Bone loss in inflammatory Bowel disease: our multicentric study

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Abstract

Patients with inflammatory bowel disease are at increased risk of developing disorder in bone and mineral metabolism. The study was aimed to determine if inflammatory bowel disease (IBD) is a risk factor for osteoporosis in 103 adult patients. We included 103 IBD patients, 67 patients with Crohn's disease (CD) and 36 with ulcerative colitis (UC). Bone mineral density was measured by dual-energy X-ray absorptiometry. We used T score to express bone loss (osteopenia: $-2.5 \text{ SD} < T < -1 \text{ SD}$, osteoporosis: $T < -2.5 \text{ SD}$). Plain x-rays were examined to search for vertebral compression or spontaneous fractures before DEXA. Among the 103 patients, 47.7% exhibited osteopenia of the femoral neck and 62.3% of the lumbar spine, with no significant difference between CD and UC. The prevalence of osteoporosis of the lumbar spine was significantly higher in CD patients (41.2% versus 8.7%). Osteoporosis is frequent in IBD patients, especially in CD patients. Female gender, malnutrition (body mass index $< 20 \text{ kg/m}^2$), disease course (> 2 years) and active disease would be risk factors of bone mineral loss in IBD.

Introduction

Patients with inflammatory bowel disease (IBD) are at increased risk of developing disorder in bone and mineral metabolism.

Osteopenia and osteoporosis are frequently seen in Crohn's disease (CD) and ulcerative colitis.^{1,2} The prevalence of osteoporotic fractures is strikingly high, both in females and males; depending on the population studied the prevalence of osteoporosis has been reported to range from 12-42% in patients with IBD.³ It has been suggested that the pathogenesis of osteoporosis in patients with IBD is multifactorial (Table 1).⁴ Disease activity and duration, low body weight or body mass index (BMI), calcium and vitamin D deficiency, small bowel involvement or resection, gender, the use of glucocorticoids to control disease activity, increasing age, immobilization and life style risk factors (e.g. smoking, excessive alcohol intake, physical inactivity) as well as genetic factors have been implicated.⁵⁻⁷ Not all studies have demonstrated a relationship between corticosteroid use and low BMD in IBD patients. In one BMD study performed on CD patients; it was shown that both groups who had a low life-time corticosteroid dose therapy with or without dietary manipulation, had a similar BMD to that of age-matched normal controls. Whereas, BMD was significantly reduced in those treated predominantly by corticosteroids.⁸ However, it is difficult to separate the effects of corticosteroids from those of disease activity.⁹ Although corticosteroids may be mechanistically responsible for bone loss, their use may also serve as a marker for more severe disease activity that is responsible for bone loss. Bone density and growth are determined by the combination of anabolic osteoblast activity (bone formation) and catabolic osteoclast activity (bone resorp-

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Table 1. Risk factor osteoporosis in inflammatory Bowel disease.

Increasing age
Malnutrition
Low Body mass index
Use of corticosteroids
Immobilization
Malabsorption of vitamin D, calcium and vitamin K
Hypogonadism
Smoking
Chronic inflammatory state

Table 2. Differential diagnosis between Crohn's disease and ulcerative colitis according to endoscopic findings.

	Crohn's disease	Ulcerative colitis
Involvement	Discontinuous	Continuous
Rectal involvement	20%	Always
Vessels	Often normal	Abnormal/lacking
Erythema/edema	++	+++
Vulnerability	(+)	+++
Bleeding	(+)	+++
Pus/mucus	+	+++
Local ulcers	+++	+++
Fissural ulcers	+++	(+)
Granularity	(+)	(+)
Cobblestone pattern	+++	+++
Pseudopolyps	++	---
Strictures	++	+++

Table 3. Truelove and Witts' classification of severity of ulcerative colitis.

Activity	Mild	Moderate	Severe
Number of bloody stools per day (n)	< 4	4-6	> 6
Temperature ($^{\circ}\text{C}$)	Afebrile	Intermediate	> 37.8
Heart rate (beats per minute)	Normal	Intermediate	> 90
Haemoglobin (g/dL)	> 11	10.5-11	< 10.5
Erythrocyte sedimentation rate (mm/h)	< 20	20-30	> 30

tion), as well as the activity of chondrocytes (cartilage formation needed to extend bone length). During normal bone growth, chondrocytes continually mature and produce cartilage at the growth plate to allow bones to lengthen (endochondral bone formation). Osteoclasts resorb the cartilage and areas of existing bone and osteoblasts form. The regulation of bone metabolism involves a complex interplay between different factors, including sex steroids.¹⁰ As of today, little is known about the prevalence of sex steroid deficiency in male CD patients and its contribution to bone loss and osteoporosis. In postmenopausal osteoporosis, the importance of sex steroid deficiency, especially estradiol (E_2) deficiency, is well established.¹¹ Women with CD and UC are at an increased risk of amenorrhoea and premature menopause. Osteoporosis is often considered to be a disease of women, men lose half as much bone with aging and have one third as many fragility fractures as do women. Previous studies investigating testosterone (T) and the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH), reported lower than normal T levels in 4/48 (8%) male CD patients with the free androgen index (FAI) low in three patients and normal gonadotropins.¹² T was positively associated with osteocalcin. Others report T deficiency in 20/45 (44.4%) male IBD patients but no effect on bone density and metabolism was detected.¹³ Lower than normal dehydroepiandrosterone sulfate (DHEAS) levels have been found in IBD patients, in part dependent on previous glucocorticoid treatment. High cortisol and low DHEAS levels were associated with higher humoral inflammatory activity, and vice versa.¹⁴ Lower levels of DHEAS plasma levels in male IBD patients were associated with lower BMD and with higher deoxypyridinoline excretion. DHEAS correlated with BMD at the lumbar spine and femoral neck. In the literature, the reported prevalence of osteoporosis/osteopenia in IBD varies from 7-56%.¹⁵ A retrospective study of a Caucasian population showed a 40% increase in the risk of fracture compared to healthy controls.¹⁶ CD seems to be associated with a slightly higher risk than UC does for osteoporosis and subsequent fractures, although this has been disputed in some studies.¹⁷ With the advent of dual-energy X-ray absorptiometry (DXA), it is easy to measure bone mineral density (BMD) non-invasively. BMD results are typically expressed as the number of standard deviations (SD) above or below the mean for a young adult population (T-score) or an age-matched population (Z-score). In most studies, either T- or Z scores have been used in evaluating predictive factors of low bone density in IBD, making comparison of results difficult. World Health Organisation¹⁸ diagnostic criteria (a bone density 2.5 or more standard deviation units below the mean value

for young adults) report rates of 13-42%.^{19,20} The aim of this cross sectional study was to determine the prevalence of osteoporosis in an unelected group of patients with CD and UC and to identify the relative importance of possible risk factors and the mechanism of bone loss.

Materials and Methods

From November 2007 to March 2010, we enrolled all consecutive IBD patients aged 20-80 years who attended our department. The study was performed according to the Helsinki declaration. All patients were informed about the nature of the study and gave their consent to participate. The diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) had been established on the basis of classical clinical, endoscopic, histological, and radiographic criteria (Table 2). Disease activity was determined with the Truelove and Wittes criteria for UC²¹ (Table 3) and the activity index for CD (Table 4).²² Exclusion criteria were

pregnancy; uncontrolled diabetes; renal, hepatic, cardiovascular or psychiatric disease; rheumatoid arthritis; ankylosing spondylitis; untreated thyroid disease; primary sclerosing cholangitis; or treatment with teriparatide, calcitonin, bisphosphonates, fluoride, androgens, active metabolites of vitamin D within the past 6 mo. Weight and height were measured without shoes and with light indoor clothing. The BMI was calculated as weight/height² (kg/m²). BMD was measured with diphotonic x-ray absorptiometry (DEXA) of the lumbar spine and the neck of the left femur. Results were expressed as T score (osteopenia: -2.5 standard deviation (SD) < T < -1 SD, osteoporosis: T < -2.5 SD) (Figure 1).²³ Plain x-rays of the pelvis and lumbar spine (anteroposterior and lateral view) were examined to search for vertebral compression (Figure 2) or spontaneous fractures before DEXA. Cumulative dose of corticosteroids was obtained by multiplying all doses of corticosteroids prescribed either orally or parenterally by the total duration of disease and relative potency to hydrocortisone (CCD=Potency* Dose*Duration).²⁴

Table 1. Activity index for Chron's disease.

Disease activity index	Sum	X Factor	Subto
Total number of liquid or very soft stools in the previous 7 days or, for stoma patients, total number of bags emptied.		X 2	=
Sum abdominal pain/cramps ratings (total for previous 7 days): 0=none, 1=mild, 2=moderate, 3=severe		X 5	=
General well being (total for previous 7 days): 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible		X 7	=
Categories currently present and presumed to be related to Crohn's disease: 0=none; 1=yes			
0 = arthritis/arthralgia		X 20	=
0 = iritis/uveitis		X 20	=
0 = erythema nodosum/pyoderma gangrenosum/aphthous stomatis		X 20	=
0 = anal fissure, fistula, other abscess		X 20	=
0 = other fistula		X 20	=
0 = fever over 37,8°C during the previous 7 days		X 20	=
During the previous 7 days has patient received antidiarrheal therapy at least once: OR During the previous 7 days has patient received opiate therapy on each of the 7 days: 0 = no 1 = yes		X 30	=
Abdominal mass: 0 = none; 2 = questionable; 5 = definite		X 10	=
Hematocrit: Males: (47-Hct)=SUM Females: (42-Hct)=SUM		X 6	=
(Standard weight- actual body weight) Standard weight		X 100 (if this value is less than -10 then enter -10) X 1	=
TOTAL=			

Results

The study population included 103 patients (61 women and 42 men). Mean age was 49 ± 15 years (range 20-80). Sixty-seven patients had CD and 36 UC. Mean disease duration was 78.5 ± 65.6 months for CD and 60.3 ± 45.1 for UC. CD was ileal in 19.7% of patients, ileocolonic in 50.7% and colonic in 29.6%. For UC, the descending colon was involved in 78.3% of patients and 21.7% had pancolonic disease. The disease was active in 39.3% of patients with CD and 52.5% of those with UC. Intestinal resection had been performed in 21.7% of patients with CD and 4.7% of patients with UC had undergone colectomy with ileoanal anastomosis. 47 patients (31 CD and 16 UC) had received corticosteroid treatments. The cumulative dose was significantly higher in CD patients (5.4 ± 6.4 vs 2.5 ± 5.8 mg prednisone equivalent, $P < 0.05$). There was no history of corticosteroid treatment in 27 patients (36.9%). BMI was significantly lower in patients with CD (18.3 ± 5.7 vs 22.7 ± 5.3 kg/m², $P < 0.01$). Nineteen women were menopausal (8 CD, 11 UC). Vertebral compression was observed on the x-rays of eleven patients (all female). Six patients reported traumatic fracture of the wrist, two patients vertebral fractures. Among the 103 patients, 47.7% exhibited osteopenia of the femoral neck and 62.3% of the lumbar spine, with no significant difference between CD and UC. The prevalence of osteoporosis of the lumbar spine was significantly higher in CD patients (41.2% vs 8.7%, $P < 0.01$). There was a similar trend for the femoral neck (32.1% vs 13.1%, $P < 0.09$) (Table 5).

Discussion

Patients with IBD have an increased risk of developing osteoporosis, associated with fragility fractures and morbidity. The overall prevalence of osteoporosis in IBD is approximately 15% but is more prevalent with older age; the overall relative risk of fractures is 40% greater when compared to the general population.²⁵ Vertebral fractures often occur spontaneously or after minimal trauma and it is estimated that only one-third of vertebral fractures come to clinical attention.²⁶ X-ray images of the spine most commonly show wedge or compression deformities. A variety of studies have demonstrated both decreased bone mineral density (BMD) in patients with IBD, and increased rates of bone loss when followed longitudinally^{27,28} in comparison to healthy controls. The current Gold standard for measuring bone mass is dual-energy X-ray absorptiometry (DEXA). The prevalence of osteoporosis in IBD is very variable. This variation is related to dif-

Table 5. Results of our study.

	Crohn's disease	Ulcerative colitis
Number of patients	67	36
Mean disease duration	78.5 ± 65.6 months	60.3 ± 45.1 months
Activity of disease	39.3%	52.5%
Corticosteroid treatment	31 patients	16 patients
Body mass index	18.3 ± 5.7 Kg/m ²	22.7 ± 5.3 Kg/m ²
Women menopausal	8 patients	1 patient
Osteoporosis of lumbar spine	41.2%	8.7%
Osteoporosis of femoral neck	32.1%	13.1%

Paziente:	C	M	ID paziente:	4432
Data di nascita:	65,5 anni		Misurato:	19/08/08 11.40.57 (10,50)
Altezza / Peso:	158,0 cm 68,0 kg		Analizzato:	19/08/08 11.44.57 (10,50)
Sesso / Etnia:	Donna Bianco

Figure 1. Example of vertebral diphotonic x-ray absorptiometry.

ferences in study populations and methodologies used to measure BMD and to select explored sites. The prevalence of bone loss in our patients is in agreement with other studies using DEXA at the same bone sites. Some studies have reported lower BMD in CD compared with UC.^{29,30} Dresner Polack *et al.*³¹ noted a trend towards lower BMD in CD, in agreement with our findings where there was a trend towards lower BMD in the femoral neck in CD compared with UC. This bone loss was significantly in the lumbar spine. We also demonstrated a trend towards an association between disease activity and osteoporosis of the femoral neck and the spine, between gender and osteoporosis of the femoral neck (women were more osteoporotic), and between BMI and disease duration with spinal osteoporosis. This associ-

Figure 2. Radiographic exam of a vertebral compression.

ation was not observed with cumulative steroid dose. Ardizzone *et al.*³² demonstrated that disease duration affects bone loss in the femoral neck in patients with CD. Our study failed to demonstrate the role of corticosteroid therapy in bone loss, probably due to insufficient statistical power. In our study, 56 patients had never received steroids. Fifteen of them (25.9%) presented osteoporosis of the femoral neck and eight osteoporosis of the lumbar spine. Roux *et al.*³³ presented a longitudinal study where 34% of patients with significant bone loss had not received steroids during the study period. Ghosh *et al.*³⁴ reported a significant fall in BMD in CD patients before corticosteroid treatment.

Conclusions

Patients with IBD are at risk for reduced BMD and the development of osteoporosis. A screening DXA to assess BMD is warranted for patients with CD and ulcerative colitis who are postmenopausal, have had vertebral fractures, or have been on prolonged corticosteroids. In conclusion, our study demonstrated that IBD patients, and particularly CD patients, have a high risk of osteoporosis. This complication appears to be related to nutritional status, disease duration, and disease activity. These results suggest patients with IBD should be monitored and treated early for bone loss in order to reduce the risk of osteoporotic fractures.

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