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ORIGINAL ARTICLE

Vitamin D Deficiency and Corticosteroid Use Are Risk Factors for Low Bone Mineral Density in Inflammatory Bowel Disease Patients

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Abstract
Background As several factors can contribute to low bone mineral density (BMD), we investigated the role of vitamin D in low BMD while controlling for other risk factors in inflammatory bowel diseases (IBD) patients.
Methods We conducted a prospective cross-sectional study between 2008 and 2012 in adult IBD patients. Demographic data including age, gender, ethnicity, BMI, along with disease type and location, vitamin D levels, prior corticosteroid use, and anti-TNF use were recorded and evaluated with DEXA results.
Results A total of 166 patients [105 Crohn's disease (CD), 61 ulcerative colitis (UC)] qualified for the study. Low BMD was found in 40 %, twice as frequently in CD than in UC ($p = 0.048$). Higher prevalence of low BMD was associated with those of male gender ($p = 0.05$), Asian ethnicity ($p = 0.02$), and history of corticosteroid use ($p = 0.001$). Age, body mass index, or disease location did not increase the risk of low BMD. The overall prevalence of low vitamin D was 60 %, with insufficiency (25-hydroxy levels between 20 and 30 ng/mL) found in 37 % and deficiency (levels <20 ng/mL) found in 23 % of the patients. Vitamin D insufficient and deficient patients were two times ($p = 0.049$) and almost 3 times ($p = 0.02$) as likely to have low BMD, respectively.
Conclusions Low vitamin D, male gender, Asian ethnicity, CD, and corticosteroid use significantly increased the risk of having low BMD, while age and disease location did not affect BMD in our IBD population. It remains important to evaluate for vitamin D nutritional deficiency and limit corticosteroid use to help prevent low BMD in IBD patients.

Keywords Bone density · Vitamin D · Inflammatory bowel disease

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Introduction

Inflammatory bowel diseases (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), are debilitating diseases associated with many sequelae, including an increased risk of developing low bone mineral density (BMD) from osteopenia and osteoporosis.

After implementation of guidelines from both American College of Gastroenterology (ACG) and American Gastroenterology Association (AGA), evaluation of BMD in IBD patients showed that approximately 44 % had osteopenia and 12 % had osteoporosis [1]. Low BMD may be associated with clinically adverse outcomes; for example, a Canadian population-based study showed that the risk of fracture in IBD patients is 40 % higher than that of the general population [2].

Several etiologies may contribute to the increased risk of low BMD in IBD including: nutritional deficiencies especially of calcium and vitamin D related to chronic malabsorption, inflammatory cytokine (e.g., IL-1, IL-6, and TNF-

alpha)-mediated alterations in bone formation and regeneration [3, 4], and chronic corticosteroid use which promotes apoptosis of osteoblasts [5].

The risk factors for low BMD in IBD are unclear. Prior studies evaluating risk factors for low BMD in IBD patients have arrived at conflicting findings. For example, in a study of 104 Israeli IBD patients, low BMD was not significantly associated with gender, IBD disease type, or lifetime corticosteroid dose [4]. In another study of 70 premenopausal women with IBD, there was a less than the recommended intake for calcium and vitamin D; however, this finding was not associated with low BMD [6]. However, a more recent study found that only 22 % of newly diagnosed adult IBD patients (median 4 years) had optimal 25OHD levels, and they were more likely to have normal BMD than the rest of the group [7]. Lastly, a Norwegian study of 120 patients found a significantly higher percentage of vitamin D deficiency (25-hydroxyvitamin D3 <30 nmol/L) in CD patients (27 %) compared to UC patients (15 %), but there was no association between vitamin D levels and BMD [8]. Therefore, we conducted a prospective cross-sectional study among IBD patients to investigate the risk factors for BMD with emphasis on vitamin D levels.

Methods

Study Setting and Design

We conducted a cross-sectional study with consecutive, prospective enrollment of adult patients diagnosed with IBD attending the Baylor Clinic IBD Center that serves residents of the greater metropolitan area of Houston, Texas, as well as the surrounding cities and nearby states. The majority of patients seen at the clinic have medical insurance. Patients were enrolled between the years 2008 and 2012.

Diagnosis of IBD was based on clinical, radiologic, endoscopic, and histological examination.

All patients underwent a baseline DEXA scan (QDR® 4500 bone densitometer—Hologic, Inc. Danbury, CT) and a measurement of serum levels of 25-hydroxyvitamin D (performed at Clinical Pathology Laboratories, Austin, TX) within the same clinic visit. Additionally, demographic data (i.e., age, gender, ethnicity), BMI, IBD type (CD, UC) and disease location, prior corticosteroid use, and anti-TNF use were recorded in a structured template and subsequently abstracted. Race/ethnicity was based on self-reported classified as Caucasian, Hispanic, African American, Asian, or other. Medication use was defined as any prior or current use recorded of corticosteroids (prednisone, methylprednisolone, budesonide) and current use of anti-tumor necrosis factor (anti-TNF) agents (infliximab, adalimumab, certolizumab).

The main outcome variable of the study, BMD obtained from the DEXA scan results, was analyzed in two mutually exclusive categories based on the WHO classification of lumbar spine and hip T scores as osteopenia defined as <−1.0 or osteoporosis defined as <−2.5. Low BMD was defined by the presence of either osteopenia or osteoporosis. The main exposure of interest was also examined in two categories as vitamin D insufficiency defined as serum vitamin D 25-hydroxy levels between 20 and <30 ng/mL, and vitamin D deficiency defined as serum vitamin D 25-hydroxy levels <20 ng/mL.

Analysis

We compared patients who had normal BMD with patients with abnormal BMD (osteopenia or osteoporosis) as well as osteopenia and osteoporosis as individual groups. We examined the association between low BMD and potential risk factors including demographic (age, gender, ethnicity), BMI, IBD type (CD, UC) and disease location, medication use, and vitamin D levels. We used chi-square tests for categorical variables. We used logistic regression models both unadjusted as well as adjusted to calculate the odds ratios (OR) and the accompanying 95 % confidence intervals (95 % CI) for each risk factor.

Ethical Considerations

The study was conducted after obtaining an approval from the Baylor College of Medicine Institutional Review Boards.

Results

Patient Characteristics

A total of 168 patients with IBD diagnosed between the ages 17 and 70 (mean age at IBD diagnosis was 36 (SD = 15.2) years of age participated in the study. Females comprised 58 % of the total cohort. The racial distribution was 73 % Caucasians, 11 % Blacks, 5 % Hispanics, 8 % Asians, and 3 % other race/ethnic group. There were 105 (63 %) patients with CD, 61 (37 %) with UC, and 2 (1 %) with IBD-undetermined (IBD-U). The 2 patients with IBD-U were excluded from the analysis due to the small number.

Associations Between Low Bone Mineral Density and Patients Demographics (Table 1)

Sixty-six (40 %) of the 166 studied IBD patients had abnormal BMD; 54 (33 %) patients had osteopenia, and 14 (8 %) patients had osteoporosis. The distribution of BMD

Table 1 Adjusted odds ratio and 95 % CI for abnormal DEXA by patients' demographics

Variable	Abnormal DEXA/total (%)	OR (95 % CI)	*p*	Osteopenia/ total (%)	OR (95 % CI)	*p*	Osteoporosis/ total (%)	OR (95 % CI)	*p*
Age group (year)									
<20	7/18 (39)	Ref		5/16 (31)	Ref		2/13 (15)	Ref	
20–29	23/56 (41)	1.1 (0.4–3.2)		21/54 (39)	1.4 (0.4–4.6)		2/35 (6)	0.3 (0.04–2.6)	
30–39	16/40 (40)	1.1 (0.3–3.3)		12/36 (33)	1.1 (0.3–3.0)		4/28 (14)	0.9 (0.1–5.7)	
40–49	10/26 (38)	1.0 (0.3–3.4)		6/22 (27)	0.8 (0.2–3.4)		4/20 (20)	1.4 (0.2–8.8)	
50–59	6/13 (46)	1.3 (0.3–5.7)		6/13 (46)	1.3 (0.3–5.7)		0/13 (0)		
≥60	6/13 (46)	1.3 (0.3–5.7)		4/11 (36)	1.2 (0.2–6.3)		2/9 (22)	1.5 (0.2–13.8)	
Gender									
Female	34/96 (35)	Ref		29/91 (32)	Ref		5/67 (8)	Ref	
Males	34/70 (49)	1.8 (0.95–3.32)		25/61 (41)	1.5 (0.76–2.9)		9/45 (20)	2.0 (1.0–3.5)	0.05*
Ethnicity									
Caucasians	44/121 (36)	Ref		35/112 (29)	Ref		9/98 (10.5)	Ref	
Blacks	11/19 (58)	2.4 (0.9–6.4)		9/17 (55)	2.5 (0.9–6.9)		2/10 (20)	2.1 (0.4–11.7)	
Hispanic	2/9 (22)	0.5 (0.1–2.4)		2/9 (22)	0.6 (0.1–3.1)		0/9 (0)		
Asians	9/13 (69)	4.1 (1.1–13.5)	0.02**	6/10 (60)	3.3 (0.9–12.4)	0.06	3/7 (43)	6.4 (1.2–33)	0.01**
Others	2/4 (50)	1.8 (0.2–12.8)		2/4 (50)	1.8 (0.2–12.8)		0/4 (0)		
BMI									
<25	29/81 (36)	Ref		22/74 (30)	Ref		7/59 (12)	Ref	
≥25	39/85 (46)	1.5 (0.81–2.82)	0.87	32/78 (41)	1.6 (0.81–2.8)		7/53 (13)	0.9 (0.3–2.8)	

* p at a significant level = 0.05

** p at a significant level <0.05

$^{\Pi}$ 13/60: (13/67-7). We excluded the osteoporosis patients in the denominator when calculate % of osteopenia and exclude the osteopenia patients when calculate % of osteoporosis

was similar across all age groups. Males had 2 times the prevalence of osteoporosis than females [20 vs. 8 %, OR 2.0 (1.0–3.5), $p = 0.05$]. We also examined the association between younger and older age (≤35 vs. >35 years) for both males and females independently. There were no associations between younger and older age group and abnormal DEXA for females [37 vs. 33 %, respectively, OR = 0.6 (0.6–2.4), $p = 0.7$] or for males [47 vs. 52 %, respectively, OR = 1.2 (0.5–3.3), $p = 0.6$].

In unadjusted analyses, Asians had a 4 times likelihood of low BMD compared to Caucasians [69 vs. 36 %, OR 4.1 (1.1–13.5), $p = 0.02$]. However, neither age nor gender was significantly associated with low BMD. Body mass index (BMI) <25 was not associated with abnormal DEXA scan.

Associations Between Low Bone Mineral Density and Study Variables (Table 2)

CD patients had a twofold increase in the risk of having low BMD than UC patients [47 vs. 31 %, OR 2.0 (CI = 1.12–3.50), $p = 0.048$]; however, no association to location of disease in either CD or UC was found. While corticosteroid use more than doubled the risk of low BMD [OR = 2.4 (1.5–3.6), $p = 0.001$], no association was found with the use of anti-TNFs.

Of the total 166 patients, 99 (60 %) had low vitamin D levels (<30 ng/dL); 61/166 (37 %) had vitamin D insufficiency, and 38/166 (23 %) had vitamin D deficiency. Patients with vitamin D insufficiency were twice as likely to have low BMD [OR 2.0 (1.0–4.1), $p = 0.049$], and those with vitamin D deficiency had almost 3 times higher likelihood of having low BMD than those who had normal vitamin D [OR 2.6 (1.5–3.6), $p = 0.02$].

In a stepwise multiple logistic regression model to analyze the study variables that were significantly associated with abnormal DEXA results in the unadjusted analysis, vitamin D deficiency and prior use of were significantly associated with low BMD (Table 3). However, CD, gender, and ethnicity were no longer significantly associated with low BMD.

Discussion

Low BMD was relatively common in our adult patients with IBD and was associated with vitamin D insufficiency or deficiency as well as corticosteroid use. Although in the

Table 2 Adjusted odds ratio and 95 % confidence interval for abnormal DEXA by the study variables among IBD patients

Associated variable	Total IBD patients			Total IBD patients			Total IBD patients		
	Abnormal DEXA/ total (%)	OR (95 % CI)	*p*	Osteopenia/ total (%)	OR (95 % CI)	*p*	Osteoporosis/ total (%)	OR (95 % CI)	*p*
IBD type									
CD	49/105 (47)	Ref		38/94 (40)	Ref		11/67(16)	Ref	
UC	18/61 (30)	2.0 (1.12–3.50)	0.05	16/58 (28)	1.8 (0.8–3.6)	0.1	3/45 (7)	2.7 (0.7–10.1)	0.12
Vitamin D									
Normal	20/67 (30)	Ref		13/60 (22)	Ref		7/54 (13)	Ref	
Insufficient (20–30)	28/61 (46)	2.0 (1.0–4.1)	0.05*	25/58 (41)	2.7 (1.2–6.1)	0.01**	3/36 (8)	0.6 (0.2–2.5)	0.5
Deficiency < 20	18/38 (53)	2.6 (1.2–5.1)	0.02*	16/34 (42)	3.2 (1.3–8.0)	0.01**	4/22 (18)	1.5 (0.4–5.7)	0.6
Use of anti-TNF									
No	28/77 (36)	Ref		22/71 (31)	Ref		6/55 (11)	Ref	
Yes	40/89 (45)	1.2 (0.7–2.6)		32/40 (36)	1.5 (0.7–1.8)		8/57 (14)	1.3 (0.4–4.1)	
Prior use of steroid									
No	23/83 (28)	Ref		18/78 (23)	Ref		5/64 (8)	Ref	
Yes	45/83 (54)	2.4 (1.5–3.6)	0.001**	36/74 (49)	3.2 (1.6–6.7)	0.001*	9/47 (19)	3.0 (0.8–8.7)	0.08
Location									
CD									
1	17/34 (50)	Ref		11/28 (39)	Ref		6/23(26)	Ref	
2	12/34 (35)	0. 5 (0.2–1.4)		12/34 (35)	0. 8 (0.3–2.4)		0/22 (0)	NA	
3	11/19 (58)	1.4 (0.4–4.3)		9/17 (53)	1. 7 (0.5–5.9)		2/10 (20)	0. 7 (0.1–4.3)	
4	9/17 (53)	1. 1 (0.3–3.6)		6/14 (43)	1. 2 (0.3–4.2)		3/11 (27)	1. 0 (0.2–5.3)	
UC									
1	6/24 (33)	Ref		4/22 (18)	Ref		2/20 (10)	Ref	
2	12/37 (32)	0. 5 (0.1–2.0)		9/34 (26)	1.6 (0.8–2.7)		3/28 (11)	1. 3 (0.1–17.1)	

* p at a significant level = 0.05

** p at a significant level <0.05

Π 13/60: (13/67-7). We excluded the osteoporosis patients in the denominator when calculate % of osteopenia and exclude the osteopenia patients when calculate % of osteoporosis

general (non-IBD) population, older age, female sex, and low BMI are considered risk factors for low BMD, we found no significant association between these factors and low BMD in our IBD population. In contrast to our findings of no association between age and BMD, 2 previous studies showed that advancing age of IBD patients (>50 years) had a significant decline in BMD [9, 10].

In direct contrast to the general population where females have a higher risk of osteoporosis than males [11], we observed a trend of low BMD in males compared to females, with the strongest association in those with osteoporosis. Three studies (2 in both UC and CD, 1 in CD) showed that male gender was associated with low BMD [12–14]. Only one study of IBD patients from Israel found no association of gender to low BMD [4]. Despite the tendency to focus on osteopenia in females, it appears that in IBD, males are actually at greater risk. One possible explanation includes low testosterone levels in young males that could contribute to this risk. We did not obtain testosterone levels in our male patients with abnormal BMD as this was not the scope of our original study design. However, it is possible that increased inflammation can contribute to lower testosterone levels thereby increasing the risk of abnormal BMD. In a nested cross-sectional study that evaluated testosterone concentrations with inflammatory markers in young men, low testosterone levels were associated with higher tumor necrosis factor alpha (TNFa) ($\beta = -0.015$; $p = 0.040$) [15]. Another study showed conflicting results: In evaluating 104 Swedish men with rheumatoid arthritis, no correlation was found between the degree of inflammation or the levels of sex hormones. However, this study did not find any correlation of low BMD to steroid treatment either, which raises concern about the validity of the hormone information [16].

Table 3 Odds ratio and 95 % CI of stepwise logistic regression model for the study variables were significantly associated with abnormal DEXA

Associated symptoms	Total patients with abnormal DEXA		Total patients with osteopenia		Total patients with osteoporosis	
	Adjusted OR (95 % CI)	*p*	Adjusted OR (95 % CI)	*p*	Adjusted OR (95 % CI)	*p*
Vitamin D						
No	Ref		Ref		Ref	
Insufficient (20–30)	1.7 (1.0–2.9)	0.05*	2.1 (1.2–4.5)	0.03**	0.5 (0.2–2.0)	0.5
Deficiency <20	2.0 (1.0–3.1)	0.04*	2.6(1.2.–26)	0.02**	1.3 (0.2–3.8)	0.4
Prior use of steroid						
No	Ref		Ref		Ref	
Yes	2.0 (1.0–1.9)	0.05*	2.8 (1.2–3.9)	0.01*	2.2 (0.8–6.9)	0.07

We have referred several of our IBD patients with osteoporosis to endocrinology, and of those tested, a few did have low testosterone levels. Upon discussion with our endocrinologists, their recommendation for management of these patients was primarily geared toward treatment of the inflammation. This would increase the testosterone levels naturally rather than them recommending testosterone supplementation. Those that were considered for testosterone replacement by endocrinology were predominately older males (greater than 55 years of age).

We found a fourfold increased risk of low BMD in Asians. This may be explained by a 69 % prevalence of vitamin D deficiency in this group. A Canadian study found a significantly higher percentage of South Asians with low vitamin D when compared to Caucasians [17]. A small study of 30 Asian IBD patients found vitamin D deficiency was associated with low BMD [18]. Also, inadequate dietary calcium intake linked the 63 % prevalence of low BMD in a study of Indian IBD patients [19]. A Malaysian study, however, showed no significant association between BMD and vitamin D levels. Their definition of normal, inadequate, and low vitamin D was slightly different from our study: 61–160 nmol/L (24–64 ng/mL), 30–60 nmol/L (12–24 ng/mL), and <30 nmol/L (<12 ng/mL), respectively [20]. They did find a greater than 50 % prevalence of osteopenia and up to 17 % prevalence of osteoporosis which is similar to our results.

Higher BMI traditionally has been a protective factor against osteoporosis and the risk of bone fractures. However, in our study, we found no association of BMI to BMD results. This is in contrast to 5 other studies in IBD patients that showed that lower BMI was associated with bone density loss [9, 10, 13, 14, 21].

It is possible that IBD patients with severe disease tend to have lower BMIs which could confound the analysis. It is also possible that higher BMI, at least in the general population, does not necessarily correlate with better nutrition. In a cross-sectional analysis of 1,250 postmenopausal women, lower socioeconomic status was associated with vitamin D deficiency, higher BMI, and lower bone density [22].

We found that CD patients are significantly more likely to have low BMD than UC patients in the unadjusted analysis, but this finding did not persist in the multivariable analyses. Small bowel disease, absorption of vitamin D, and potentially increased levels of inflammatory cytokines of TNF-alpha and IL-6 in CD could account for this difference. However, several studies of IBD patients did not show significant differences in BMD between those with CD and UC [13, 21, 23, 24]. Only 2 studies had similar findings of lower BMD in CD patients compared to UC patients [9, 25].

In regard to disease location, we did not find any differences in low BMD in relation to IBD location for CD or for UC. Only one study evaluating CD patients found that those with jejunal disease had significantly lower BMD than those with disease at other sites [14].

Despite a patient population from the southern United States, we found 60 % of our patients had low vitamin D, with insufficiency found in 37 % and deficiency found in 23 %. Although sun exposure is not the only source of vitamin D, limited nutritional intake as well as increased metabolism could account for this high prevalence. It is interesting to note, however, that 6 prior studies showed no association between vitamin D levels and BMD in IBD patients [6, 20, 24, 26–28]. However, in our study, vitamin D insufficiency doubled the likelihood of low BMD and those with vitamin D deficiency had 2.6 times higher likelihood of low BMD. Although the Institute of Medicine had reduced the lower limit of normal vitamin D level to 20 ng/mL, our results indicate that IBD patients should maintain a level >30 to reduce their likelihood of low BMD.

Vitamin D may play different roles in UC versus CD. For example, a retrospective study of 30 patients with CD and 18 patients with UC showed higher prevalence of low BMD in UC patients; however, only 55 % of UC patients had vitamin D deficiency compared with 83 % of CD

patients [29]. In contrast, a Japanese study showed that CD patients had significantly lower vitamin D levels and lower BMD scores than UC patients [30]. They did note that these factors were associated with the patients' fat intake, but not with their oral intake of this vitamin.

Low vitamin D levels correlated significantly with low BMD in IBD patients from Portugal [31], in Asian IBD patients living in Egypt [18], in the Iranian UC patients [32], and in Japanese UC patients [33]. In the Manitoba cohort study of recently diagnosed IBD patients, low vitamin D levels correlated with lower baseline BMD [7]. Those that had improvement in their vitamin D levels during follow-up also correlated with a gain in total body BMD suggesting that early optimization of vitamin D may prevent IBD-related bone disease [7].

In our study, corticosteroid use accounted for the most significant association of decreased bone density in univariate and multivariate analysis. This is not surprising as corticosteroids have been shown to impair osteoblast function and induce osteoblast apoptosis, and numerous studies have confirmed the association of corticosteroid use and low BMD [3, 34, 35].

We found no differences in anti-TNF use and bone density. Although one could expect that anti-TNF treatment could improve bone density (by reducing inflammation burden of cytokines that could contribute to osteoclastic and osteoblastic activity, as well as a reduce corticosteroid use), it is possible that patients with more severe disease are usually on anti-TNFs and disease activity may negative the beneficial effects of these medications.

A review of available data which included results from pediatric CD patients from the REACH study [36], prospective analysis from the UK in CD patients [37], and adult IBD patients in the USA [38] regarding the effect of anti-TNF therapy on bone metabolism and BMD in IBD patients showed improvement in bone formation markers such as bone alkaline phosphatase and osteocalcin in CD, but data in UC patients are lacking [39]. Long-term effects of anti-TNF therapy on bone structure and the effect of cessation of anti-TNF therapy on bone metabolism are unknown. Long-term, prospective studies are needed. Additionally, prospective monitoring of these patients for the risk of fractures, improvement of bone density after treatment of vitamin D deficiency, and reduction in bone resorptive cytokines such as IL-6 could provide early perspective of treatment and prevention of bone loss. Early evaluation and treatment of those patients at risk of low BMD as described by Schulte and colleagues of those with genetic variations in the Il-6 and IL-1ra gene may also prevent bone loss [40].

Despite the increased prevalence of low BMD in IBD patients, BMD testing is underutilized [41]. If our findings are confirmed in other studies, practice guidelines from ACG, AGA, and CCFA on osteoporosis screening in IBD patients may need to be re-evaluated. Traditional indications for BMD screening which included corticosteroid use, postmenopausal status, advanced age, hypogonadal state, family history, and low impact fracture history may miss a significant number of IBD patients with low BMD as found in our study. It is important to assess BMD in IBD patients regardless of traditional risk factors. Evaluation of vitamin D levels and implementation of treatment to >30 ng/mL and limiting corticosteroid use may help reduce the risk of low BMD in these patients.

Conflict of interest None.

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