2-902.8)	<0.001	860.4 (810.9-896.9)	875.0 (851.3-897.3)	.175
Bone Microstructure						
HR-pQCT Cortical thickness (mm)	1.120 (0.945-1.263)	1.335 (1.170-1.520)	<0.001	1.080 (0.975-1.305)	1.290 (1.140-1.490)	.007
HR-pQCT Periosteal circumference (mm)	116.2 (110.1-121.1)	114.8 (107.5-121.6)	0.515	111.9 (103.2-119.0)	113.7 (106.5-121.5)	.478
HR-pQCT Trabecular volumefraction (%)	17.4 (15.4-18.3)	18.1 (16.3-19.5)	0.008	16.4 (15.1-17.3)	18.6 (16.6-20.2)	<.001
HR-pQCT Trabecular number (mm^{-1})	2.015 (1.813-2.263)	2.050 (1.833-2.250)	0.435	1.930 (1.640-2.275)	2.010 (1.830-2.265)	.167
HR-pQCT Trabecular thickness (mm)	0.084 (0.076-0.089)	0.088 (0.081-0.095)	0.011	0.083 (0.075-0.089)	0.091 (0.084-0.099)	.002
HR-pQCT Trabecular separation (mm)	0.424 (0.363-0.466)	0.399 (0.356-0.451)	0.217	0.435 (0.367-0.519)	0.405 (0.358-0.451)	.048

Difference between groups were tested with Mann–Whitney *U* test. All values are presented as median (IQR).
Abbreviations: BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; IBD, inflammatory bowel disease; SMI, skeletal muscle index; XCT, XtremeCT (High-resolution peripheral quantitative computed tomography).

IBD have reported deficits in either the cortical[19] or the trabecular[18] structures, but not in both. Deficiencies in either of these microstructures are reported to affect the bone strength.[30]

We show that patients with ulcerative colitis and those with Crohn's disease have deficiencies in both their cortical and trabecular structures compared with controls. The deficiencies were most prominent in cortical area and vBMD

Table 4. Multiple linear regression analyses showing the associations of having an IBD diagnosis and bone microstructure measurements, with adjustments for skeletal muscle index and physical exercise.

	Standardized Coefficients	*P*	Unstandardized Coefficients	Standard Error	95.0% Confidence Interval for B	
	Beta		B		Lower Bound	Upper Bound
Total area (mm²), adj. R² (0.083)						
IBD vs Controls	0.06	.33	22.78	23.31	−23.10	68.65
Physical exercise (h/w)	−0.03	.57	−1.31	2.32	−5.87	3.25
SMI (kg/m²)	0.31	<.001	50.96	9.54	32.18	69.74
Cortical area (mm²), adj. R² (0.247)						
IBD vs Controls	−0.26	<.001	−20.41	3.98	−28.24	−12.59
Physical exercise (h/w)	0.05	.32	0.40	0.40	−0.38	1.17
SMI (kg/m²)	0.39	<.001	11.85	1.63	8.65	15.05
Trabecular area (mm²), adj. R² (0.049)						
IBD vs Controls	0.10	.08	42.68	24.08	−4.71	90.07
Physical exercise (h/w)	−0.04	.46	−1.77	2.39	−6.48	2.94
SMI (kg/m²)	0.24	<.001	39.82	9.86	20.42	59.21
Volumetric BMD (mg/cm³), adj. R² (0.137)						
IBD vs Controls	−0.31	<.001	−39.99	6.98	−53.71	−26.26
Physical exercise (h/w)	0.05	.37	0.62	0.69	−0.75	1.98
SMI (kg/m²)	0.17	<.001	8.46	2.86	2.84	14.08
Cortical BMD (mg/cm³), adj. R² (0.079)						
IBD vs Controls	−0.30	<.001	−27.69	5.23	−37.98	−17.40
Physical exercise (h/w)	0.02	.77	0.15	0.52	−0.87	1.17
SMI (kg/m²)	−0.04	.51	−1.40	2.14	−5.61	2.82
Cortical thickness (mm), adj. R² (0.133)						
IBD vs Controls	−0.26	<.001	−0.20	0.04	−0.28	−0.12
Physical exercise (h/w)	0.07	.25	0.01	0.00	0.00	0.01
SMI (kg/m²)	0.22	<.001	0.06	0.02	0.03	0.10
Periosteal circumference (mm), adj. R² (0.092)						
IBD vs Controls	0.04	.45	1.18	1.55	−1.86	4.22
Physical exercise (h/w)	−0.03	.56	−0.09	0.15	−0.39	0.21
SMI (kg/m²)	0.33	<.001	3.57	0.63	2.33	4.82
Trabecular volume fraction (%), adj. R² (0.121)						
IBD vs Controls	−0.24	<.001	−0.02	0.00	−0.02	−0.01
Physical exercise (h/w)	0.00	.98	0.00	0.00	0.00	0.00
SMI (kg/m²)	0.25	<.001	0.01	0.00	0.00	0.01
Trabecular number (mm⁻¹), adj. R² (0.159)						
IBD vs Controls	−0.03	.57	−0.02	0.04	−0.11	0.06
Physical exercise (h/w)	−0.03	.60	0.00	0.00	−0.01	0.01
SMI (kg/m²)	0.41	<.001	0.13	0.02	0.09	0.16
Trabecular thickness (mm), adj. R² (0.070)						
IBD vs Controls	−0.25	<.001	−0.01	0.00	−0.01	0.00
Physical exercise (h/w)	0.04	.46	0.00	0.00	0.00	0.00
SMI (kg/m²)	−0.17	<.001	0.00	0.00	0.00	0.00
Trabecular separation (mm), adj. R² (0.158)						
IBD vs Controls	0.08	.14	0.02	0.01	−0.01	0.04
Physical exercise (h/w)	0.01	.81	0.00	0.00	0.00	0.00
SMI (kg/m²)	−0.40	<.001	−0.03	0.00	−0.04	−0.02

Abbreviations: CI, confidence interval; h/w, hours/week; IBD, inflammatory bowel disease; SMI, skeletal muscle index

in patients with IBD; this should not be due to bone size differences, as controls were matched for height and age. In contrast, Haschka et al[19] reported such extensive deficits in patients with Crohn's disease only.

The widespread cortical and trabecular deficits seen in young adult men with childhood-onset IBD may be attributable to the fact that disease-onset occurred during childhood in our patients, thereby affecting a crucial phase of

bone development. Other possible explanations for the discrepancies are our larger control cohort than previous studies and that we studied male patients in early adulthood only. It is known that young adult males have thicker cortical[31] and trabecular[32] microstructures compared with young adult females, resulting in increased variation of bone parameters when analyzing both genders together. Moreover, recent studies using DXA have indicated that men with IBD may have more extensive BMD deficits than women with IBD, both early[6] and later[11] in adulthood.

To determine if the changes in bone geometry and microstructure are independently associated with a diagnosis of IBD, we performed a series of multiple regression analyses. The results of these regression analyses confirmed that IBD is independently associated with deficits in both cortical and trabecular structures when adjustments are made for SMI and physical exercise. The IBD diagnosis per se entails several disease-specific risk factors for BMD deficits, such as chronic inflammation,[33] nutritional deficiency,[34] and prednisolone treatment.[35] These factors are also likely to affect the bone microstructure, especially the trabecular bone structures, which represent the more metabolically active part of the bone.[36]

Our present findings indicate that young adult men with childhood-onset IBD have disturbances in bone microstructure leading to weaker bones, which may increase the risk of fracture.[16,37] Interestingly, SMI was independently associated with thicker and denser cortical bone and a more robust trabecular structure, indicating the importance of skeletal muscle for structural bone development in patients with IBD. This supports the previous findings of Werkstetter and colleagues,[38] who measured the muscle cross-sectional area and bone geometry with pQCT in children with IBD. They reported positive correlations between gains in the muscle cross-sectional area, in both cortical and trabecular vBMD, and in cortical thickness.

The positive effects of physical exercise to BMD and bone microstructures are well known.[39] However in the current study, physical exercise was not independently associated with bone geometry or microstructure changes. Our research group has previously found a strong association between higher levels of physical exercise and increased SMI.[22] This indicates that the association of physical exercise and bone microstructure is probably mediated through SMI, indicating the importance of building skeletal muscle mass in patients with IBD, so as to counteract the detrimental effects on the bone linked to the chronic inflammatory state.

The strengths of the present study are a relatively large cohort of young adult male patients with childhood-onset IBD in early adulthood and a robust control population that is matched for gender, age, and height. Furthermore, our cohort includes patients representing the whole clinical spectrum of childhood-onset IBD. A limitation of the study is that approximately one-third of the patients in our cohort were lost to follow-up. However, these patients did not clearly differ from the participants regarding diagnosis, age at diagnosis, medical regime, or gender; thus in our opinion, the present data remain representative for the cohort. Furthermore, in our multivariable regression models, all significant factors had a P value $< .001$. Therefore, we did not apply corrections for the multiple regression analysis, as this would not change the fact that our findings are statistically significant ($P < .05$).

To summarize, our research group has previously shown that our group of male patients in early adulthood with childhood-onset IBD have lower aBMD than normative matched controls.[6] In the current study, we show that these young adult male patients with IBD are at increased risk of having compromised bone microstructure, with deficits of primarily in the cortical envelope but also in the trabecular bone compartment.

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Author Contributions

G.V.S, R.S., and M.L. contributed to the study design, data collection, data analysis, and manuscript writing.

S.S., D.M., and C.O. contributed to the study design, data collection, and manuscript review.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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