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Evaluation of Bone Densitometry Parameters in Children with Inflammatory Bowel Disease

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Abstract

Background: The present study was performed to assess densitometry indices in pediatric patients affected by Inflammatory Bowel Disease (IBD) in Mashhad city, east of Iran.

Methods: Seventy pediatric IBD patients (8-18 age range) in Akbar Hospital in Mashhad were evaluated in terms of clinical parameters (age, sex, weight, height, IBD type, IBD activity, duration of disease, affected organ, management methods, treatment duration, hospitalization time, nutritional status and puberty), laboratory parameters (serum levels of vitamin D, albumin (Alb), calcium (Ca), phosphorous (P), sodium (Na), magnesium (Mg), Urea, creatinine (Cr) along with important hepatic enzymes aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP)). Also, Dual-energy X-ray Absorptiometry (DXA) was applied for whole body and lumbar spine Bone Mineral Density (BMD) measurement.

Results and conclusion: IBD was mostly manifested as ulcerative colitis (UC) (62.9%) and the disease duration and treatment course were mostly reported to be "over 6 months", with 88.6% and 84.3%, respectively. Most patients had normal (n = 43; 61.4%) and decreased (n = 20; 28.6%) nutritional status, sorted in tanner stage 4 (n = 40; 57.1%), had no hospitalization (81.4%), and received prednisolone (n = 33; 47.1%). Moreover, left colitis (n = 39; 55.7%) and pan colitis (n = 24; 34.3%) were the most affected parts. No statistically significant correlation was reported regarding lumbar BMD values in terms of gender, disease duration, treatment time, and IBD type. Also, there was no statistical association between the treatment type and involved tissues with lumbar and femoral BMD values among 70 examined children in the present study. Still, more studies are recommended to truly evaluate the bone densitometry parameters in children with inflammatory bowel disease.

Key Words: Bone Mineral Density (BMD), Crohn's Disease (CD), Dual-energy X-ray absorptiometry (DXA), Inflammatory Bowel Disease (IBD), Pediatrics, Ulcerative Colitis (UC).

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1- INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder affecting the gastrointestinal tract, mostly diagnosed in adolescents and young adults (1). It has been associated with different causes including toxins, infections, autoimmune responses, irradiation, and ischemia (2). A progressive trend has been observed in the occurrence of IBD among children, particularly those under 5 years of age, which manifests as a more severe, invasive disease with exclusive sequelae such as growth disorders (3). In general, the risk of IBD onset in family members of an affected patient ranges between 7% to 30%, and a child with two affected parents may develop the disease with 35% probability (4). Immune dysregulation in the intestinal mucosa may trigger IBD, and further activate cytokines and cascades of responses, leading to intestinal inflammation (5). Extraintestinal manifestations such as skeletal-articular involvement are one of the sequelae in IBD, being more common during CD than in UC (6). Non-destructive peripheral arthritis is one of the important extraintestinal manifestations of IBD, which may emerge as migratory arthritis, ankylosing spondylitis, and sacroiliitis (7). In about 15-40% of CD-affected children, there is a significant decrease in height growth. Moreover, this phenomenon has been observed in about 90% of those CD patients diagnosed in childhood or adolescence (8). Several factors result in changes in bone growth among IBD-affected individuals, including chronic inflammation, the release of inflammatory cytokines, steroid therapies, poor nutritional status, intestinal malabsorption, reduced levels of vitamin D, and low physical activity (9). Children with IBD are at risk of developing reduced bone mineral density (BMD), an index associated with one's bone health, fracture risk, and diagnosis of osteoporosis (10).

Several studies have investigated the impact of IBD on bone health in pediatric patients using dual-energy X-ray absorptiometry (DXA), the gold standard for assessing BMD (11). These studies have consistently reported lower BMD in children with IBD compared to healthy controls (12-17). Additionally, the severity and duration of IBD have been associated with decreased BMD in these patients (18). Furthermore, alterations in bone turnover markers, such as increased levels of osteoclast activity markers, and decreased levels of bone formation markers have been observed in IBD populations, indicating an imbalance in bone remodeling (19). The evaluation of bone densitometry parameters in children with IBD is essential for identifying individuals at risk of developing osteoporosis and implementing appropriate preventive strategies. Early identification of reduced bone density can guide the selection of therapies aimed at improving bone health, such as calcium and vitamin D supplementation, weight-bearing exercises, and optimizing IBD management (20). The present study was performed to assess densitometry indices in 70 pediatric patients affected by IBD in Akbar Hospital, Mashhad, and east of Iran.

2- MATERIALS AND METHODS

2-1. Study population and settings

The present cross-sectional study was performed on 70 pediatric patients affected by IBD (CD and/or UC) within the 8-18 age range undergoing ESPAGHAN management guidelines for IBD in Akbar Pediatric Hospital in Mashhad, east of Iran. Based on Sznurkowska et al. 's (2016) study (21), considering $\alpha = 0.05$ and $\beta = 0.2$, the sample size was calculated to be 64 patients, which was increased to 70 due to a 10% drop in study participants.

2-1.1. Inclusion criteria

Inclusion criteria encompassed those non-pregnant patients affected by IBD and without coeliac, hepatic, renal, and skeletal diseases and lacking any fractures and malignancies, being treated for less than 6 months or more than 6 months since the onset of the disease. In any part of the study, if the patient or his/her parents did not want to continue participation, they were excluded from the study.

2-2. Procedure

At the onset, the serum levels of vitamin D, albumin (Alb), calcium (Ca), phosphorous (P), sodium (Na), magnesium (Mg), Urea, creatinine (Cr) along with important hepatic enzymes aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) were appraised for each individual. Moreover, clinical data regarding the parameters such as age, sex, weight, height, IBD type, IBD activity, duration of disease, affected organs, management methods, treatment duration, hospitalization time, nutritional status, and puberty were collected for each patient. For assessment of IBD activity, the Pediatric Ulcerative Colitis Activity Index (PUCAI) and Pediatric Crohn's Disease Activity Index (PCDAI) were evaluated for each affected child (2), and the nutritional status was demonstrated using CI, sorting patients into obese, overweight, normal nutrition and malnutrition (2). Also, tanner stages were used to evaluate puberty in children (22). DXA was used as a gold standard method for BMD analysis in the nuclear medicine section of Ghaem hospital, using Norland XR-008 apparatus (202 kg body weight, 193 × 67 cm scan window area, USA) and lumbar spine BMD (S-BMD) and the whole body BMD (TB-BMD) were evaluated (g/cm2). The device output for each patient was reported as a Z-score, being calculated using reference values related to the age and sex of children provided by the manufacturer.

2-3. Data analysis

Quantitative data was reported using mean and standard deviation (SD), while qualitative data was illustrated as tables, graphs, percentages, and frequency. To compare the qualitative and quantitative variables between the two groups, chi-square and independent T-tests were used, respectively. In case of abnormal distribution of data, their non-parametric equivalents were used. Also, paired T-test or its non-parametric equivalent was employed to compare quantitative variables in two associated groups (6 months before and 6 months after IBD diagnosis). Analysis of data normality was done using the Shapiro-wilk test, after which the Student's test as well as Mann-Whitney and Kruskal-Wallis tests were used for normal and abnormal distribution of data. Pearson's correlation coefficient was used to check the correlations. The significance level was set at 0.05 and all statistical analyses were done using SPSS software V. 24 (IBM Statistics, USA) and Statistica V. 12 (Germany).

3- RESULTS

3-1. General characteristics of the study participants

In the present study, 70 individuals with an equal number from both sexes, aged between 8-18 with height and weight ranges of, respectively, 107-185 and 16-83 were included. Among these, IBD disease duration and treatment course were mostly reported to be "over 6 months", with 88.6% and 84.3%, respectively (**Table 1**).

Based on the type of IBD, UC was the predominant type in 44 cases (62.9%), in contrast to the CD, which only contracted 26 individuals (37.1%). The disease intensity was moderate in most cases (n=47; 67.1%), while only 14 cases (12.9%) were of severe type. The most prevalent treatments were prednisolone (n=33; 47.1%) and other therapies (n=27; 38.6%), and most affected parts comprised

left colitis (n=39; 55.7%) and pan colitis (n=24; 34.3%), respectively. Most patients had normal (n=43; 61.4%) and decreased (n=20; 28.6%) nutritional status, and most of them were sorted in tanner stage 4 (n=40; 57.1%). Regarding hospitalization status, 57 cases (81.4%) had no hospitalization and only 2 cases (2.9%) needed hospitalization (**Table 2**).

Table-1: Minimum, maximum, mean, and SD of some important variables

Variable	Range	Median	Mid-quartile domain	Mean ± SD
Age	8.00 - 18.00	15.00	6.00	13.56 ± 3.61
Height	107.00 - 185.00	156.5	30.00	151.34 ± 19.51
Weight	16.00 - 83.00	45.5	27.00	45.06 ± 16.34
Diagnosis time	Lower than 6 months -10 months	2.50	3.10	3.12 ± 2.13
Disease duration	Lower than 6 months - 10 months	3.0	2.80	3.23 ± 2.12
Treatment time	Lower than 6 months - 10 months	2.50	3.1	3.09 ± 2.12

Table-2: Number and percentage of some important variables

Variable		Number (percentage)
Gender	Male	35 (50)
	Female	35 (50)
IBD type	CD	26 (37.1)
	UC	44 (62.9)
Disease severity	Mild	14 (20)
	Moderate	47 (67.1)
	Severe	9 (12.9)
Treatment type	Prednisolone	33 (47.1)
	Prednisolone + Cinnora	6 (8.6)
	Prednisolone + Remicade	2 (2.9)
	Budesonide	2 (2.9)
	Other therapies	27 (38.6)
Involved tissue	Left colitis	39 (55.7)
	Pancolitis	24 (34.3)
	Ileum terminal	3 (4.3)
	Procto sigmoid	2 (2.9)
	Terminal ileum stenosis	2 (2.9)
Rate of hospitalization	No hospitalization	57 (81.4)
	1-day hospitalization	11 (15.7)
	2-day hospitalization	2 (2.9)
Nutritional status	Decreased	20 (28.6)
	Normal	43 (61.4)
	Increased	7 (10)
Sexual puberty	Tanner stage 1	13 (18.6)
	Tanner stage 2	8 (11.4)
	Tanner stage 3	9 (12.9)
	Tanner stage 4	40 (57.1)

3-2. Bone-associated laboratory indices and BMD evaluation

The mean ± SD of different laboratory indices associated with bones were analyzed in the present study for 70 participants, including AST (21.09 ± 6.22), ALT (24.63 ± 7.32), ALP (365.79 ± 152.1), Ca (9.36 ± 0.4), P (4.37 ± 0.6), Vitamin D (27.24 ± 9.53), urea (12.21 ± 3.07), Cr (0.7 ± 0.17), Mg (2.07 ± 0.19), Alb (4.28 ± 0.34), and Na (138.49 ± 2.12). With respect to lumbar bone, the lowest and highest BMD were -1.44 and 0.54, respectively (mean ± SD: -0.44 ± 0.41). Also, the lowest and highest BMD values in femur bone were -2.34 and 0.47, respectively (mean ± SD: -0.85 ± 0.46). The distribution of the final outcome was normal in 68 cases (97.1%), while it was low in only 2 cases (2.9%). Full details of the maximum, minimum, and median of laboratory bone indices and BMD evaluation are presented in **Table 3**.

Table-3: The distribution of bone-associated laboratory indices along with lumbar and femur BMD

Variable	Range	Median	Mid-quartile domain	Mean ± SD
AST	11.00 - 37.00	21.5	8.0	21.09 ± 6.22
ALT	11.00 - 39.00	25.0	10.0	24.63 ± 7.32
ALP	116.00 - 661.00	352.00	262.00	365.79 ± 152.10
Ca	8.5 - 10.30	9.40	0.7	9.36 ± 0.4
P	3.00 - 6.5	4.2	0.8	4.37 ± 0.6
Vitamin D	7.00 - 57.00	27.5	9.5	27.24 ± 9.53
Urea	6.00 - 21.00	12.00	3.00	12.21 ± 3.07
Cr	0.4 - 1.1	0.7	0.2	0.7 ± 0.17
Mg	1.7 - 2.5	2.0	0.24	2.07 ± 0.19
Alb	3.5 - 4.9	4.25	0.5	4.28 ± 0.34
Na	134.00 - 143.00	138.00	3.00	138.49 ± 2.12
Lumbar BMD	-1.44 - 0.54	-0.48	0.41	-0.44 ± 0.41
Femur BMD	-2.34 - 0.47	-0.82	0.33	-0.85 ± 0.46

3-3. Distribution and statistical significance of BMD based on different parameters

Data normality was found regarding lumbar BMD values in terms of gender, disease duration, treatment time, and IBD type, based on the Shapiro-wilk test, and no statistically significant correlation was reported according to the student's test. Moreover, femur BMD values were not found to be normal in such variables, relying on the Mann-Whitney test. Also, there was no statistical association between the treatment type and involved tissues with lumbar and femoral BMD values among the 70 examined children (**Table 4**).

4- DISCUSSION

Children with chronic diseases have been found to experience abnormal bone health and an increased risk of fractures. Bone densitometry, specifically DXA, is a crucial tool for assessing BMD in children with IBD. Existing evidence has demonstrated a considerable rate of altered BMD among pediatric patients with IBD, with remarkable predictors such as low body mass index (BMI), decreased calcium levels, and ileocolonic disease location.

Table-4: Distribution and statistical significance of BMD based on gender, disease duration, treatment time, treatment type, IBD type, and involved tissue

Variable			Data normality	Median	Mid-quartile domain	Mean ± SD	Test statistic (P value)
Lumbar BMD	Gender	Male	0.053	-0.48	0.36	-0.48 ± 0.37	t = -0.88 P = 0.382
		Female	0.141	-0.47	0.71	-0.39 ± 0.45	
Femur BMD		Male	0.004	-0.82	0.37	-0.83 ± 0.41	t = -0.24 P = 0.810
		Female	0.074	-0.82	0.48	-0.87 ± 0.5	
Lumbar BMD	Disease duration	<6	0.252	-0.58	1.15	-0.37 ± 0.6	t = -0.394 P =0.695
		>6	0.343	-0.47	0.39	-0.44 ± 0.39	
Femur BMD		<6	0.360	-0.89	0.67	-0.85 ± 0.72	t = -0.34 P = 0.808
		>6	0.10	-0.82	0.34	-0.85 ± 0.42	
Lumbar BMD	Treatment time	<6	0.203	-0.62	0.82	-0.5 ± 0.55	t = -0.512 P = 0.610
		>6	0.448	-0.47	0.39	-0.43 ± 0.39	
Femur BMD		<6	0.043	-0.89	0.4	-0.86 ± 0.6	t = -0.387 P = 0.698
		>6	0.2	-0.82	0.37	-0.85 ± 0.43	
Lumbar BMD	IBD type	CD	0.873	-0.5	0.49	-0.46 ± 0.48	t = -0.31 P = 0.760
		UC	0.167	-0.47	0.41	-0.42 ± 0.37	
Femur BMD		CD	0.001	-0.86	0.3	-0.92 ± 0.42	t = -1.39 P =0.164
		UC	0.230	-0.76	0.47	-0.81 ± 0.48	
Lumbar BMD	Treatment type	Prednisolone	0.093	-0.47	0.62	-0.39 ± 0.44	K = 2.73 P =0.603
		Pred+Cinnora	0.704	-0.46	0.67	-0.44 ± 0.53	
		Pred+Remicade	-	-0.1	-	-0.1 ± 0.18	
		Budesonide	-	-0.49	-	-0.49 ± 0.06	
		Other	0.884	-0.5	0.53	-0.52 ± 0.37	
Femur BMD		Prednisolone	0.007	-0.9	0.29	-0.85 ± 0.52	K = 3.17

Variable			Data normality	Median	Mid-quartile domain	Mean ± SD	Test statistic (P value)
		Pred+Cinnora	0.685	-0.65	1.10	-0.61 ± 0.55	P = 0.530
		Pred+Remicade	-	-0.5	-	-0.5 ± 0.53	
		Budesonide	-	-0.74	-	-0.74 ± 0.1	
		Other	0.492	-0.85	0.51	-0.93 ± 0.34	
Lumbar BMD	Involved tissue	L. colitis	0.238	-0.49	0.41	-0.47 ± 0.35	K = 2.44 P = 0.655
		P. colitis	0.782	-0.43	0.62	-0.37 ± 0.46	
		Ileum terminal	0.265	-0.47	-	-0.74 ± 0.62	
		Procto sigmoid	-	-0.58	-	-0.58 ± 0.25	
		Il.Terminal.Sten	-	-0.1	-	-0.1 ± 0.71	
Femur BMD		L. colitis	0.092	-0.86	0.52	-0.88 ± 0.44	K = 0.26 P = 0.992
		P. colitis	0.062	-0.81	0.32	-0.8 ± 0.48	
		Ileum terminal	0.165	-0.79	-	-0.96 ± 0.35	
		Procto sigmoid	-	-0.55	-	-0.55 ± 1.15	
		Il.Terminal.Sten	-	-0.85	-	-0.85 ± 0.07	

Considering the negative role of IBD in pediatric BMD, DXA scans can play a substantial role in early diagnosis and monitoring of bone health in these patients. In this sense, the present study was accomplished to evaluate densitometry indices in 70 pediatric patients affected by IBD in Akbar Hospital, Mashhad, and east of Iran.

In the current investigation, 70 children and adolescents aged between 8 to 18 years old in Akbar Hospital, Mashhad City were selected, most of which were affected by UC (62.9%), undergoing treatment for over 6 months (84.3%), particularly by prednisolone administration (47.1%), and suffered the moderate type of IBD (67.1%). Osteopenia was evident in only 2.9% of the examined pediatric cases. There was no statistical difference regarding lumbar and femoral BMD among CD and UC patients; this is in contrast with the results of multiple previous studies. A BMD Z-score of less than -2.0 is considered indicative of low bone density in children with IBD.

In an initial retrospective study encompassing a cohort of adults, a substantial portion of participants was diagnosed with osteoporosis, while a significant number displayed osteopenia. However, in a more recent cross-sectional investigation involving young females, notably different outcomes were observed. Among this group of females, a markedly lower percentage exhibited osteoporosis, with a significant portion demonstrating osteopenia. It's crucial to emphasize that these prevalence rates were notably less pronounced compared to those often encountered in pediatric patients grappling with Inflammatory Bowel Disease (IBD). It's worth noting that there is a well-established association between IBD and reduced Bone Mineral Density (BMD), a phenomenon that holds true in various regions globally. This correlation underscores the prevalent occurrence of diminished BMD in pediatric IBD patients, particularly those afflicted with Crohn's disease (CD). Another study conducted in Saudi Arabia reported a notable prevalence of osteoporosis when evaluating total body and anterior-posterior (AP) spine scans, with corresponding figures for osteopenia (18, 23, 24). However, it's important to consider that this particular investigation concentrated solely on patients diagnosed with CD. In contrast, a study conducted in the Middle East documented noteworthy prevalence rates of osteoporosis and osteopenia among pediatric IBD patients. Additionally, research conducted in diverse global regions has revealed varying degrees of osteoporosis prevalence, with distinct patterns noted in France, Sweden, and the USA. Similarly, the prevalence rates of osteopenia have exhibited considerable variations, reflecting different observations in these regions based on assessments involving total body and AP spine scans (5, 13, 25-27). This observation aligns with a prior study that identified a connection between reduced weight and height Z-scores and the onset of osteoporosis in individuals with Crohn's disease. However, it's noteworthy that low BMI Z-scores had not demonstrated a significant association with diminished BMD in that study. Intriguingly, in contrast to our findings, a recent study reported markedly lower BMD Z-scores in obese IBD patients characterized by higher BMI levels compared to their counterparts in the control group. Furthermore, another study observed that individuals with IBD exhibiting higher BMIs tended to display reduced BMD levels (11, 26, 28, 29).

The correlation between the age at which IBD is diagnosed and the outcomes of Bone Mineral Density (BMD) scans has sparked debates. Our study's results indicate the absence of a noteworthy link between these two variables. This corresponds with the conclusions drawn

from several other investigations, all of which failed to establish a connection between the age of IBD diagnosis and a decline in BMD. However, these findings stand in contrast to the results of three recent studies, asserting that older age was strongly correlated with lower BMD Z-scores among pediatric patients diagnosed with IBD (20, 26, 30-33).

Vitamin D plays a pivotal role in upholding calcium equilibrium and bone metabolism. It undergoes conversion into active metabolites within the liver and kidneys. This active form of vitamin D facilitates calcium absorption in the gastrointestinal tract and the reabsorption of calcium and phosphate within the kidneys processes of utmost importance for bone mineralization (1, 34-36). A notable diminish in vitamin D levels was reported to be predictive of reduced Bone Mineral Density (BMD). In contrast, several other studies failed to establish any substantial link between vitamin D levels and diminished BMD. People grappling with IBD face an elevated risk of vitamin D deficiency due to diminished oral intake and hindered vitamin D absorption, primarily stemming from the inflammatory processes associated with their condition, particularly during periods of disease exacerbation (6, 20, 34, 35).

5- CONCLUSIONS

Based on the findings of our study, children with chronic illnesses, such as Inflammatory Bowel Disease (IBD), often face issues related to bone health and an elevated risk of fractures. Bone densitometry, particularly Dual-energy X-ray Absorptiometry (DXA), serves as a crucial tool for assessing Bone Mineral Density (BMD) in pediatric IBD patients. Numerous studies have highlighted a notable prevalence of altered BMD in these patients, with significant predictors including low body mass index (BMI), reduced calcium levels, and the location of ileocolonic disease. Given the adverse impact of IBD on pediatric BMD, DXA scans play a pivotal role in early diagnosis and ongoing monitoring of bone health. This study encompassed 70 children and adolescents with IBD, aged 8 to 18, in Akbar Hospital, Mashhad, East of Iran. Most participants had Ulcerative Colitis (UC), had been undergoing treatment for over 6 months, primarily involving prednisolone; and presented with a moderate form of IBD. Interestingly, only 2.9% exhibited osteopenia, and there was no significant difference in lumbar and femoral BMD between Crohn's Disease (CD) and UC patients, which contrasts with prior research findings.

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