Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Decreased Bone Mineral Density in Inflammatory Bowel Disease: The Prevalence and Risk Factors

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ARTICLE INFO

Article type
Original article

Article history
Received: 05 Jul 2024
Revised: 06 Jul 2024
Accepted: 10 Jul 2024

Keywords
Bone densitometry
Crohn's disease
Ulcerative colitis
Vitamin D

ABSTRACT

Introduction: In recent decades, the prevalence of inflammatory bowel disease (IBD) has increased, and the incidence of osteoporosis is higher in the population with IBD than in the normal population. Therefore, it seems necessary to carefully examine the risk factors associated with decreased bone mineral density (BMD) among these patients.

Methods: Patients with IBD completed a questionnaire including demographic characteristics, drug history, underlying disease (past medical history), and family history. Afterward, their bone density was measured with a DEXA device. Laboratory samples were also prepared, and densitometry results were placed in three groups: normal, osteoporotic, and osteopenia. The data were analyzed by SPSS software (version 23).

Results: This study was conducted on 63 patients (58 with ulcerative colitis and 5 with Crohn's disease). Bone density was normal in 40 patients, while 16 had osteopenia, and 7 had osteoporosis. There was a significant relationship between bone density and age (P<0.001), smoking (P=0.049), past medical history (P<0.001), extraintestinal involvement (P=0.008), duration of the disease (P=0.023), and menopause (P=0.002). In addition, corticosteroid consumption (P=0.014), the level of calcium (P=0.017), and the level of vitamin D (P< 0.001) in the blood had a significant relationship with bone density.

Conclusion: This study showed that age, smoking status, underlying conditions, extraintestinal involvement, corticosteroid consumption, the level of vitamin D and calcium, and menopause are risk factors associated with decreased BMD in IBD patients.

Please cite this paper as:
Ahadia M, Fazel Hashemi S, Farsi F, Mazloum Khorasani Z, Dabbagh Kakhki VR, Morovatdare N. Decreased Bone Mineral Density in Inflammatory Bowel Disease: The Prevalence and Risk Factors. Rev Clin Med. 2024;11(2): 44-50.

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are diseases with currently unknown etiologies. Various causes have been suggested, including genetic predisposition, changes in the microbiota, environmental variables, and autoimmune involvement [1]. In addition to gastrointestinal-related complications, patients with IBD are at risk for extraintestinal complications, such as osteoporosis [2].

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Metabolic bone diseases, such as osteopenia and osteoporosis, heighten the susceptibility to bone fractures and have a detrimental impact on the quality of life and ability to live independently among older adults. Patients diagnosed with IBD have been found to have a higher likelihood of developing metabolic bone diseases [3-5]. Factors linked to the development of osteoporosis in patients with IBD include advanced age [6], female gender [7], menopausal status in women, corticosteroid consumption [8, 9], malnutrition, deficiency of calcium and vitamin D, immobility, low body mass index (BMI) [10], and smoking [11]. Furthermore, it has been reported that inflammatory cytokines, such as tumor necrosis factor (TNF)-a, which impact the immune system in IBD, can increase the breakdown of bones [12]. Nevertheless, the prevalence of osteoporosis and osteopenia in individuals with IBD differs in previous research, as do the documented factors that contribute to the risk. Therefore, the development of metabolic bone diseases in individuals with IBD is caused by multiple factors, is intricate, and is only partially comprehended.

The present study aimed to explore the prevalence and risk factors associated with low bone mineral density (BMD) in individuals with IBD. The study used demographic, clinical, and paraclinical factors in conjunction with dual-energy X-ray absorptiometry (DEXA) to identify patients at an increased risk of having a low BMD.

Materials and Method

Study design

This cross-sectional study was conducted on IBD patients referred to one public and four private IBD clinics. A total of 63 IBD patients between 18 and 65 years were enrolled. This study followed the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (ethics code: IR.MUMS.MEDICAL.REC. 1400.626). The exclusion criteria were a lack of consent to participate in the study or undergo a DEXA scan, consumption of antiresorptive medication, a medical history of diseases associated with developing osteoporosis, and a history of treatment due to osteopenia or osteoporosis.

Data collection and definitions

Relevant data were collected using a questionnaire that included demographic characteristics, socio-economic details, family medical history, past medical conditions, fracture history, type of IBD, and drug history. The questionnaires were filled out by reviewing patients' files and directly interrogating them.

The assessment of each patient included obtaining anthropometric measurements, such as height and weight, determining the BMI, and performing fasting blood tests to determine calcium and 25-hydroxy vitamin D levels (25[OH] Vit-D). The samples underwent analysis at a singular laboratory utilizing an enzyme-labeled chemiluminescent immunometric test. Clinical manifestations of hypocalcemia, which was defined as a serum calcium level of less than 8 mg/dL or 2.12 mmol/L, can affect various organs and systems and can range from being asymptomatic to life-threatening. On the other hand, hyperkalemia was characterized by a serum calcium level greater than 10.5 mg/dL or 3.5 mmol/L [13-15]. Vitamin D level was determined by the laboratory measurement of 25(OH)Vit-D and classified into the following four subcategories, according to the established criteria [16]:

1.Deficiency: less than 10 ng/ml
2.Insufficiency: between 10 and 30 ng/ml
3.Normal: 30-100 ng/ml
4.Toxic level: above 100 ng/ml

Bone densitometry

Bone mineral density in this study was assessed using DEXA densitometry via the HOLOGIC discovery model. If the patient had not undergone bone marrow densitometry within the last two years, they were referred to the nuclear medicine center for this purpose. The scans measured the BMD of the whole hip, femoral neck, and lumbar spine in grams per square centimeter. Additionally, a whole-body scan and a vertebral fracture assessment were performed. As to the official viewpoint of the International Society of Clinical Densitometry [17], a Z-score of less than -2 standard deviations (SD) at the hip or spine is considered to be below the predicted BMD range in premenopausal women and men under the age of 50. In the remaining patients, the T-score was employed for diagnostic purposes, where a T-score of below -2.5 SD and a T-score of between -2.5 and -1 SD indicated osteoporosis and osteopenia, respectively. The patients were categorized into two groups: one group had a normal BMD, while the other group had a poor BMD (defined as a Z-score of less than -2 SD in premenopausal women and men under 50 years and a T-score of less than -1 SD in others, respectively). Glucocorticoid exposure was measured as either no exposure (less than three months) or positive exposure (greater than three months, with a dosage of prednisone exceeding 7.5 mg/day).

Statistical analysis

The data analysis was conducted using SPSS software (version 25). Descriptive statistics were utilized. A t-test was also employed to examine the correlation between quantitative variables in the two groups. Qualitative variables were compared using the Chi-squared test and Fisher's exact test. If deemed necessary, a regression model was employed to control for the impact of confounding variables. All tests were Two-tailed, and the significance level was below 0.05.

Results

The study was conducted to investigate the rate and risk factors associated with osteoporosis in patients with IBD. Overall, 15 men and 48 women were included in the study, 40 of whom had IBD but did not suffer from decreased bone marrow density, 16 (3 men and 13 women) were osteopenic, and 7 (2 men and 5 women) were osteoporotic. Table 1 shows the association between different characteristics and BMD status. The results showed a significant relationship between bone density and smoking, underlying disease, and age.

As for IBD subtypes, there were 58 patients with UC versus 5 with CD. Eight patients had a disease duration of less than a year, 22 between 1 and 3 years, and 33 more than 3 years. One patient with normal densitometry had undergone surgery, and the other 62 patients had not undergone gastrointestinal surgery. In terms of gastrointestinal involvement, 20 patients had proctitis, 25 had proctosigmoiditis, 8 had left-sided colitis, 5 had pancolitis, and 5 had ileocolitis. Regarding extraintestinal involvement, 82.5% of patients had no extraintestinal involvement, 11.1% had joint involvement (none of which were osteoporotic), and 4 of the osteopenic patients had skin involvement. The results showed that among the factors associated with IBD course, only disease duration or having other symptoms had a significant association with BMD status (P=0.02 and P>0.01, respectively) (Table 2).

In the studies conducted, patients with IBD had proton pump inhibitors (PPI), selective serotonin-reuptake inhibitors (SSRI), anticonvulsant drugs, lithium, azathioprine, vitamin D, calcium, and corticosteroids in their drug history, and all patients had a history of mesalazine use. The results showed a significant relationship between corticosteroid consumption and bone density

Table 1. Comparison of baseline characteristics of study participants among normal, osteopenia, and osteoporosis groups

		Normal N (%)	Osteopenia N (%)	Osteoporosis N (%)	P-value
Gender	Male	10 (25)	3 (18.8)	2 (28.6)	0.84
	Female	30 (75)	13 (81.2)	5 (71.4)	
Marital status	Single	7 (17.5)	2 (12.5)	0 (0)	0.46
	Married	33 (82.5)	14 (87.5)	7 (100)	
Education	Secondary education	20 (50)	8 (50)	5 (71)	0.09
	Tertiary education	20 (50)	8 (50)	2 (29)	
Profession	Unemployed	18 (45)	8 (50)	3 (42.9)	0.11
	Employee	5 (12.5)	4 (25)	4 (57.1)	
	Freelancer	15 (37.5)	4 (25)	0 (0)	
	Student	2 (5)	0 (0)	0 (0)	
Smoking status	No	31 (77.5)	16 (100)	7 (100)	0.04
	Yes	9 (22.5)	0 (0)	0 (0)	
Alcohol consumption	No	34 (85)	16 (100)	7 (100)	0.14
	Yes	6 (15)	0 (0)	0 (0)	
Opium addiction	No	35 (87.5)	12 (75)	4 (51.7)	0.05
	Yes	5 (12.5)	4 (25)	3 (42.9)	
Underlying diseases	None	31 (7.5)	5 (31.3)	0 (0)	<0.001
	Gastritis	3 (7.5)	5 (31.3)	0 (0)	
	Minor thalassemia	5 (2)	0 (0)	0 (0)	
	GERD	1 (2.5)	0 (0)	3 (42.9)	
	Bile duct stone	0 (0)	1 (6.3)	0 (0)	
	IHD	1 (2.5)	1 (6.3)	2 (28.6)	
	Renal stone	2 (5)	0 (0)	0 (0)	
History of fracture	No	33 (82.5)	11 (68.8)	5 (71.4)	0.53
	Yes	7 (17.5)	5 (31.2)	2 (28.6)	
Menopause	No	28 (90.3)	11 (73.3)	1 (20)	0.002
	Yes	3 (9.7)	4 (26.7)	4 (80)	

Table 2. Association between IBD course, drug history, family history, anthropometric findings, vitamin D and calcium levels, and BMD status

Characteristics associated with IBD									
Item	**IBD type**		**Disease duration**		**GI surgery**	**Involved site**			**Other symptoms**
P-value	0.18		0.02		1.00	0.17			>0.01
Drug history									
Item	PPI	SSRI	Anti-convulsive	Li	Mesalazine	azathioprine	Vit D	Ca	Corticosteroid
P-value	0.28	0.58	0.61	0.82	-	0.12	0.38	0.57	0.01
Family history of IBD and osteoporosis									
Item	IBD					Osteoporosis			
P-value	0.81					0.65			
Age and anthropometric findings									
Item	Age		Height		Weight				BMI
P-value	<0.001		0.68		0.36				0.07
Vitamin D and calcium levels									
Item	Vitamin D				Calcium				
P-value	<0.001				0.01				

(P=0.01) (Table 2).

The family history of IBD and osteoporosis was examined among the 63 patients, and it was found that 55 patients had no family history of IBD, and 5 and 3 had a history of UC and CD, respectively. Additionally, 50 patients (79.3%) did not have any history of fractures or osteoporosis in their family, and 13 (20.7%) had a history of osteoporosis in their family. The results showed no significant associations between these two variables and BMD status (P=0.81 and P=0.65, respectively) (Table 2).

Furthermore, the results showed a significant association between age and BMD status (P<0.001), while height, weight, and BMI did not show any significant associations. This study also evaluated the association between vitamin D and calcium, and BMD status, the results of which showed significant associations (P<0.001 and P=0.01, respectively) (Table 2).

In order to investigate the effect of confounding variables on the study, regression analysis was run, which showed that the risk ratio of bone density reduction based on the independent variables of age, underlying disease (having gastritis), vitamin D level, menopause, corticosteroid consumption (a dose of greater than 5.7-5 mg/day for more than three months), duration of the disease (more than three years), and other manifestations were measured independently, as well as together with the other mentioned variables, and the adjusted difference was not significantly different from the raw difference (Table 3). As a result, no confounding effects were observed.

Discussion

This study aimed to examine the prevalence of osteoporosis in individuals with IBD and identify

Table 3. Calculated odds ratio for the variables with a statistically significant association with BMD changeS

Variable		**Odds ratio (confidence interval)**	**P-value**
Age		1.14 (1.26-1.98)	0.03
Underlying disease	Gastritis	6.33 (2.56-8.67)	0.04
	Minor thalassemia	1.32 (1.11-1.96)	0.68
	GERD	0.97 (0.87-1.12)	1.00
	Bile duct stone	1.26 (0.85-1.56)	1.00
	IHD	2.43 (1.84-3.17)	0.68
	Renal stone	0.99 (0.87-1.43)	1.00
Vitamin D level	Deficient	4.10 (3.00-5.87)	0.01
	Insufficient	6.16 (4.55-8.94)	0.02
Menopause		2.36 (1.87-3.78)	0.48
Corticosteroid	>5-7.5 mg Per day for >3 months	11.87 (8.85-13.44)	0.02
	>5-7.5 mg Per day for ≤3 months	1.86 (1.52-2.23)	0.57
Disease duration	1-3 years	0.89 (0.77-1.24)	1.00
	>3 years	2.45 (1.88-2.92)	0.03
Other symptoms	Joint involvement	2.01 (0.88-2.92)	0.59
	Skin involvement	1.55 (0.85-2.33)	1.00

the associated risk factors. It was conducted on a total of 15 male participants and 48 female participants. Out of the whole sample size, 40 individuals had a normal bone density, 16 had osteopenia, and 7 had osteoporosis. An analysis of the biographical data revealed an association between bone density and factors such as smoking, underlying disease, menopause, and age. There was, on the other hand, no discernible association between a family history of IBD and bone density.

Smoking was a significant contributor to decreased BMD among IBD patients in this study. Smoking has been recognized as a risk factor for decreased BMD in the general population [18]. Although the exact mechanisms are not yet known, some attribute this effect to an unhealthy lifestyle among smokers (that is, decreased intake of vitamin D and calcium and insufficient physical activity) [19]. However, the results of studies on the effects of smoking on decreased BMD among patients with IBD are not consistent. Zali et al. reported no association between BMD changes and smoking among IBD patients [20]. On the other hand, Silvennoinen et al. reported a decreased BMD among women who were either current or ex-smokers [21]. Furthermore, smoking has been linked to relapses and disease activity, particularly in the case of CD, and has also been found to contribute to the need for steroids, which has a deleterious impact on bone metabolism. Therefore, it is imperative to promote smoking cessation among individuals with IBD as it can mitigate other consequences, such as cardiovascular diseases, lung cancer, and alterations in bone health [22].

Patients with decreased BMD in this study also had a significantly higher disease duration. This was in line with previous findings; de Jong DJ et al. [23] and other previous studies [24-26] verified a significant inverse association between BMD and disease duration. The length of the disease may have a considerable effect on bone metabolism in IBD due to factors such as persistent systemic inflammation and medication. Patients with frequent disease relapses are commonly prescribed corticosteroids, and an elevated level of inflammatory cytokines is a significant independent risk factor for rapid bone loss [27, 28].

IBD is on the rise in different parts of the world, including Asian countries [29]. Furthermore, a recent study has expected a 2.5-fold rise in the prevalence of IBD in Iran [30]. The present study showed that gender was a significant contributor to the BMD status of IBD patients. Other studies, however, have shown results in favor of and in contrast to ours. Ardizzone et al. [25] examined a total of 91 patients with IBD. The BMD of the spine and femur was shown to be lower in male patients with UC compared to female patients with UC. However, no significant difference was identified in the BMD of male and female patients with CD. On the other hand, Andreassen et al. demonstrated that being a female was a significant predictor of poor BMD in individuals with CD, along with age and weight [31]. Although the present study did not find a significant association between gender and BMD status, osteoporosis or osteopenia was more frequent in female patients than in male patients. Osteoporosis primarily affects female patients with IBD, although there is some evidence suggesting that it may potentially have a preventive effect [32], making the final conclusion in this regard dependent on further research.

This study showed that a history of corticosteroid consumption is a significant contributor to changes in BMD. In contrast, a recent study on 232 patients showed that the use of glucocorticoids is not a risk factor for developing osteopenia. Nevertheless, it should be considered that during the initial stages of treatment, stronger dosages are typically administered, leading to a greater occurrence of severe resorption. However, in long-term treatment, there is a greater emphasis on reducing bone growth [33, 38]. When evaluating their influence, it is important to consider that corticosteroids are employed in inflammatory conditions, which in turn lead to osteoporosis, the extent of which is determined by their potency [13]. On the other hand, the use of corticosteroids disrupts the equilibrium between osteoblasts and osteoclasts. Corticosteroids promote the development and activation of osteoclasts, while also causing apoptosis in osteoblasts, resulting in a decrease in bone production [34, 35]. In their study, Abraham et al. [36] examined 166 individuals with IBD and found that the use of corticosteroids increased the probability of low BMD by more than 2-fold (OR=2.4 (1.5-3.6), P=0.001). Ezzat et al. [37] also found evidence of a negative association between low BMD and the cumulative dose and duration of corticosteroid treatment. Nevertheless, some studies have not discovered a definitive correlation between low BMD and the use of corticosteroids. Andreassen et al. [31] conducted a study on 113 CD patients and could not find any association between BMD and the total amount of corticosteroids administered.

The present study had some limitations. In addition to the limitations inherent to a cross-sectional study, the sample size was relatively small, and the grouping of patients was

heterogenic. Furthermore, we could not minimize the effects of the confounding variables. We also did not group patients based on the treatment they received. As a strength in this study, however, all patients underwent densitometry using a single instrument.

Conclusion

The present study showed that among Iranian patients with IBD, age, smoking status, underlying conditions, extraintestinal involvement, corticosteroid consumption, levels of vitamin D and calcium, and menopause were significant contributors to decreased BMD.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors would like to express their gratitude to Mashhad University of Medical Sciences, Mashhad, Iran.

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