

## CLINICAL STUDY

# The prevalence and risk factors for osteoporosis in patients with inflammatory bowel disease

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**Abstract:** *Aim:* Osteoporosis is a known chronic complication of inflammatory bowel diseases (IBD).

The aim of our study was to describe the prevalence of reduced bone mineral density (BMD) in IBD patients and to identify crucial risk factors for osteoporosis.

*Methods:* The cohort consisted of 76 IBD patients, 40 with Crohn's disease (CD) and 36 with ulcerative colitis (UC). Clinical characteristics of every patient were recorded, i.e. age, sex, duration of the disease, clinical behavior, location of disease according to Montreal classification, surgeries, steroid medication, sIBDQ, and smoking habits. We examined the serum 25-hydroxyl vitamin D3 (25-OHD3) in each patient. The BMD was determined by dual-energy X-ray absorptiometry (DXA) at the lumbar spine and femoral neck.

*Results:* Osteoporosis was documented in 10 IBD patients (13.2 %), while osteopenia in 35 of them (46.1 %). Patients with CD have significantly lower femoral Z score than patients with UC. Femoral Z score was strongly associated with disease duration, and in CD patients suffering from stricturing form, with ileic or ileocolic location and history of proctocolectomy or total colectomy. Patients with osteoporosis had a significantly lower level of 25-OHD3 than patients with normal BMD.

*Conclusion:* Patients with long disease duration and those suffering from stricturing form of CD with ileic/ileocolic location and history of proctocolectomy/total colectomy are at higher risk of developing osteoporosis than other IBD patients. The high proportion of osteopenia/osteoporosis in our study underlines the importance of BMD measurement in all IBD patients as a base for initiating the appropriate treatment (Tab. 1, Fig. 3, Ref. 63). Full Text in PDF [www.elis.sk](http://www.elis.sk).

**Key words:** Crohn's disease, ulcerative colitis, bone density, osteoporosis, risk factors, vitamin D deficiency.

**Abbreviations:** CD – Crohn's disease, BMD – bone mineral density, BMI – body mass index, IBD – inflammatory bowel disease, CI – confident interval, DXA – dual-energy X-ray absorptiometry, ECLIA – electrochemiluminescence immunoassay, SD – standard deviation, sIBDQ – short inflammatory bowel disease questionnaire, UC – ulcerative colitis

Inflammatory bowel disease (IBD), i.e. Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory intestinal diseases. Extraintestinal complications of IBD affecting the musculoskeletal system are frequent, occurring in 20–50 % of patients (1). Osteoporosis and increased risk of fractures (RR 1.4 versus general population) are a serious problem (2, 3, 4). The prevalence of osteopenia in IBD has been reported in 22–77 % of patients and osteoporosis in a range of 12–42 % (5–7).

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The etiology and exact mechanism of bone mass loss in IBD has not been properly clarified. There are several possible risk factors such as age (8, 9), low body mass index (BMI) (8, 10), malabsorption, vitamin D and calcium deficiencies (11, 12), bowel resection (9, 13), hypogonadism, corticosteroid treatment (9, 12, 13, 14, 15), smoking (16), reduced physical activity and genetic factors (17).

The results of studies evaluating the possible risk factors for osteoporosis are various. The study of Tsironi et al on 122 IBD patients documented several independent risk factors for low BMD, namely age  $\geq 55$  years (OR 5.08, 95% CI 1.90–13.57,  $p=0.001$ ), cumulative lifetime dose of prednisolon  $\geq 5$  g (OR 3.41, 95% CI 1.50–7.73,  $p=0.004$ ) and low BMI (8). Study of van Hogenzad on 145 CD patients shows that the ileum resection was the most predictive factor for osteoporosis: RR 3.84 (CI 1.24–9.77,  $p=0.018$ ), followed by age: RR 1.05 (CI 1.02–1.08,  $p<0.001$ ) and current or past glucocorticoid use: RR 1.94 (CI 0.92–4.10,  $p=0.08$ ) (9). There are several multivariate studies showing also BMI as a significant risk factor for low BMD (8, 10, 18). Vitamin D deficiency has been reported more frequently in patients with ulcerative colitis and Crohn's disease compared with healthy population (19, 20). In their study, McCarthy et al. documented the correlations between the lower vitamin D status in patients with CD and elevated levels of markers of bone turnover (21).

Although there is evidence that long-term corticosteroid therapy reduces the BMD (9, 12, 13, 14, 15, 22, 23, 24), some of stud-

ies have suggested that BMD in IBD is unrelated to corticosteroid use (25, 26, 27, 28, 29). Considering the fact that newly diagnosed patients already have a reduced bone mineral density (BMD), there is a strong case for suggesting that demineralization in patients with IBD occurs primarily as a consequence of intestinal inflammation. Activated T-lymphocytes and other inflammatory cells like macrophages lead to the production of various pro-inflammatory cytokines and mediators which interfere with bone regulatory systems like RANK/RANKL/OPG and thus change the rate of bone formation and bone resorption (30, 31, 32, 33, 34). These findings suggest that intestinal inflammation itself plays an important role in the development of osteopenia/osteoporosis, and that low BMD cannot be attributed solely to the treatment with steroids.

The aim of our study was to analyze the prevalence of bone density changes in cohort of IBD patients. Further we wanted to study the risk factors associated with decreased BMD that could move us to understanding the etiology of bone loss and thus to identifying IBD patients who are at higher risk of fractures.

## Patients and methods

### Study design and patients

The study cohort consisted of 76 adult patients with IBD (46 with CD, 30 with UC) followed up at the Department of Gastroenterology, University Hospital Bratislava, Ruzinov. The clinical characteristics of the cohort are given in Table 1. All patients included in our study signed an informed consent to the research. The diagnosis of IBD was established on the basis of clinical, radiological, endoscopic and histological findings. The disease duration was calculated as time elapsed from the onset of symptoms, which may have preceded the clinical diagnosis by several years. The data on glucocorticoid use (daily average dose of prednisone or prednisone-equivalent dose in milligrams, cumulative dose of prednisone in grams or prednisone-equivalent dose and total lifetime of using glucocorticoids in months), disease location and clinical behavior according to Montreal classification and details of surgical intervention (ileum and/or colon resection) were obtained from patients' records. Patients filled in a detailed questionnaire concerning the onset of symptoms of IBD and smoking habits. Disease activity was established by a short inflammatory bowel disease questionnaire (sIBDQ) (35). The level of 25-OHD3 was measured by an electrochemiluminescence immunoassay (ECLIA) - Roche and the levels were not corrected for seasonal variation. No patient of the cohort took a substitution of vitamin D3 at the time of measurement of 25-OHD3.

### Bone mineral density measurements

BMD was measured in all 76 patients from our cohort at the lumbar spine (L1–L4) and hip (total hip) by dual X-ray absorptiometry (DXA - Hologic Discovery). BMD results are expressed in g/cm<sup>2</sup> and in T and Z-score. The T score is the number of standard deviations above or below the mean value for young adults of the same sex, whilst the Z score is the number of standard deviations above or below the age-related mean value. We used The WHO

definition for osteopenia/osteoporosis: osteopenia as a T score of  $\leq 1$  but  $\geq 2.5$ , whilst osteoporosis is defined as a T score of  $-2.5$  or lower (36). We decided to use femoral and lumbar Z score in the analysis of relationship between bone mineral density and observed clinical parameters.

### Statistical analysis

Data are presented as a  $\pm$  SD for the normally distributed parameters according to Shapiro-Wilk's test or as a median and interquartile range for data showing departures from normality. Frequencies are expressed as counts and percentages of the total of observations. The standard Student t test and one-way ANOVA with post-hoc Tukey–Kramer test were employed for detailed multiple comparisons between means (for more than two groups) in the case of data showing no departures from normality (according to Shapiro–Wilk's test). Group differences in the variables that showed the right-skewed distribution were analyzed with the relevant nonparametric tests: Mann–Whitney U test, Kruskal–Wallis test (more than two groups) and post-hoc all-pairwise Conover–Inman test. The chi-square or alternatively Fisher's exact test were used to compare the observed frequencies in the investigated variables (groups). Simple regression analysis was employed to estimate linear dependence between dependent variable of interest and the corresponding regressor. To estimate the associations between variables showing departures from normality, we used Spearman rank correlation ( $\rho$ ) (for testing the null hypothesis of independence between two variables). All p values cited are two-sided alternatives; differences resulting in a p value of less or equal to 0.05 were declared statistically significant. For statistical analysis, we employed the statistical program StatsDirect 2.7.8 software.

### Characteristics of patients

Twenty (45.67 %) patients with CD, among whom none had UC, underwent bowel resection. The most frequently performed operation in these cases was the resection of the ileum either in isolation (n=13) or in combination with right hemicolectomy (n=2). Five CD patients underwent proctocolectomy or total colectomy (Tab. 1).

## Results

### Prevalence of osteoporosis

The prevalence of low BMD in our cohort was 45/76 (59.2 %) patients (Fig. 1).

Osteoporosis was observed in 10/76 (13.2 %) patients, including 7/46 (15.2 %) CD patients and 3/30 (10 %) UC patients. Osteopenia was observed in 35/76 (46 %), including 22/46 (47.8 %) CD patients and 13/30 (43.3 %) UC patients.

The lumbar spine was more affected than the femoral neck, emphasized by DXA T score below  $-1$  SD (52.6 % vs 27.6 %,  $p=0.0018$ ).

The prevalence of low BMD among patients, who were never been treated with corticosteroids, was (22.36 %).

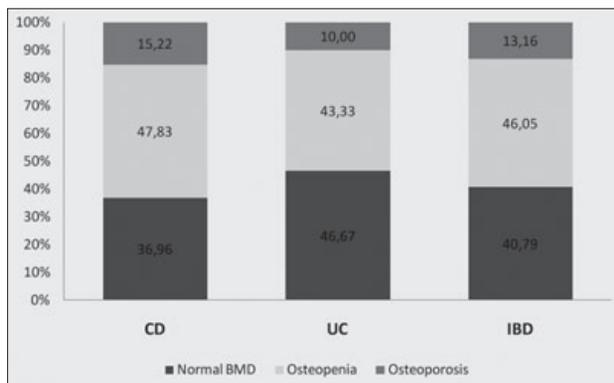
There was a significant difference in the femoral Z score between patients with CD ( $-0.8 \pm 1.05$ ) and UC ( $0.0 \pm 1.05$ ,  $p=0.004$ ).

**Tab. 1. Clinical characteristics of the cohort.**

Clinical characteristic	All cohort (n=76)	Ulcerative colitis (n=30)	Crohn disease (n=46)
Male/female (%)	36/40 (47/53%)	15/15 (50/50%)	21/25 (47/53%)
Age (range) /yr/	36 (19–73)	47 (19–73)	36 (19–70)
Duration of disease (median, range) /yr/	8.2 (1.4–41.2)	10.5 (1.5–41.2)	7.7 (1.4–35.2)
Age at diagnosis /yr/			
≤ 16 (%)	14 (18.4%)	5 (16.7%)	9 (19.6%)
17- 40 (%)	44 (57.9%)	11 (36.7%)	33 (71.7%)
≥41 (%)	18 (23.7%)	14 (46.6%)	4 (5.2%)
Location of disease			
Terminal ileum	-	-	18 (39.1%)
Ileal and colon (%)	-	-	7 (15.2%)
Colon only (%)	-	-	20 (43.4%)
Upper GIT	-	-	1 (2.17%)
Proctitis(%)	-	8 (26.7%)	-
Distal colitis (%)	-	6 (20%)	-
Pancolitis (%)	-	16 (53.3%)	-
Clinical behaviour in CD			
Non-stricturing, non-penetrating	-	-	14 (30.43%)
Stricturing	-	-	14 (30.43%)
Penetrating	-	-	18 (39.13%)
Severity in UC			
Mild	-	10 (33.3%)	-
Moderate	-	12 (30%)	-
Severe	-	8 (26.7%)	-
History of bowel resection	20 (26.3%)	0	20 (45.67%)
Ever smokers	18 (24%)	11 (36.7%)	7 (15.21%)
History of glucocorticoid treatment	50 (65.8%)	21 (70%)	29 (63%)
Daily average dose of prednisone (mg)(median, range)	16 (0–32)	17.3 (0–26)	15 (0–32)
Cumulative dose of prednisone* (g)(median, range)	2 (0–42)	2.6 (0–42)	1.8 (0–16.8)
Total lifetime of using glucocorticoids (in months)	7 (0–121)	9 (0–28)	6 (0–121)
25-OH vitamin D3**(median,range)	18.6 (0–35.1)	17.9 (0–35.1)	18.6 (7.8–46)
Femoral Z score (median, range)	-0.6 (-3.7–2.3)	-0.3 (-1.8–2.3)	-0.9 (-3.7–2.1)
Lumbar Z score (median, range)	-0.85 (-3.8–2.2)	-0.3 (-3.7–2.2)	-1.0 (-3.8–1.5)

\*The steroid dose is expressed as grams of prednisone or as prednisone-equivalent dose.

\*\* serum level of 25-OH vitamin D3 in ng/ml, yr: year



**Fig. 1. Prevalence of osteopenia and osteoporosis in 76 IBD patients determined by DXA at lumbar spine and femoral neck.**

### Univariate analysis of clinical risk factors

#### All IBD patients

There was a significant difference correlation between the femoral Z score and the duration of disease ( $r = -0.265$ ,  $p = 0.02$ ).

#### Subgroup of CD patients

Significantly lower femoral Z score had CD patients with stricturing type of disease compared to non-stricturing, non-penetrating

(median Z score  $-1.25$  vs  $-0.35$  SD,  $p = 0.007$ ) or penetrating type of disease (median Z score  $-1.25$  vs  $-0.5$  SD,  $p = 0.04$ ) and those with location of disease at ileum, or ileocolon comparing to colon location (ileum vs colon : medians Z score  $-0.85$  vs  $-0.1$ ,  $p = 0.006$ ; ileocolon vs colon : medians Z score  $-0.75$  vs  $-0.1$ ,  $p = 0.009$ ) (Figs 2 and 3).

Patients with CD who had undergone proctocolectomy or total colectomy had significantly low medians of femoral Z score compared with patients with intact gut ( $-0.4$  vs  $-0.9$ ,  $p = 0.005$ ).

CD patients with ileum resection isolated or with right hemicolectomy had a higher tendency to lower medians of Z score than patients with intact gut, but these findings have not been statistically significant ( $p = 0.09$ ).

#### Subgroup of UC patients

There was no significant difference between Z score of hip/lumbar spine in UC after dividing patients according to location and behavior of the disease.

In all IBD there was no relationship between Z score of hip/lumbar spine and age, sex, smoking habits, sIBDQ, history of oral glucocorticoid use ever, cumulative steroid dose of prednisone and total lifetime use of glucocorticoids in months. We found a significant positive correlation between the average dose of prednisone and femoral BMD ( $r = 0.27$ ,  $p = 0.025$ ).

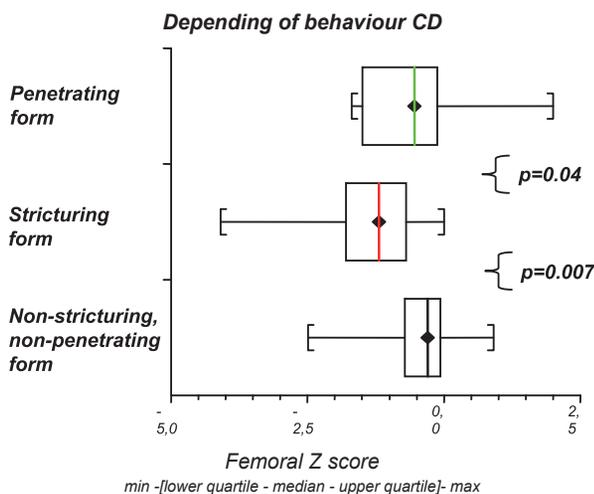


Fig. 2. Box & whisker plot of medians of femoral Z scores.

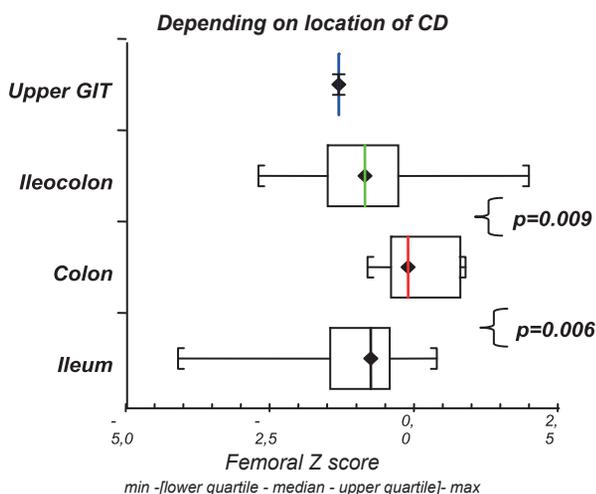


Fig. 3. Box & whisker plot of medians of femoral Z scores.

#### Analysis of 25-OHD3

There were 69/76 (91.10 %) IBD patients with vitamin D3 deficiency (<30 ng/ml). Very low (<10 ng/ml) level of 25-OHD3 was observed in 13/76 (9.6 %) patients. No difference in level of 25-OHD3 was found between CD and UC.

IBD patients with osteoporosis had a significantly lower serum level of 25-OHD3 than patients with normal bone density (14.2 vs 17.5 ng/ml,  $p=0.02$ ).

#### Discussion

Inflammatory bowel disorders are associated with several factors potentially deleterious to the skeleton but the exact relationship between this cytokine-mediated disorder and increased risk of osteoporosis and fractures remains unclear. Moreover, the results of studies dealing with risk factors for reduced BMD in IBD are very controversial. The questions we posed in this study were aimed at assessing the prevalence of osteoporosis in our cohort of IBD

patients, as well as at identifying the clinical features of IBD most closely associated with bone demineralization.

The focus of our study is limited in several aspects. Firstly, we did not apply strict exclusion criteria, mostly as to older population and postmenopausal women. This selection bias could have shifted the ratio of rates of altered bone density in lumbar spine and those of hip towards the former. Secondly, the relatively small size of the study group did not enable us to analyze fractures and multivariate analysis. Mainly in UC it could affect the results after categorizing the patients to subgroups according to behavior and location of disease. Other weakness of our study stems from the fact that we did not include in it the analysis of effect of azathioprin or biologics on bone mineral density. As is known from recent literature, this immunosuppressive therapy, mostly anti-TNF therapy, may have a positive influence upon bone turnover in IBD patients (37, 38).

We found 59 % of IBD patients to be affected by osteopenia and 13 % of patients to be affected by osteoporosis. This is comparable with recent studies where the prevalence of osteoporosis ranged between 12 to 15 % (7, 8, 10, 13). Other studies reported even higher prevalence of osteoporosis in IBD, namely of around 26 to 40 % (5, 28, 29). As a possible explanation we suggest a higher rate of postmenopausal women in one study (5) or higher percentage of patients under long-term glucocorticoids therapy in cohorts of older studies (28, 29) when compared to our study.

It should be noted, that the proportion of IBD patients with osteopenia in our study reached 59 %. This underlines the importance of careful assessment of all IBD patients for BMD as well as subsequent initiation of appropriate preventive treatment in those with pathological BMD. Recent literature contains clear evidence of the clinical benefit from bisphosphonates in osteoporosis associated with IBD, while calcium and vitamin D should remain the baseline treatment in osteopenic and osteoporotic patients (39, 40).

In our IBD cohort, the lumbar spine was found to be affected more often by pathological BMD than hip. There are just few studies with the same findings (13, 41, 42); most of published studies report higher prevalence of osteoporosis at the femoral neck (9, 28, 29, 43). This discrepancy could have been influenced by a selected bias of our tertiary gastroenterologic center.

Patients with CD had a significantly lower femoral Z-score than patients with UC. This finding is confirmed by other studies (7, 18, 27, 44). Jahnsen et al (45) reported that mean Z-scores were significantly lower in patients with CD compared to patients with UC or healthy patients, while the impact of glucocorticoid treatment leading to low BMD seems to be more significant in UC (44).

In agreement with de Jong DJ et al (41) and other studies (29, 46, 47, 48) we confirmed a significant negative correlation between BMD and disease duration in both diagnoses. The duration of disease may have a measurable impact on bone metabolism in IBD for several reasons including chronic systemic inflammation and drug therapy. Corticosteroids are more often given to patients with frequent relapse of the disease but an increased level of inflammatory cytokines seems to be an important independent risk factor for accelerated bone loss (49, 50).

The valuable asset of our study is the analysis of behavior and location of CD with BMD. These findings are not yet well known

in literature. In our study, the stricturing form of disease was significantly more associated with lower Z score than its non-penetrating, non-stricturing or penetrating form. We suggest that these data may result from a reduced food intake related to intestinal obstruction, higher rate of malabsorption, longstanding intestinal inflammation and longer disease duration occurring typically in the stricturing form of CD.

Location of disease may contribute to low BMD. There is a report of lower BMD in CD patients with small bowel disease (47) although other studies failed to show such effects (9, 13, 16, 40). Our study documented no relationship between BMD and location of UC; however the location of CD in ileum or ileocon, typically associated with the stricturing form, was in strong correlation with lower femoral Z score.

Patients of our cohort who had undergone bowel resections had significantly lower medians of Z score compared with patients with intact gut. In CD, the highest risk was mostly associated with proctocolectomy or total colectomy often performed in patients with severe disease activity. CD patients with ileum resection isolated or with right hemicolectomy had a trend for lower Z score than patients with intact gut but these findings have not been statistically significant. Results of studies evaluating the bowel surgery as a potential risk factor for developing osteoporosis are controversial. In several published studies, the history of bowel resection is not considered as a risk factor (16, 28, 46), whereas other studies assessing patients who had undergone ileal resection reported that ileum resection was one of the predictive factors for osteoporosis in patients with CD (9,13, 41, 47).

The skeletal effects of glucocorticoids are well documented with the main brunt of bone loss observed at trabecular sites (23, 24, 51, 52). The role of glucocorticoids in the pathogenesis of osteoporosis especially in IBD is complex. Whilst some studies have shown a clear relationship between lifetime corticosteroid dose in IBD and vertebral fracture rate (4, 52) or low BMD (14, 16, 43, 45, 47) other studies have suggested that BMD is unrelated to corticosteroid use (25, 26, 27, 28, 29). Our study did not find a negative relationship between the cumulative or total lifetime dose of glucocorticoids and BMD, moreover almost 23 % of patients with osteopenia/osteoporosis have never used glucocorticoids during their disease. We also documented a significant positive correlation between the average dose of prednisone and femoral BMD implicating that intestinal inflammation itself probably plays an important role in the development of osteopenia/osteoporosis, and that low femoral BMD cannot be attributed solely to treatment with glucocorticoids. Recent studies on patients with rheumatoid arthritis, a disease with analogical effect of chronic inflammation on bone loss due to production of pro/inflammatory mediators interfering with bone regulatory systems, have even shown a protective effect of long-term low-dose prednisone on inflammation and BMD (53, 54).

The other important finding of our study was that IBD patients with osteoporosis had a significantly lower serum level of 25-OHD3 than patients with normal bone density. There are several possible explanations for the relationship between vitamin D3, BMD and disease activity. It may be a consequence of reduced

efficiency of intestinal absorption of vitamin D, disrupted enterohepatic circulation, reduced dietary intake or reduced sun exposure (55, 56), but it can also be a pathological effect of low vitamin D3 on immune system and therefore disease activity (59, 60). Poor vitamin D status has already been linked to auto-immune diseases like diabetes type 1, multiple sclerosis, rheumatoid arthritis, as well as IBD (55, 59, 60). We documented a high percentage of vitamin D3 deficiency with no difference between CD and UC. Very low (<10 ng/ml) level of 25-OHD3 of was observed in nearly 10 % of IBD patients. The hypothesis that vitamin D deficiency is not only a consequence but also a cause playing an important role in the development of intestinal inflammatory process, is recently supported by findings of the essential function of vitamin D receptors (VDRs). The VDRs contribute to the protection of colonic mucosa by regulating the intestinal homeostasis (62). Although a significant progress has been achieved concerning the role of vitamin D and its receptor, the exact mechanism is not yet fully understood and its study could lead to interesting findings concerning the pathological immune response in IBD (61, 62, 63).

In conclusion we confirmed high prevalence of osteopenia/osteoporosis among IBD patients. Reduced BMD, especially in total hip, was strongly associated with the duration of disease and low serum level of vitamin D3. The most important finding of our study was that the stricturing form and ileic or ileocolic locations of CD appear to be the major risk for bone loss relating probably to intestinal obstruction, longstanding intestinal inflammation and longer duration typically occurring in this form of CD.

Our study found no negative relationship between glucocorticoids treatment and BMD, moreover we documented a significant positive correlation between the average dose of prednisone and femoral BMD implicating that intestinal inflammation itself probably plays an important role in bone loss, and that a low femoral BMD cannot be attributed solely to treatment with glucocorticoids.

On the basis of our findings we conclude that demineralization of bone in IBD patients occurs primarily as a consequence of intestinal and systemic inflammation, and secondarily as a consequence of complex relationship between disease severity, location, malabsorption, drug therapy and other risk factors.

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