International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2010; **13:** 259–265

ORIGINAL ARTICLE

The frequency of low bone mineral density and its associated risk factors in patients with inflammatory bowel diseases

Yasser EZZAT[1] and Khaled HAMDY[2]

[1]*Department of Rheumatology, Al-Fayoum University and* [2]*Department of Gastroenterology, Ain Shams University, Al-Fayoum, Cairo, Egypt*

Abstract

Objective: To detect the frequency and the predictive factors of low bone mineral density in inflammatory bowel disease (IBD) patients, so as to optimize bone mineral density (BMD) monitoring and treatment for those at risk.

Subjects and methods: Thirty Asian patients were included in this study and were divided into 18 patients with ulcerative colitis (UC), and 12 patients with Crohn's disease (CD). All patients were diagnosed by colonoscopy and histopathological biopsy and were subjected to routine laboratory investigations in addition to 25 hydroxy vitamin D levels as well as serum calcium, phosphorus and alkaline phosphatise. BMD was measured by using dual-energy X-ray absorptiometry (DEXA) scan at lumbar spine and femoral neck; predictive factors for BMD were analyzed by group comparison and step-wise regression analysis.

Results: There was increased frequency of osteoporosis and osteopenia involving the lumbar spine in patients with IBD being more common among CD patients than in the UC group. Positive correlations were found between low BMD measurements and vitamin D levels, body mass index (BMI) ($P < 0.001$) as well as steroid cumulative dose and duration of therapy ($P < 0.001$); stepwise regression analysis showed that CD and vitamin D deficiency are predictive factors for both osteoporosis and osteopenia ($P = 0.024$, $P = 0.027$, respectively).

Conclusion: Low BMD was found to be more frequent among patients with CD than UC; in addition CD and vitamin D deficiency act as predictive factors for low BMD. We recommend that calcium and vitamin D should be given to all IBD patients; in addition, bisphosphonate administration should be put into consideration.

Key words: bone mineral density, Crohn's disease, osteopenia, osteoporosis, ulcerative colitis.

INTRODUCTION

Low bone mineral density (BMD) is common in patients with inflammatory bowel diseases such as Crohn's disease (CD) or ulcerative colitis (UC). In cross-sectional studies, low BMD has been found in approximately 30% of these patients; mean BMD has been about 10% lower than that of matched normal subjects.[1,2] In several studies, osteoporosis (T-score < −2.5) has been noted in approximately 18–42% of patients with established inflammatory bowel diseases. The prevalence of osteopenia (T-score between −1 and −2.5) ranges 22–77%.[3] In some[4–6] but not all[2,7,8] studies, low bone mass is more

Correspondence: Dr. Yasser Ezzat, Lecturer, Department of Rheumatology, Al-Fayoum University, Al-Fayoum, Egypt.
Email: Yasser_ezzat74@yahoo.com

common in patients with CD than UC. Inflammatory bowel diseases (IBD) patients have up to 20% more fractures than the general population,[9] with an increased risk of both vertebral and hip fractures.[10] It is generally accepted that osteoporosis in IBD has a multifactorial pathogenesis, with potential risk factors such as reduced food intake, low body mass index (BMI), malabsorption and vitamin D deficiency, small bowel resection, hypogonadism, corticosteroid treatment,[11] smoking[12] and genetic factors.[13] It has not been elucidated how these factors interact in patients with IBD, but indications that these effects and associations are overshadowed by the effect of the inflammatory bowel disease itself,[4,14] came from several studies[15–17] in which patients did not have conventional risk factors for reduced BMD.

Considering the fact that newly diagnosed patients with untreated CD have reduced BMD, there is a strong case for suggesting that demineralization in patients with IBD occurs primarily as consequence of intestinal inflammation, for example the immune response, mediated by T-lymphocytes and other inflammatory cells like macrophages, leads to production of various pro-inflammatory cytokines such as interleukin (IL)-2 and tumor necrosis factor alpha (TNF-α), interleukins 1α and 1β (IL-1α, IL-1β), IL-6, IL-11, IL-17, transforming growth factor alpha, epidermal growth factor, and prostaglandin E2, where they play significant roles in osteoclast activation, stimulation of osteoblasts, apoptosis, and subsequently bone resorption.[18–21]

The clinical implications of reduced BMD in patients with inflammatory bowel diseases indicate significant morbidity due to spine, hip and radial fractures;[1] thus, this analysis of the frequency of low BMD and the risk factors for the development of both osteoporosis and osteopenia could help to identify those IBD patients who have a higher incidence of fractures, so as to optimize BMD monitoring and treatment for those at risk.

SUBJECTS AND METHODS

Our study included 30 Asian patients with IBD (CD and UC), confirmed by colonoscopy and histopathological biopsy and clinical criteria.[22] Our study showed that the terminal ileum was the part affected in all patients with CD, while the rectosigmoid part of the colon was involved in all patients with UC. The 30 patients were subjected to full history-taking, general and local examination and were divided into 18 patients with UC (60%) and 12 with CD (40%).

Our study was conducted on 11 men (36.7%) and 19 women (63.3%); five of the 19 women were postmenopausal (26.3%), two in CD group and three in UC group.

Out of the 30 patients, five were smokers, three in the UC group and two in CD group. The medications received by the patients including steroids (prednisolone), azathioprin (Immuran), mesalamine (Pentasa) and the anti-TNF infliximab (Remicade) were taken into consideration.

Extra-intestinal manifestations, including arthralgia and arthritis, cutaneous affection in the form of pyoderma gangerenosum or erythema nodosum, spinal affection, iritis and conjunctivitis, were included in the history-taking and examination, while past history of any serious diseases or of bowel resection were taken into consideration. In addition, plain X-ray was performed at the lumbosacral region and hips to detect any osteoporotic fractures.

Laboratory investigations were performed, including complete blood count, erythrocyte sedimentation rate by Westergreen method, quantitative C-reactive protein levels as indirect markers of disease activity, liver and kidney function tests (serum creatinine and albumin to evaluate nutritional status), serum calcium, phosphate and alkaline phosphatase, together with 25 hydroxy vitamin D (25-OHD).

For all our patients we performed BMI calculated as weight in kilograms divided by height in meter-squared (kg/m^2),[23] and BMD was determined by standard dual-energy X-ray absorptiometry (DEXA: Lunar Prodigy Series; GE Medical Systems, Raleigh, NC, USA) at the lumbar spine L2–4 and in the femur (femoral neck, Ward's triangle, femoral trochanter and shaft). The results of BMD were expressed as either Z scores or T scores. Z scores indicate the number of standard deviations (SD) from the normal sex- and age-specific mean value, while the T scores were calculated in relation to sex-matched healthy young adults at the age of peak bone mass.

According to the World Health Organization[24] criteria, osteoporosis was defined as a T score below −2.5 SD, and osteopenia was defined by a T score below −1 SD, but not more than 2.5 SD below the average.

Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 (SPSS Inc., Chicago, IL, USA) was used for analysis of data. Data was presented as number (%) and mean ± SD. Mann–Whitney test, which is a non-parametric test to compare two population means

from equal sample sizes was used for analysis of two quantitative datasets. Spearman correlation was used for detection of the relation between two variables. *P*-value was considered significant at < 0.05. Stepwise logistic regression analysis was performed; $P < 0.05$ was considered statistically significant.

RESULTS

Study population

A total of 30 Asian patients (11 males and 19 females) were enrolled in the study, 18 with UC and 12 with CD. The ages of the two tested groups ranged between 19 and 69 years with a mean of 40.6 ± 15.3 years and their disease duration ranged between 6 and 72 months with a mean of 70.2 ± 63 months. Nineteen patients received medications in the form of steroids expressed in mg of prednisolone (9 CD, 10 UC), as well as 14 patients using azathioprine at a dose of 50 mg; 11 patients were using mesalamine (Pentasa) 500 mg twice/daily, while nine patients were using infliximab (Remicade) 5 mg/kg. Patients' descriptive data as well as characteristics involving the two groups are shown in (Table 1), while comparison of the laboratory data involving the two groups is shown in (Table 2). None of the patients included in this study showed evidence of either extra-intestinal manifestation of inflammatory bowel diseases, history of bowel resection or evidence of symptomatic fracture.

Bone density studies

Our study showed an increased frequency of: osteoporosis in eight patients with IBD (26.7%), six CD (50%) and two UC (11.1%); and osteopenia in nine patients with IBD (30%), five CD (41.6%) and four UC (22.2%) (Fig. 1).

The lumbar spine was more affected than the femoral neck, emphasized by significant DEXA T score ($P = 0.006$) while the Z score was irrelevant.

Biochemical data

In our study we found that C-reactive protein levels were significantly increased ($P = 0.0302$) and that the levels of 25-OHD was lower in patients with CD. A significant positive correlation was found between low BMD and 25-OHD levels ($P < 0.001$) (Fig. 2), while there was no correlation between low BMD and serum calcium, phosphate and alkaline phosphatise, or other laboratory parameters.

Correlations between BMD and disease-related variables

No relationship was found between BMD and age, sex, duration of disease, smoking and menopause in women.

On the other hand, there was a positive significant correlation between BMD and BMI ($P = 0.042$), as well as steroid cumulative dose and duration of use in

Table 1 Descriptive data and characteristics of inflammatory bowel disease patients involving the two groups, Crohn's diseases and ulcerative colitis

	IBD ($n = 30$)	CD ($n = 12$)	UC ($n = 18$)	*P*-value*
Age in years†	40.6 ± 15.3	39.0 ± 14.7	44.2 ± 16.3	0.28
Sex (male/female)	11/19	4/8	7/11	0.33
Postmenopausal women (no.)	5/19	2/8	3/11	0.61
Smoking (no.)	5	2	3	0.77
Disease duration (months)†	70.2 ± 63	80.4 ± 72.1	61.8 ± 54.1	0.89
BMI (kg/m^2)†	22.5 ± 4.3	22.6 ± 3.9	23.6 ± 5.0	0.042
Femoral BMD(g/cm^2)				
Femoral T score†	−1.32 ± 0.98	−1.42 ± 0.99	−1.01 ± 0.9	0.53
Femoral Z score†	−0.30 ± 0.89	−0.42 ± 0.55	−0.24 ± 1.04	0.32
Lumbar BMD (g/cm^2)				
Lumbar T score†	−1.51 ± 0.99	−1.68 ± 1.02	−1.01 ± 0.74	0.0006
Lumbar Z score†	−0.52 ± 1.40	−0.50 ± 0.79	−0.54 ± 1.65	0.22
Corticosteroids (oral prednisolone/mg)				
Steroid therapy (percentage)	19 (63%)	9 (75%)	10 (55%)	
Cumulative steroid dose (g)†	26.7 ± 46.8	32.6 ± 56.7	20.6 ± 38.8	< 0.001
Duration of steroid therapy (months)†	40.8 ± 65.8	47.9 ± 69.7	32.6 ± 61.9	< 0.001

**P* value denotes differences between patients with ulcerative colitis and Crohn's disease. †Value are mean ± SD. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; BMI, body mass index.

Table 2 Comparison of laboratory data among the two studied groups of patients

Laboratory parameters	CD (n = 12)	UC (n = 18)	P-value
ESR 1st hour (mm/h)*	28.36 ± 11.9	30.3 ± 12.2	0.67
CRP (mg/L)*	23.7 ± 32.6	3.9 ± 5.0	0.03
Serum creatinine (mg/dL)*	0.98 ± 0.33	1.02 ± 0.35	0.89
AST (U/L)*	30.93 ± 8.56	30.8 ± 8.16	0.99
ALT (U/L)*	28.75 ± 7.59	28.8 ± 8.13	0.92
Serum albumin (g/L)*	36.4 ± 5.5	41.7 ± 3.5	0.13
Serum calcium (mg/dL)*	9.35 ± 0.68	9.42 ± 0.62	0.19
Serum phosphate (mmol/L)*	1.12 ± 0.17	1.08 ± 0.17	0.44
Serum alkaline phosphatase (U/L)*	83.9 ± 57.6	61.9 ± 17.8	0.68
25-hydroxy vitamin D (μg/L)*	18.7 ± 8.6	28.5 ± 11.7	0.004

*Values are mean ± SD. CD, Crohn's disease; UC, ulcerative colitis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase.

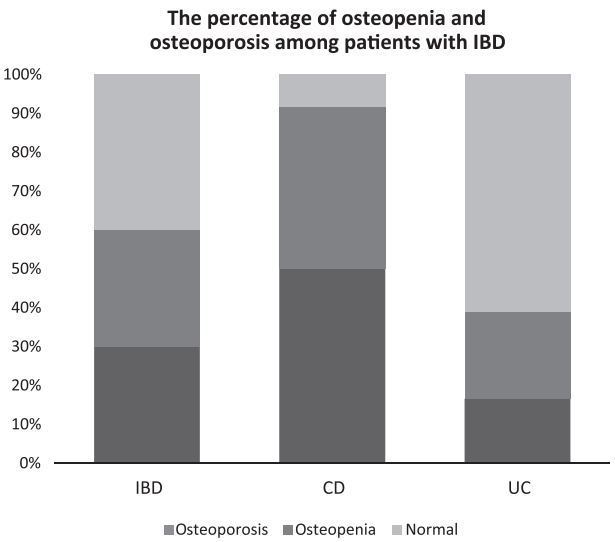

Figure 1 The percentage occurrences of osteoporosis and osteopenia in patients with inflammatory bowl disease (IBD). CD, Crohn's disease; UC, ulcerative colitis.

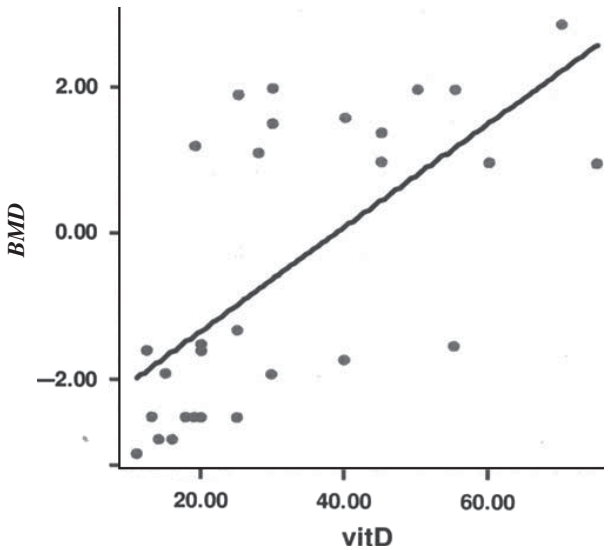

Figure 2 Correlation between bone mineral density (BMD) and 25-hydroxy vitamin D levels (vitD).

months ($P < 0.001$), while there was no significant correlation between low BMD and infliximab, mesalamine or azathioprine ($P \leq 0.6$, $P = 1.000$ and $P = 0.901$, respectively). Furthermore, there was significant negative correlation between the use of infliximab (Remicade) and prednisolone with C-reactive protein levels ($P = 0.011$, $P = 0.018$, respectively).

Stepwise regression analysis was done to identify predictive factors for osteoporosis and osteopenia and we found that patients with CD and vitamin D deficiency have a significant increase in the risk of developing both ostoeporosis and osteopenia ($P = 0.024$ and $P = 0.027$, respectively; Table 3).

DISCUSSION

Low BMD and increased risk of fracture in gastrointestinal diseases have a multifactorial pathogenesis. IBD has been associated with an increased risk of osteoporosis and osteopenia and epidemiologic studies have reported an increased prevalence of low bone mass in patients with IBD.[25]

Certainly, genetics plays an important role, along with other factors such as systemic inflammation, malnutrition and hypogonadism, glucocorticoid therapy and other lifestyle factors. At the molecular level, the pro-inflammatory cytokines that contribute to intestinal immune response in IBD are known to enhance bone resorption.

Table 3 Predictive factors for osteoporosis and osteopenia, as assessed by stepwise logistic regression

Significant predictors	Exp (B)	*P*-value
CD versus UC	7.857	0.024
Vitamin D	0.91	0.027
BMI	0.97	0.303
Steroid use	3.711	0.38
Age	1.31	0.79
Anti-TNF (Remicade)	0.438	0.56

Exp (B) indicates the increase in the risk of osteoporosis and osteopenia by the respective parameter. $P < 0.05$ was considered statistically significant. BMI, bone mineral density; CD, Crohn's disease; UC, ulcerative colitis; TNF, tumour necrosis factor.

In our study we tried to identify the incidence of bone loss in IBD and to correlate it to the different risk factors.

Our data recognized the increased frequency of both osteoporosis and osteopenia among inflammatory bowel disease patients; this coincides with the results of both Compston[1] and Pigot *et al.*[2] where they emphasized the close relation between osteoporosis and osteopenia in inflammatory bowel diseases in conjuction with common risk factors, including corticosteroid use, low BMI and vitamin D deficiency, which coincides with the findings of our current work. Also our study showed an increased in the incidence of both osteoporosis and osteopenia among our CD group more than our UC group (50.0% and 41.6%, respectively). This may be related to the facts shown in our present study regarding the increased incidence of low BMI and increased amount of steroids used in patients with CD. Emphasizing our data was the stepwise regression analyses performed, which showed that CD itself is a predictive factor for osteoporosis and osteopenia ($P = 0.024$).

In agreement was Ghosh *et al.*[6] and Staun *et al.*,[26] where they stated that BMD was reduced at the time of diagnosis in patients with CD but not in those with UC. Szathmari *et al.*[27] reported that CD patients without previous treatment appear to have significantly lower average BMD of the lumbar vertebrae when compared with UC patients.

The study by Pallone *et al.*[28] relates the increased incidence of osteoporosis involving patients with CD more than with UC, stating that although both diseases are the consequence of T cell activation, CD inflammation is thought to be triggered by TH1 cells, increasing the levels of TNF-α and IL-6, which stimulate osteoclast activity, resulting in bone remodelling impairment. In contrast, cytokines predominating in UC include IL-4 and IL-10, where their effect on bone remodeling are unknown. However, this difference between CD and UC has not been found in all series.[2,14]

In our present study, the lumbar spine T score was found to be more affected in the femoral neck ($P = 0.0006$), while Z score was irrelevant. There is no obvious reason for this, although it may be that treatment with corticosteroids results in more bone loss at the trabecular bone sites such as the lumbar spine.[29]

Our study also showed a positive significant correlation between low BMD and BMI ($P = 0.042$) which is in agreement with Noble *et al.*,[30] who stated that low BMI is one of the predictors of osteoporosis in patients with inflammatory bowel diseases.

In our current work, we have found a significant positive correlation between vitamin D levels and low BMD ($P \leq 0.001$). In addition, vitamin D levels were lower in the CD group ($P = 0.004$).

Stepwise regression analysis emphasized this data by showing that vitamin D deficiency is a predictive factor for osteoporosis and osteopenia ($P = 0.027$). This agrees with Leichtmann *et al.*[31] who stated that ileal and small intestine involvement in Crohn's disease, which is confirmed in our study, leads to increase in vitamin D malabsorption and subsequently more bone loss, while Driscoll *et al.*[32] stated that 65% of patients with Crohn's disease had low serum (25-OHD) concentration. This problem is in part due to malabsorption, disturbed enterohepatic circulation of vitamin D, reduced dietary intake and reduced exposure to sunlight.[4] On the other hand, Schoon *et al.*[33] did not find any significant difference between reduced vitamin D concentrations in recently diagnosed CD and UC patients. However, BMD is reduced in many patients who are vitamin D-sufficient.[7,15] Thus, vitamin D deficiency is not the main cause of osteoporosis in most patients with inflammatory bowel disease.

In our present study, none of the patients had a history of bowel resection. Multivariate analysis further revealed a history of bowel resections as a significant predictive variable of low BMD values. This issue is controversial in the literature, since some studies have described bowel resections as a risk factor[34] whereas others have not found a correlation.[35,36]

Although we did not find any evidence of fracture among our patients, Vestergaard *et al.*[37] and Klaus *et al.*[10] had found that asymptomatic vertebral fractures are common in patients with CD.

In our present work, we have found an increase in the percentage of patients taking steroids in CD (75%)

more so than in UC patients (55.5%), which is related to the inflammatory activity in patients with CD confirmed by histopathological biopsies and the increase of C-reactive protein levels, indicating the need for a higher dose of steroids to control the inflammatory cascade. In addition we have found a significant negative correlation between low BMD and steroid cumulative dose and duration of use ($P < 0.001$).This confirms previous observations showing that systemic corticosteroids are a risk factor for osteoporosis in inflammatory bowel diseases patients.[11,34] The main mechanism by which corticosteroids cause bone loss is impairing osteoblast function, inducing osteoblast apoptosis, reducing intestinal calcium absorption and increasing renal excretion of calcium.[38,39]

In our current work, we have found that there was significant negative correlation between the use of infliximab (Remicade), prednisolone and C-reactive protein levels ($P = 0.011$ and $P = 0.018$, respectively), which highlights the effect of these medications in improving patient condition, and explains the absence of any extra-intestinal manifestations in this study due to the control of the disease-related inflammatory activity.

A limitation of our study was the small number of patients, which needs to be further evaluated in a large cohort of patients to determine the exact prevalence of osteoporosis and osteopenia among inflammatory bowel disease subjects. In addition, our study needed a longer period of follow-up to evaluate closely the long-term effect of the medications on BMD findings, especially infliximab (Remicade).

CONCLUSION

Crohn's disease and vitamin D deficiency may act as predictive factors for osteoporosis and osteopenia. In addition, the increased frequency of both osteoporosis and osteopenia in this study underlines the importance of monitoring by DEXA scan, not only for high-risk patients, but all inflammatory bowel disease patients, and to start initiating appropriate treatment with calcium and vitamin D in patients with low BMD values. Whether anti-resorptive therapy with bisphosphonates should be started in patients with low BMD should be evaluated and put into consideration.

REFERENCES

1 Compston JE, Judd D, Crawley EO, *et al.* (1987) Osteoporosis in patients with inflammatory bowel disease. *Gut* **28**, 410–5.

2 Pigot F, Roux C, Chaussade S, *et al.* (1992) Low bone mineral density in patients with inflammatory bowel disease. *Dig Dis Sci* **37**, 1396–403.

3 Ali T, Lam D, Bronze MS, Humphrey MB (2009) Osteoporosis in inflammatory bowel disease. *Am J Med* **122**, 599–606.

4 Jahnsen J, Falch JA, Aadland E, Mownickel P (1997) Bone mineral density is reduced in patients with crohn's disease but not in patients with ulcerative colitis: a population based study. *Gut* **40**, 313–9.

5 Gokhale R, Favus MJ, Karrison T, *et al.* (1998) Bone mineral density assessment in children with inflammatory bowel disease. *Gastroenterology* **114**, 902–11.

6 Ghosh S, Gowen S, Hannan WJ, Ferguson A (1994) Low bone mineral density in crohn's disease, but not in ulcerative colitis at diagnosis. *Gastroenterology* **107**, 1031–9.

7 Bjarnason I, Macpherson A, Mackintosh C, *et al.* (1997) Reduced bone density in patients with inflammatory bowel disease. *Gut* **40**, 228–33.

8 Lee SH, Kim HJ, Yang SK, *et al.* (2000) Decreased trabecular bone mineral density in newly diagnosed inflammatory bowel disease patients in Korea. *J Gastroenterol Hepatol* **15**, 512–8.

9 Siffledeen JS, Siminoski K, Jen H, Fedorak RN (2007) Vertebral fractures and role of low bone mineral density in crohn's disease. *Clin Gastroenterol Hepatol* **5**, 721–7.

10 Klaus J, Armbrect G, Steinkamp M, *et al.* (2002) High prevalence of osteoporotic vertebral fractures in patients with crohn's diseaes. *Gut* **51**, 654–8.

11 Dear KL, Compston JE, Hunter JO (2001) Treatment for Crohn's disease that minimise steroid doses are associated with a reduced risk of osteoporosis. *Clin Nutr* **20**, 541–6.

12 Silvennoinen JA, Lehtola JK, Niemela SE (1996) Smoking is a risk factor for osteoporosis in women with inflammatory bowel disease. *Scand J Gastroenterol* **31**, 367–71.

13 Schulte C, Goebell H, Roher HD, Schulte KM (2001) Genetic determinants of IL-6 expression levelsdo not infl uence bone loss in inflammatory bowel disease. *Dig Dis Sci* **46**, 2521–8.

14 Abitbol V, Roux C, Chaussade S, *et al.* (1995) Metabolic bone assesment in patients with inflammatory bowel disease. *Gastroenterology* **108**, 417–22.

15 Bernstein CN, Seeger LL, Sayre JW, Anton PA, Artinian L, Shanahan F (1995) Decreased bone mineral density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. *J Bone Miner Res* **10**, 250–6.

16 Bischoff SC, Herrmann A, Goke M, Manns MP, Von zur Muhlen A, Barban G (1997) Altered bone metabolism in inflammatory bowel disease. *Am J Gastroenterol* **92**, 1157–63.

17 Pollak RD, Karmeli F, Eliakim R, Ackerman Z, Tabb K, Rachmilewitz D (1998) Femoral neck osteopenia in

patients with inflammatory bowel disease. *Am J Gastroenterol* **93**, 1483–90.
18 Redlich K, Hayer S, Ricci R, *et al.* (2002) Osteoclasts are essential forTNF-alpha-mediated joint destruction. *J Clin Invest* **110**, 1419–27.
19 Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN (2000) The incidence of fracture among patients with inflammatory bowel disease. *Ann Intern Med* **133**, 795–9.
20 Manolagas SC (1998) The role of IL-6 type cytokines and their receptors in bone. *Ann NY Acad Sci* **840**, 194–204.
21 Keen RW, Woodford-Richens KL, Lanchbury JS, Spector TD (1998) Allelic variation at the interleukin-1 receptor antagonist gene is associated with early postmenopausal bone loss at the spine. *Bone* **23**, 367–71.
22 Lennard-Jones JE (1989) Classification of inflammatory bowel disease. *Scand J Gastroenterol* **24** (Suppl 170), 2–6.
23 Must A, Dallal GE, Dietz WH (1991) Reference data for obesity (1991) 85th and 95th percentiles of body mass index (wt/ht2) and triceps skinfold thickness. *Am J Clin Nutr* **53**, 839–46.
24 World Health Organization (1994) *Assessment of Fracture Risk and Its Application to Screening of Post-Menopausal Osteoporosis*. Technical report series 843. WHO, Geneva.
25 Rodriguez-Bores L, Barahona-Garrido J, Yamamoto-Furusho JK (2007) Basic and clinical aspects of osteoporosis in inflammatory bowel disease world. *J Gastroenterol* **13**, 6156–65.
26 Staun M, Tjellesen L, Thale M, Schaadt O, Jarnum S (1997) Bone mineral content in patients withCrohn's disease. Alongitudinal study in patients with bowel resections. *Scand J Gastroenterol* **32**, 226–32.
27 Szathmari M, Pronai L, Tulassay Z (1998) Altered bone metabolism in inflammatory bowel disease. *Am J Gastroenterol* **93**, 848–9.
28 Pallone F, Monteleone G (1998) Interleukin 12 and Th1 responses in inflammatory bowel disease. *Gut* **43**, 735–41.
29 De Jong DJ, Corstens FH, Mannaerts L, van Rossum LG, Naber AH (2002) Corticosteroids-induced osteoporosis: does it occur in patients with Crohn's disease? *Am J Gastroenterol* **97**, 2011–5.
30 Noble CL, McCullough J, Ho W, *et al.* (2008) Low body mass not vit D receptor polymorphism predict osteoporosis in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* **27**, 588–96.
31 Leichtmann GA, Bengoa JM, Bolt MJG, Sitrin MD (1991) Intestinal absorption of cholecalciferol and 25-hydroxy cholecalciferol in patients with both crohn's disease and intestinal resection. *Am J Clin Nutr* **54**, 548–53.
32 Driscoll RH Jr, Meredith SC, Sitrin M, Rosenberg IH (1982) Vitamin D defiency and bone disease in patients with crohn's disease. *Gastroenterology* **83**, 1252–8.
33 Schoon EJ, Blok BM, Geerling BJ, Russel MG, Stockbrugger RW, Brummer RJM (2000) Bone mineral density in patients with recently diagnosed inflammatory bowel disease. *Gastroenterology* **119**, 1203–8.
34 Von Tirpitz C, Steder-Neukamm U, Glas K, *et al.* (2003) Osteoporosis in infl ammatory bowel disease results of a survey among members of theGerman Crohn's and Ulcerative Colitis Association. *Z Gastroenterol* **41**, 1145–50.
35 Silvennoinen JA, Karttunen TJ, Niemela SE, Manelius JJ, Lehtola JK (1995) A controlled study ofbone mineral density in patients with inflamatory bowel disease. *Gut* **37**, 71–6.
36 Stockbrugger RW, Schoon EJ, Bollani S, *et al.* (2002) Discordance between the degree of osteopenia and the prevalence of spontaneous vertebral fractures in Crohn's disease. *Aliment Pharmacol Ther* **16**, 1519–27.
37 Vestergaard P, Krogh K, Rejnmark L, *et al.* (2000) Fracture risk is increased in crohn's disease but not in ulcerative colitis. *Gut* **46**, 176–81.
38 American College of Rheumatology Task Force on Osteoporosis Guidelines (1996) Recommendations for the prevention and treatment of glucocorticoid inducedosteoporosis. *Arthritis Rheum* **39**, 1791–801.
39 Van Staa TP, Leufkens HG, Abenhaim L, *et al.* (2000) Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)* **39**, 1383–9.