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High prevalence of low bone mineral density in patients with Inflammatory Bowel Disease in the setting of a peripheral Dutch hospital

Fiona D.M. Van Schaik [b], Marc A.M.T. Verhagen [a], Peter D. Siersema [b], Bas Oldenburg [b,*]

[a] Department of Gastroenterology, Diakonessenhospital Utrecht/Zeist, The Netherlands
[b] Department of Gastroenterology, University Medical Centre Utrecht, The Netherlands

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Abstract

Background and aims: Osteopenia and osteoporosis are frequently encountered in patients with Inflammatory Bowel Disease (IBD). Our aims were to evaluate the actual practice of screening for low bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA), to determine the prevalence of low BMD and to investigate the risk factors associated with a low BMD in the IBD population of a regional Dutch hospital.
Methods: A retrospective chart review was performed in 474 patients (259 with ulcerative colitis, 210 with Crohn's disease and 5 with indeterminate colitis). DEXA results and potential predictive factors of low BMD were documented. Predictive factors of low BMD were assessed by logistic regression.
Results: DEXA was performed in 168 IBD patients (35.4%). A low BMD (*T*-score<-1) was present in 64.3%. Osteoporosis (*T*-score<-2.5) was found in 23.8%. Low BMI, older age at the moment of diagnosis and male gender were found to be predictive factors of low BMD. For patients with osteoporosis, disease duration was an additional predictive factor. After subgroup analysis predictive factors were found to be the same in patients with Crohn's disease.
Conclusions: The prevalence of osteopenia and osteoporosis in IBD patients in a regional centre is as high as the prevalence rates reported from tertiary referral centres. A low BMI, an older age at the moment of diagnosis and male gender were predictive factors of low BMD. Prediction of osteoporosis and osteopenia using risk factors identified in this and previous studies is presently not feasible.

1. Introduction

Osteopenia and osteoporosis have been reported frequently in patients with Inflammatory Bowel Disease (IBD) with prevalence rates for osteoporosis up to 42%.[1–19] Several factors were found to be associated with a lower bone mass density in

Abbreviations: BMD, bone mineral density; CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis.

* Corresponding author. Department of Gastroenterology, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Tel.: +31 30 250 9111; fax: +31 30 250 5566.
E-mail address: B.Oldenburg@UMCUtrecht.nl (B. Oldenburg).

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IBD patients, including low body mass index (BMI), systemic use of corticosteroids, male gender, age, prior bowel resection, disease duration and smoking.[1,3–8,11–15,17,18] Previous studies have mainly included patients from tertiary referral centres. This might have resulted in a selection of patients with a more severe disease and consequently a higher rate of osteoporosis. To date, in most Dutch hospitals screening for osteoporosis in IBD patients is not routinely performed, although guidelines recommend DEXA screening in IBD patients with particular risk factors of low BMD such as postmenopausal state, age over 60 years, history of low trauma fractures, ongoing steroid treatment and cumulative prior use of corticosteroids exceeding 3 months.[3,9,20]

The aims of the present study were to evaluate the actual practice of screening for low BMD within the IBD population in a non-academic setting, to determine the prevalence of osteopenia and osteoporosis within this population and to investigate the risk factors associated with a low BMD in patients with IBD.

2. Patients and methods

2.1. Study design and patients

A retrospective chart review was performed of the IBD patient population of the Diakonessen hospital located in Utrecht and Zeist. From all patients, the clinical diagnosis has been recorded in a hospital database since 2003. From this database, patients with a recorded diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or indeterminate colitis (IC) were selected. At the start of this study, 482 IBD patients were identified. Patients were diagnosed using a combination of endoscopy, histology and radiology. The following data were obtained from the charts when available: gender, body weight and height, age at the moment of diagnosis, disease phenotype according to the Montreal classification,[21] disease duration, number of exacerbations, history of steroid usage, duration of corticosteroid usage, duration of topical steroid usage, history of pathologic (hip and/or lumbar spine) fractures, smoking habits, history of bowel resection and relevant comorbidity. Exacerbations were defined as complaints requiring hospitalization or initiation of corticosteroid treatment. Body mass index (BMI) was calculated as weight/height^2 (kilogram per square meter). Corticosteroid and budesonide usage was documented as the number of months patients were on more than 5 mg prednisone or on oral budesonide. Steroid enema use was not documented. Comorbidity was scored when a patient suffered from one of the following diseases: (para)thyroidal disease, renal or liver disease, diabetes, ankylosing spondylitis or hypogonadism.

2.2. BMD measurement

Measurement of BMD of the lumbar spine and the hip was performed using DEXA (Norland XR-46, Scanner Software version 2.3.1, Houst Software version 3.9.6) at the Department of Nuclear Medicine. The results were expressed in absolute values (g/cm^2), *Z*-score and *T*-score. The *Z*-score is the number of standard deviations (SD) from the normal mean value of a reference population of the same sex and age. The *T*-score indicates the number of SD from a reference population at the age of peak bone mass with the same sex. The World Health Organisation defines osteopenia as a *T*-score between −1 and −2.5, and osteoporosis as a *T*-score

Table 1 Differences in variables between population with a DEXA and controls

Variable	DEXA (*N*=168)	Controls (*N*=306)
Disease diagnosis (%)		
Crohn's disease	108 (64.3) [a]	102 (33.3) [a]
Ulcerative colitis	59 (35.1) [a]	200 (65.4) [a]
Indeterminate colitis	1 (0.6) [a]	4 (1.3) [a]
Gender (%)		
Male	54 (32.1) [b]	141 (46.1) [b]
BMI (kg/m^2)	23.8 [14.5–42.2]	23.4 [13.2–42.0]
BMI could be calculated (*N*)	134	230
Age at diagnosis (yr)	30 [12–77] [c]	34.5 [9–79] [c]
Age at start of study (yr)	44.5 [15–87]	42.5 [18–90]
Disease extension (Montreal) (%)		
Crohn's disease		
Ileal (L1)	19 (17.6)	29 (28.4)
Colonic (L2)	49 (45.4)	43 (42.2)
Ileocolonic (L3)	40 (37.0)	30 (29.4)
Ulcerative colitis		
Ulcerative proctitis (E1)	3 (5.1)	24 (12.0)
Left-sided UC (E2)	38 (64.4)	120 (60.0)
Extensive UC (E3)	18 (30.5)	56 (28.0)
Indeterminate colitis		
Proctitis	0 (0.0)	1 (25.0)
Left-sided colitis	0 (0.0)	3 (75.0)
Pancolitis	1 (100.0)	0 (0.0)
Disease duration (yr)	5.5 [0–58]	7 [0–49]
Number of exacerbations	1.5 [0–9] [d]	1 [0–10] [d]
Ever used steroids (%)	145 (86.3) [e]	183 (60.0) [e]
Duration corticosteroid usage (mo)	9 [1–139] (*N*=137)	7 [1–216] (*N*=173)
Duration topical steroid usage (mo)	4 [1–46] (*N*=41)	5 [1–82] (*N*=44)
Fractures (%)	3 (1.8)	6 (2.0)
Smokers (%)		
Total population	51 (34.5) [f]	53 (21.0) [f]
Smoking could be documented (*N*)	148	252
Crohn's disease	46 (46.5)	32 (39.0)
Smoking could be documented (*N*)	99	82
Ulcerative colitis	4 (8.3)	19 (11.4)
Smoking could be documented (*N*)	48	166
Bowel resection (%)	36 (21.4)	45 (14.7)
Concomitant diseases (%)	15 (8.9)	22 (7.2)

N — number of patients; yr — years; mo — months.
Results are expressed as number (percentage) or as median [range].
[a] Fisher's Exact test; $p=0.000$.
[b] Chi-square test; $p=0.003$.
[c] Mann–Whitney *U* test; $p=0.032$.
[d] Mann–Whitney *U* test; $p=0.000$.
[e] Chi-square test; $p=0.000$.
[f] Chi-square test; $p=0.003$.

Table 2 Differences in variables between patients with normal and low BMD in total population with DEXA

Variable	Normal (*N*=60)	Osteopenia (*N*=68)	Osteoporosis (*N*=40)	Low BMD (*N*=108)
Diagnosis (%)				
CD	40 (66.7)	40 (58.8)	28 (70.0)	68 (63.0)
CU	20 (33.3)	28 (41.2)	11 (27.5)	39 (36.1)
IC	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.9)
Gender (%)				
Man	14 (23.3)	20 (29.4)	20 (50.0)	40 (37.0)
BMI (kg/m^2)	25.8 [20.0–42.2][a,b,c]	23.5 [17.8–30.8] [b]	22.1 [14.5–36.6] [c]	23.0 [14.5–36.6] [a]
BMI could be calculated (*N*)	48	56	30	86
Age at moment of diagnosis (yr)	29 [17–69]	29.5 [15–76]	35.5 [12–77]	32 [12–77]
Disease extension (%)				
Crohn's disease				
Ileal (L1)	6 (15.0)	8 (20.0)	5 (17.9)	13 (19.1)
Colonic (L2)	20 (50.0)	17 (42.5)	12 (42.9)	29 (42.6)
Large and small bowel (L3)	14 (35.0)	15 (37.5)	11 (39.3)	26 (38.2)
Ulcerative colitis				
Ulcerative proctitis (E1)	0 (0.0)	3 (10.7)	0 (0.0)	3 (7.7)
Left-sided UC (E2)	14 (70.0)	14 (50.0)	10 (90.9)	24 (61.5)
Extensive UC (E3)	6 (30.0)	11 (39.3)	1 (9.1)	12 (30.8)
Indeterminate colitis				
Extensive UC	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)
Disease duration (yr)	6 [0–58]	5 [0–33]	8 [0–44]	5 [0–44]
Number of exacerbations	1 [0–9]	1 [0–8]	2 [0–8]	2 [0–8]
Ever used steroids (%)	50 (83.3)	60 (88.2)	35 (87.5)	95 (88.0)
Duration corticosteroid usage (mo, all patients)	4 [0–139]	6 [0–86]	10 [0–105]	6.5 [0–105]
Duration budesonide usage (mo, all patients)	0 [0–18]	0 [0–28]	0 [0–46]	0 [0–46]
Fractures (%)	0 (0.0)	1 (1.5)	2 (5.0)	3 (2.8)
Smokers (%)	17 (31.5)	20 (32.8)	14 (42.4)	34 (36.2)
Smoking could be calculated (*N*)	54	61	33	94
Bowel resections (%)	10 (16.7)	14 (20.6)	12 (30.0)	26 (24.1)
Concomitant diseases (%)	5 (8.3)	5 (7.4)	5 (12.5)	10 (9.3)

N — number of patients; yr — years; mo — months.
Results are expressed as number (percentage) or as median [range].
[a] Mann–Whitney *U* test; $p=0.004$.
[b] Mann–Whitney *U* test; $p=0.015$.
[c] Mann–Whitney *U* test; $p=0.013$.

below −2.5. Osteopenia and osteoporosis were defined by the lowest *T*-score of one of the three measured sites: lumbar spine, femur collum or femur trochanter.

2.3. Statistical analysis

Variables between patients with a DEXA and without a DEXA were compared using a nonparametric test (two-tailed Mann–Whitney *U* test). When variables were categorised, the Chi-square test or the Fisher's Exact test was used. Two-tailed Mann–Whitney *U* tests or Chi-square tests were used likewise to compare variables between patients with normal and low BMD.

Factors predictive of low BMD were determined using logistic regression with backward stepwise selection. Normal BMD was defined as all *T*-scores more than −1. Low BMD was defined as at least one *T*-score lower than −1. A p-value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS 13.0) was used for analysis.

3. Results

3.1. Patient characteristics

Eight patients (1.6%) were excluded because their charts could not be retrieved. From the remaining 474 patients, 259 (54.6%) were diagnosed with ulcerative colitis, 210 patients

Table 3 Predictive factors of low BMD in the total population

	B	S.E.	Sig
BMI (kg/m^2)	−0.150	0.055	0.007
Gender (male vs. female)	0.894	0.448	0.046
Age at the moment of diagnosis (yr)	0.039	0.017	0.018

yr — years; *B* — regression coefficient; S.E. — standard error; Sig — significance.

Table 4 Predictive factors of osteoporosis

	B	S.E.	Sig
BMI (kg/m^2)	−0.207	0.089	0.020
Gender (male vs. female)	1.306	0.617	0.034
Age at the moment of diagnosis (yr)	0.065	0.023	0.005
Disease duration (yr)	0.066	0.033	0.048

yr — years; *B* — regression coefficient; S.E. — standard error; Sig — significance.

Table 6 Predictive factors of osteoporosis in patients with Crohn's disease

	B	S.E.	Sig
BMI (kg/m^2)	−0.232	0.116	0.046
Gender (male vs. female)	−1.989	0.798	0.013
Age at the moment of diagnosis (yr)	0.079	0.033	0.016
Disease duration (yr)	0.083	0.041	0.045

yr — years; *B* — regression coefficient; S.E. — standard error; Sig — significance.

(44.3%) with Crohn's disease and 5 patients (1.1%) with indeterminate colitis. This population comprised 195 men (41.1%) and 279 women (58.9%). The median age was 43 years [15–90]. Sixty-five percent had ever used corticosteroids, with a median duration of 8 months [1–216]. The median duration of disease was 6 years [0–58], the median number of exacerbations was found to be 1 [0–10]. The median BMI was 23.5 kg/m^2 [13.2–42.2].

In the subgroup of CD patients, the large bowel was affected in 92 (43.8%), the small bowel in 48 (22.9%) and both the large and small bowel in 70 patients (33.3%). In the UC patients, proctitis was diagnosed in 27 (10.4%), proctosigmoiditis in 82 (31.7%), left-sided colitis in 76 (29.3%) and pancolitis in 74 patients (28.6%). Bowel resection had been performed in 32.9% of the CD patients and 4.6% of the UC patients. Only 9 patients had a documented pathologic fracture. In 36 patients concomitant diseases were documented (9 thyroid disease, 12 diabetes, 6 liver disease, 5 ankylosing spondylitis, 1 renal and thyroid disease, 1 liver and thyroid disease and two patients with both diabetes and thyroid disease). In 110 patients the BMI could not be calculated.

3.2. Baseline and bone mineral density characteristics

Baseline characteristics of patients in whom a DEXA scan was performed and of control patients are shown in Table 1. Median age of patients in the DEXA group at start of the study was 44.5 years [15–87] compared to 42.5 years [18–90] in the controls. In the DEXA group significantly more females (67.9% vs. 53.9%) and more patients with Crohn's disease (64.4% vs. 33.3%) were found than in the control group. Furthermore, these patients were significantly younger at diagnosis (30 vs. 34.5 years), had experienced a higher number of exacerbations (1.5 vs. 1), used more frequently steroids (86.3% vs. 60.0%) and were more often smokers (34.5% vs. 21.0%).

BMD valuables were available in 108 CD patients, 59 UC patients and 1 patient with an indeterminate colitis. In 108 patients (64.3%) a low BMD was present at one of the three measured sites. Osteopenia was found in 68 patients (40.5%) and osteoporosis in 40 patients (23.8%). Patient characteristics of the populations with normal BMD, low BMD, osteopenia and osteoporosis are shown in Table 2. BMI was significantly lower in both patients with osteopenia and osteoporosis.

Table 5 Predictive factors of low BMD in patients with Crohn's disease

	B	S.E.	Sig
BMI (kg/m^2)	−0.134	0.063	0.035
Gender (male vs. female)	−1.122	0.563	0.046
Age at the moment of diagnosis (yr)	0.055	0.025	0.028

yr — years; *B* — regression coefficient; S.E. — standard error; Sig — significance.

3.3. Predictive factors of low BMD

Based upon univariate analysis (see Table 2) and a thorough review of literature, the following potential predictive factors of a low BMD were included in the logistic regression model: number of exacerbations, BMI, concomitant diseases, bowel resection, budesonide use, duration of corticosteroid usage, gender, age at the moment of diagnosis, smoking, diagnosis, disease duration and disease localisation. After excluding patients with missing values, 121 patients were included in the model. Using logistic regression analysis with backward stepwise selection, a low BMI, an older age at the moment of diagnosis and male gender turned out to be predictive factors of low BMD (Table 3).

When the same model was applied to the 69 patients with osteoporosis, BMI, gender, age at diagnosis and disease duration were found to be predictive factors for osteoporosis (Table 4). A longer duration of disease turned out to be an additional predictive factor for osteoporosis.

A separate analysis for patients with Crohn's disease (n=81) revealed that BMI, gender and age at diagnosis were predictive factors for a low BMD in these patients as well (Table 5). In this analysis, a longer duration of disease was also found as additional predictive factor for osteoporosis (Table 6).

4. Discussion

This study shows that high prevalence rates for osteopenia (40.5%) and osteoporosis (23.8%) can be found in the setting of a regional hospital and that these are comparable with data from tertiary referral centres.[1–19] In this study few patients underwent bowel resection and the median number of exacerbations was low. Thus, despite the relative mild course of disease a high prevalence of osteoporosis was found in this group of patients. Only a minority of the enrolled patients were younger than 18 years old, had an isolated proctitis or concomitant disease predisposing to secondary osteoporosis, all of which could have resulted in a biased outcome.

For all IBD patients with a low BMD, three predictive factors were found: a low BMI, male gender and an older age at diagnosis. This is in line with published data from earlier studies. A wealth of data confirms the predictive value of a low

BMI.[1,3–5,7,8,11,12,14,17] The positive correlation with age (more osteopenia and osteoporosis in the elderly) is in agreement with earlier studies as well.[1,8] We found a significant higher frequency of a low BMD in men as compared to women. Recently, Bartram et al.[1] demonstrated a significant correlation between male gender and osteoporosis in patients with Crohn's disease. This was confirmed by Ardizzone[15] in patients with ulcerative colitis. When we applied the logistic regression model to the subgroup with osteoporosis, disease duration was identified as an additional predictive factor. Two previous studies confirm this significant correlation between low BMD and disease duration.[15,18] Although statistical analysis identified age at the moment of diagnosis and disease duration as independent risk factors for a low BMD, we cannot exclude some bias. Both factors are related to advanced age, which is a known risk factor for osteopenia and osteoporosis.

DEXA screening was performed in 35.4% of our IBD population. To our knowledge only one other study reports on practice-based screening[10] with a percentage of 25% of patients screened. Although the majority of the patients in our population were not screened, the number of 168 IBD patients with a DEXA is among the highest reported in literature. One might assume that patients in the present study were selected for DEXA scanning by their treating gastroenterologists because an increased fracture risk was suspected. The fact that screened IBD patients were more often females, smokers, patients with Crohn's disease, patients who were younger at diagnosis or had a history of a more severe course of disease underscores this assumption. Apparently, those parameters cannot predict a low BMD reliably. The risk factors, identified in the present study (a lower BMI, an older age at the moment of diagnosis, male gender and longer disease duration) were distributed more or less evenly in both groups. We do not feel that the use of these factors to identify patients at risk would be of significant help in this respect.

Although the incidence of fractures among patients with IBD seems to be increased,[22,25,26] Bernstein states that the magnitude of the excess risk is limited and is most evident in the elderly.[9] Our study confirms this small risk of fracture. Fractures were documented in only 1.9% of the total population. Only 2.8% of the patients with low BMD and none of the patients with normal BMD had ever had a pathologic fracture. However, it has previously been shown that two out of three of all vertebral fractures are clinically not evident.[9] The low fracture rate in our study might therefore be due to the fact that fracture questionnaires were lacking and vertebral X-rays were not routinely performed.

Our study has some limitations. Data on BMI and smoking habits were missing in 20 and 34 cases respectively. These cases were excluded from the logistic regression analysis. Furthermore, data could not be documented at the (exact) moment of DEXA. We could not reproduce the putative association of a low BMD measurement with decreased vitamin D levels, sex hormone status and markers of systemic inflammation as reported in previous studies[5,6,12,13,15,16,18,22–24] due to missing data. In addition, data on the familial history were incomplete.

Instead of performing DEXA's in all IBD patients, we support the note of Lichtenstein,[2] that a conservative, cost-effective approach that limits screening to selective patients with risk factors for low bone mass seems more appropriate. Consensus on treatment of IBD patients with a low BMD, however, is lacking. According to the American Gastroenterological Association (AGA)[26] there is a need for therapeutic intervention studies specifically aimed at bone health in gastrointestinal diseases. Presently, recommendations concerning the management of low BMD in patients with IBD are extrapolated from postmenopausal osteoporosis and the rheumatology literature.[3,27] Moreover, DEXA measurement might not be able to reliably predict fracture risk in IBD. The use of DEXA's is derived from studies in postmenopausal osteoporosis which pathophysiology differs undoubtedly from IBD-associated osteoporosis.[9]

In conclusion, the prevalence of osteopenia and osteoporosis in IBD patients in a regional centre is as high as the prevalence rates reported from tertiary referral centres. Low BMI, male gender and older age at the moment of diagnosis were predictive factors of low BMD; disease duration was found to be an additional predictive factor in patients with established osteoporosis. We conclude that prediction of osteoporosis and osteopenia using risk factors identified in this and previous studies is presently not feasible.

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