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Alimentary Tract

Pediatric-onset inflammatory bowel disease poses risk for low bone mineral density at early adulthood

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ABSTRACT

Background: Inflammatory bowel disease (IBD) is known to pose a risk for low bone mineral density (BMD) in children and adults. We aimed to evaluate the impact of pediatric-onset IBD on BMD in adulthood.
Methods: Records of pediatric-IBD patients were retrospectively reviewed for documentation of dual-energy X-ray absorptiometry (DXA) scans in adulthood. BMD was expressed as z-score.
Results: Sixty one patients were included. Mean (±SD) age at diagnosis was 14.7 (±2.4) years. Mean age at first DXA scan in adulthood was 23.9 years (±4.8). Median BMD z-score was −1.2 SD (IQR, −1.8 to −0.4), significantly lower than expected in normal population ($p < 0.001$). Osteopenia (BMD z-score ≤−1 SD) was noted in 44.3% (n = 27), and osteoporosis (BMD z-score ≤−2.5 SD) in 8.2% (n = 5). Bone-status showed no correlation with age, disease severity, vitamin D status at diagnosis, IBD subtype or duration of disease. Positive correlation ($r = 0.306$) was identified between low weight z-score at diagnosis and abnormal bone-status in adulthood. Among 36 patients with multiple DXA scans, there was no significant change in BMD during follow-up of 2.4 years.
Conclusions: Osteopenia and osteoporosis are frequent in adult IBD patients with pediatric-onset disease and correlates with low weight z-score at diagnosis.

1. Introduction

Inflammatory bowel disease (IBD) is known to pose a risk for metabolic bone diseases, including osteopenia, osteoporosis, poor growth and high prevalence of fractures [1]. The pathogenesis of bone disease in IBD patients is multifactorial, including the impact of inflammatory cytokines on bone homeostasis, the effects of medical therapies such as corticosteroids on bone metabolism, the consequences of poor nutritional status, lack of physical activity, and environmental factors including smoking [2–4].

Bone mass is accrued mostly during childhood, and reaches its peak by the end of the second decade of life. Most studies refer to peak bone mass accrual by the age of approximately 18 and 20 years, in females and males respectively [5], but some reported further bone mass accrual until the age of 23 years [6].

The onset of IBD during childhood and adolescence may compromise final bone mineral density (BMD) via negative effect on growth and development, as well as the potential detrimental impact on the normal process of bone mass accrual, in this critical period. Most studies reporting the prevalence and risk factors of metabolic bone disease in IBD were performed on adult population, thus lacking data regarding the effect of pediatric-onset IBD on bone mass accrual and BMD at early adulthood.

The aim of this study was to evaluate the impact of pediatric-onset IBD, on BMD at early adulthood.

2. Methods

2.1. Patients

We conducted a retrospective chart review of all pediatric onset IBD patients, diagnosed between the ages 2–17 years at the Schneider Children's Medical Center of Israel Between 1981 and 2013 who had documentation of dual energy X-ray absorptiometry (DXA) scans at early adulthood. Diagnosis of IBD was performed according to accepted criteria [7,8]. Data were retrieved from both pedi-

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atric medical charts (Schneider Children's Medical Center) and adult medical charts for patients followed-up into adulthood (Rabin Medical Center).

For this study adult age was defined as the average age of peak bone mass accrual-18 years for females and 20 years for males [5]. In addition we analyzed the changes in BMD in patients who had more than one DXA scan during follow-up years, regardless of the age at which the scan was performed.

The study protocol was approved by the Rabin Medical Center Internal Review Board which represents both the Schneider Children's Medical Center and the Rabin Medical Center.

2.2. Description of variables

Age at onset; gender; anthropometric measurements; laboratory findings; medical treatments and clinical characteristics of the disease were thoroughly investigated by reviewing medical records. Disease activity was assessed using the Harvey Bradshaw Index (HBI) for CD and the Pediatric UC Activity index (PUCAI) for UC.

2.3. Bone mineral density measurements

Bone mineral density was measured by Dual Energy X-Ray Absorptiometry (DXA), (LUNAR DPX 5548 till 2006, and LUNAR IDEXA ME + 200181 from 2007). DXA was performed on lumbar spine L1–L4 and femoral neck routinely, with addition of total-body DXA in all children, and in some adults according to clinical request. The BMD was expressed as z-score, calculated using the lower measurement between lumbar and femoral-neck BMD for each patient. Osteopenia was defined as z-score ≤ -1 SD whereas osteoporosis was defined as z-score of ≤ -2.5 SD.

2.4. Statistical analysis

Categorical variables were described as frequency and percentages. Continuous variables were evaluated for normal distribution using histogram and Q–Q plots. Chi square test and Fisher's exact test were used to evaluate the impact of categorical variables at diagnosis on early adulthood bone status. Independent sample T test and Mann–Whitney test were used for continuous variables. Correlations between continuous variables were assessed using Pearson Correlation Coefficient. One Sample Chi-square test and One Sample Binomial test were used to compare the bone status of the study cohort with that of the normal population.

Multivariable logistic regression using backward-likelihood ratio method was used to evaluate the association between various potential predictors (gender, age at diagnosis, diagnosis, weight z-scores, low vitamin D, years to peak BMD), and bone status. Univariate and multivariate linear mixed models were used to assess changes in BMD during follow-up.

$p < 0.05$ was considered as statistically significant. All tests were two-tailed.

SPSS version 23 (IBM Corp. Armonk, NY) was used for all statistical analysis.

3. Results

Sixty one patients with DXA scans performed during early adulthood were included in the study (31 males, 50.8%). The study group was composed of 42 patients diagnosed with Crohn's disease (CD) and 18 patients with Ulcerative Colitis (UC). Mean (±SD) age at diagnosis was 14.7 (±2.4) years, and mean age at first DXA scan in adulthood was 23.9 years (±4.8).

There were no significant differences between UC and CD patients regarding: male to female ratio; age at diagnosis; weight, height and BMI z-scores at diagnosis; age at first DXA scan in adulthood; mean BMD z-score, prevalence of osteopenia and osteoporosis. There was a greater portion of clinically severe disease, (defined by PUCAI for UC patients, and HBI for CD patients) among the UC group-70.6%, compare to 33.3% of the CD patients ($p = 0.01$). Low vitamin D status (defined as 25-Hydroxy Vitamin D <50 nmol/L) was observed in 20.3% of the patients (n = 12) at time of IBD diagnosis.

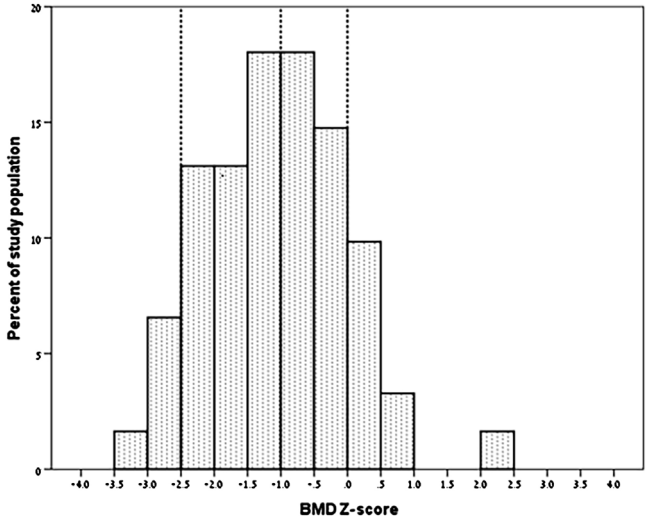

Fig. 1. Bone mineral density (BMD) distribution in adulthood. BMD distribution demonstrates a median BMD z-score of −1.2 SD (IQR, −1.8 to −0.4) with 44.3% (n = 27) patients showing osteopenia, and 8.2% (n = 5) osteoporosis.

Results of BMD distribution are demonstrated in Fig. 1. The median BMD z-score was −1.2 SD (IQR, −1.8 to −0.4), significantly lower than the median of zero expected in normal population ($p < 0.001$). Overall, abnormal BMD (z-score ≤ -1 SD) was found in 52.5% of the patients (n = 32), with 44.3% (n = 27) identified with Osteopenia, and 8.2% (n = 5) with Osteoporosis.

Table 1 outlines the association between baseline and follow-up parameters with bone status, categorized as either normal (>−1 SD), or abnormal (≤ -1 SD). Except for weight z-score, no other diseases' or patients' parameters at diagnosis showed any correlation to the bone status at early adulthood, including age and gender; disease type (Crohn's vs. UC); disease severity at diagnosis; vitamin D status at diagnosis, or the duration of disease until adulthood or until first DXA scan in adulthood.

Furthermore, the course and severity of the disease during follow up, as reflected by rates of exacerbations, hospitalizations and need for surgical treatments-did not demonstrate any association with final BMD (as outlined in Table 1). Moreover, the rates of corticosteroids courses per year were similar: 0.7 courses per year of follow-up in the group of patients with normal adulthood BMD, vs. 0.85 courses per year in the group with abnormal adulthood BMD ($p = 0.42$). The prevalence of anti-TNF exposure was 68% in both groups.

Using multivariable logistic regression analyses, a positive correlation was found, after adjustment for age at diagnosis, between weight z-score at diagnosis and BMD z-score at early adulthood, $r = 0.306$ ($p = 0.017$). Median weight z-score at diagnosis was −0.8 (IQR, −1.8 to −0.15) for patients with abnormal bone status, versus −0.33 (IQR, −0.9 to 0.47) for patients with normal bone status (Fig. 2).

During follow-up, 36 patients had more than one DXA scan. Mean (±SD) age at first DXA scan was 17.8 years (±4.7), and median time between first and second DXA scan was 2.4 years (IQR, 1.6–4.5).

Table 1
Patients' characteristics at baseline and follow-up, grouped by bone status[a] at adulthood.

	Normal bone status	Abnormal bone status	Significance (p value)
Age at diagnosis, years (mean, SD)	14.3 (±2.8)	15.1 (±2.0)	0.45
Male gender (n, %)	14 (48.3%)	17 (53.1%)	0.68
Weight z-score at diagnosis (median, IQR)	−0.33 (−0.9 to 0.47)	−0.8 (−1.8 to −0.15)	0.05
Height z-score at diagnosis (median, IQR)	0.05 (−0.92 to 0.48)	−0.39 (−1.2 to 0.07)	0.12
Crohn's disease (n, %)	19 (65.5%)	24 (75%)	0.42
Ulcerative Colitis (n, %)	10 (34.5%)	8 (25%)	0.42
Low vitamin D at diagnosis (n, %)	6 (21.4%)	6 (19.4%)	0.84
Mild disease at diagnosis (n, %)	17 (58.6%)	16 (53.3%)	0.68
Moderate-severe disease at diagnosis (n, %)	12 (41.4%)	14 (46.7%)	0.68
Exacerbation rate per year of FU (median, IQR)	0.65 (0.25–1)	0.6 (0.2–0.9)	0.77
Hospitalizations rate per year of FU (median, IQR)	0.2 (0–0.4)	0.17 (0–0.35)	0.66
Courses of corticosteroids per year of FU (median, IQR)	0.7 (0.3–1.1)	0.85 (0.3–1.3)	0.42
Anti-TNF exposure (n, %)	20 (68.9%)	22 (68.7%)	0.99
Surgical treatment (n, %)	12 (41.4%)	12 (37.5%)	0.62
Disease duration until peak BMD, years (median, IQR)	3.6 (2.9–6.7)	3.7 (2.3–5.0)	0.48

BMD, bone mineral density; FU, follow-up; IQR, inter-quartile range; SD, standard deviation; TNF, tumor necrosis factor.
[a] "Normal bone status" = BMD z-score in adulthood > −1 SD, "abnormal bone status" = BMD z-score ≤ −1 SD.

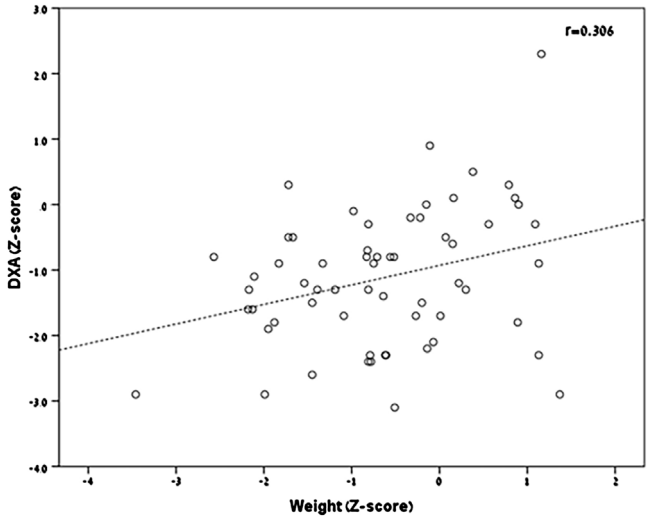

Fig. 2. Correlation between DXA scan results in adulthood, and patients' weight z-score at diagnosis.
After adjustment for age at diagnosis, DXA scan results (expressed as bone mineral density z-scores) correlated with patient's weight z-score at diagnosis (r = 0.306). DXA = dual-energy X-ray absorptiometry.

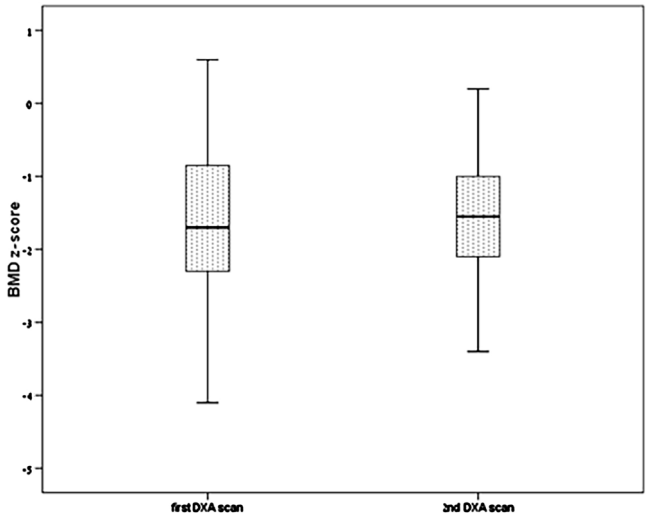

Fig. 3. Distribution of BMD z-scores at first and second DXA scans during follow-up.
No significant differences were noted between DXA scans during a median follow up of 2.4 (IQR, 1.6–4.5) years (p = 0.6). BMD = bone mineral density. DXA = dual-energy X-ray absorptiometry.

Overall, no significant differences were noticed in BMD z-scores during follow-up (p = 0.6). The median difference in BMD z-score was −0.1 SD (IQR, −0.5 to 0.7), as outlined in Fig. 3.

4. Discussion

IBD occurring during childhood and adolescence might have a detrimental impact on bone metabolism, growth and mass accrual. In this group of 61 patients with pediatric-onset IBD we found a substantially diminished BMD at early adulthood, with the majority of patients (52.5%) demonstrating abnormal bone status identified as osteopenia or osteoporosis in DXA scans. Prior studies [9] showed lower prevalence of osteopenia in adult IBD patients (32%–36%), with only modest effect of IBD on the BMD [1]. The results of our study are concordant with low BMD rates of 47% reported in children with IBD [10]. Our observation may imply on a negative impact of disease occurrence specifically during the period of growth and bone maturation at childhood and pubertal years, on the bone mass at early adulthood.

The etiology of bone loss in IBD is complex and multifactorial. The principle mechanism of metabolic bone disease in IBD is the chronic systemic inflammatory process, which suppresses osteoblast activity and bone formation via circulating cytokines [4,11]. Other contributing mechanisms are malnutrition, malabsorption of vital vitamins and minerals, diminished physical activity, and treatment with glucocorticoids [12]. These characteristics are highly prevalent in IBD occurring in the pediatric age group, with further insult to the normal process of bone mass accrual due to delayed puberty and reduced sex-hormones levels [13].

Interestingly, disease duration failed to show any correlation with BMD. The study also found no correlation with other presumed risk factors including gender, corticosteroid therapy, vitamin D blood levels at diagnosis, disease severity at diagnosis and clinical course. The only exception was the demonstrated association between weight z-score at diagnosis and BMD z-score at early adulthood. This finding might be attributed to a more severe disease causing undernutrition and weight loss ultimately resulting in low BMD. Similarly, a previous study performed in young adults with IBD, found a positive correlation between low BMI and reduced BMD and a lack of correlation with disease duration [14]. Regardless of disease severity and inflammatory burden, underweight by itself is known as an independent risk factor for reduced BMD and altered bone maturation, probably through altered hormonal processes

affecting the bone, and reduced mechanical load on the skeleton [3,15].

We also found no significant difference in the prevalence of osteopenia/osteoporosis between patients with CD and UC. Previous adult studies are contradictory, with some reporting lower BMD in CD patients compare to UC patients [16,17], while others showing little or no differences between groups [14,18]. A possible explanation might stem from the fact that compared with adult disease, pediatric UC is characterized by a more severe phenotype, reflected by more extensive disease and a higher rate of acute severe exacerbations [19]. Indeed, a great portion of pediatric UC patients in our study presented with clinically severe disease.

A subpopulation of our study group included patients with more than one BMD measurement. Among those 36 patients, no significant differences in BMD were noted during a median follow-up period of 2.4 years. This lack of change in BMD over time, was also demonstrated in previous studies in adults [20,21]. Studies among pediatric patients with IBD, especially during pubertal years, have also found no significant changes in BMD z-scores during follow-up, despite clinical disease remission [22,23] suggesting that alterations in BMD are determined early in the disease course.

Our study has several limitations. First, our cohort is relatively small and therefore findings may be at risk of type II error. Moreover, as a retrospective study, some longitudinal data are missing, including pubertal status of patients at diagnosis and the timing of pubertal onset during follow-up. It is also important to note that DXA scan does not reflect a real bone density, but rather a ratio of bone mineral content over an area, which can result in underestimation of BMD in stunted patients, and lacks the ability to explore changes in trabecular vs. cortical bone. Regarding the effect of vitamin D status on bone maturation, our data on vitamin D blood levels during follow-up were random and could not represent a long standing status of vitamin D, hence were not included in the analysis. None the less, this study indicates that despite patients' diversity, the peak bone mass at the end of puberty is substantially compromised in pediatric-onset IBD patients, and is the first to examine pediatric risk factors associated with early adulthood BMD.

In conclusion, this study shows that osteopenia and osteoporosis are highly prevalent in young adults with pediatric-onset IBD, and that disease onset during childhood and adolescence might significantly compromise bone mass accrual. Regardless of disease duration and other potential risk factors, BMD does not improve significantly over the course of disease. The diminished peak bone mass in early adulthood might have serious implication on bone strength and fractures risk at late adulthood. Further research is needed in order to assess the impact of possible interventions in pediatric IBD patients with low BMD.

Conflict of interest

None declared.

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