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# Bone Loss in Patients with Inflammatory Bowel Disease: A Prospective Study

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**Abstract.** To assess the rate of bone loss in patients with inflammatory bowel disease, we prospectively studied 35 patients (17 women) aged 36 ± 13 (range 17–60) years, 14 of whom had Crohn's disease and 21 with ulcerative colitis (including 12 with ileoanal anastomosis). Bone mineral density was measured by dual-energy X-ray absorptiometry at the lumbar spine and femoral neck. The follow-up was 19 ± 8 months. During this period, 14 patients received oral steroids. Lumbar bone density changes expressed as a percentage per year were −3.1 ± 4.9%, −6.4 ± 7.5% and +2.0 ± 4.0% in Crohn's disease and ulcerative colitis without and with ileoanal anastomosis respectively ($p = 0.007$). The same pattern was observed at the femoral neck. Mean annual lumbar bone density changes were −6.2 ± 7.0% and +0.9 ± 3.9% in patients with and without steroids during follow-up ($p = 0.002$). We conclude that patients with inflammatory bowel disease are at risk of lumbar and femoral bone loss. However, bone loss is not observed in patients with ileoanal anastomosis.

**Keywords:** Bone mineral density; Ileoanal anastomosis; Inflammatory bowel disease; Osteoporosis

## Introduction

Patients with inflammatory bowel disease (IBD) are at risk of bone disease, osteoporosis (as a result of corticosteroid therapy, reduced physical activity, inflammatory factors, calcium malabsorption, vitamin D deficiency, hypogonadism, etc.) or osteomalacia (as a result of small bowel disease or resection, sclerosing cholangitis, etc.) [1,2]. A low bone mineral density (osteopenia) has been reported in cross-sectional studies [3–5]. Its prevalence depends on the definition of osteopenia, the site of bone measurements and the technique used for bone density measurement, as well as the proportion of patients studied with small bowel resection or vitamin D deficiency. It is estimated that 31%–59% of patients with IBD have osteopenia [3–5]. Increased rates of bone loss have been reported at the lumbar spine and radius using quantitative computed tomography or single photon absorptiometry [6–8]. We undertook this prospective study to assess the rate of bone loss at the lumbar spine and femoral neck in patients with IBD, using dual-energy X-ray absorptiometry.

## Methods

### *Patients*

Thirty-five consecutive patients with IBD who were attending the gastroenterology department (17 women, 18 men; mean age 36.1 ± 12.8 years, range 17–70 years), were followed for a period of 19 ± 8 (range 4–31)

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**Table 1.** Characteristics of patients at baseline (mean ± SD)

| | Ulcerative colitis | Crohn's disease | Ileoanal anastomosis | $p^a$ |
|---|---|---|---|---|
| Number | 9[b] | 14[b] | 12[b] | |
| Age (years) | 38.6±13.6 | 36.1±15.7 | 34.3±8.6 | 0.74 |
| Disease duration (months) | 63.2±73.38 | 77.4±76.3 | 80.0±61.9 | 0.84 |
| Sex (M/F) | 6/3[b] | 5/9[b] | 7/5[b] | |
| BMI (kg/m$^2$) | 20.99±3.42 | 21.16±3.77 | 22.05±4.05 | 0.76 |
| Variation in weight (%) | −9.64±7.1 | −2.67±10.68 | −1.13±12.83 | 0.16 |
| Corticosteroids | | | | |
| Number | 3[b] | 8[b] | 8[b] | |
| Total dose (mg) | 3125±3468 | 14560±20757 | 7554±3591 | 0.57 |
| Daily dose (mg/day) | 8.25±8.97 | 11.27±15.01 | 5.72±3.56 | 0.59 |
| *Z*-scores | | | | |
| Lumbar spine | −0.37±1.36 | −1.12±1.38 | −0.96±0.96 | 0.34 |
| Femoral neck | −0.28±1.37 | −1.01±1.85 | −0.57±0.97 | 0.52 |
| *Z*-scores <−1 SD | 4[b] | 7[b] | 4[b] | |
| *Z*-scores <−2 SD | 2[b] | 4[b] | 1[b] | |
| Biochemical assessment | | | | |
| ESR (mm/h) | 42.2±20.5 | 45.3±34.9 | 16.7±16.1 | 0.05 |
| Albumin (g/l) | 34.4±7.9 | 36.3±5.3 | 43.6±4.9 | 0.01 |
| Osteocalcin (ng/ml) | 3.16±2.20 | 2.86±2.02 | 3.52±3.15 | 0.81 |
| 25(OH)D (ng/ml) | 7.80±3.85 | 17.23±12.78 | 11.33±5.38 | 0.04 |
| 1,25(OH)$_2$D (pg/ml) | 30.72±10.36 | 27.58±10.08 | 30.21±9.60 | 0.71 |
| PTH (pg/ml) | 28.8±9.7 | 27.2±17.9 | 29.8±10.3 | 0.86 |

ESR, erythrocyte sedimentation rate.
[a] Statistical significance of the difference between groups determined by ANOVA.
[b] Number of patients.

months. For 2 patients the period between the two measurements was 4 and 6 months respectively. At baseline, clinical assessment included, as previously described [5], body mass index (BMI, weight in kilograms divided by height in meters squared), variation in weight between the beginning of the disease and baseline (in %) and dietary calcium inquiry.

Characteristics of the patients at baseline are reported in Table 1. Of the 35 patients, 14 had Crohn's disease (8 patients with small intestinal disease), 9 had ulcerative colitis, and 12 had undergone coloproctectomy with ileoanal anastomosis (IAA) after ulcerative colitis. In the women hormonal status was clinically assessed by menstrual history. None of the premenopausal women had any menstrual irregularities. None of the patients had bone or muscular pain. None was bedridden at the time of evaluation. Mean dietary calcium intake was 677, 732 and 713 mg per day in patients with Crohn's disease, ulcerative colitis and IAA respectively.

Anteroposterior and lateral radiographs of the thoracic and lumbar spine were reviewed for vertebral fractures at baseline only. They revealed vertebral fractures in 3 patients (2 women, 1 man; 47, 61 and 70 years old). One patient was taking vitamin $D_2$ (daily dosage 2000 IU) and 6 (3 IAA, 3 Crohn's disease) were receiving oral calcium supplements (1 g daily).

Twenty-five patients had previously received corticosteroid therapy. The total lifetime dose of prednisone at the start of the study was 10 500 ± 13 000 mg (median 7162 mg), and the mean daily dose (calculated as the ratio between the cumulative dose and duration of the disease) was 8.8 ± 9.7 mg (median 6.25 mg).

### *Biochemical Assessment*

Biochemical assessment was performed at baseline only. Serum concentrations of calcium, phosphorus, alkaline phosphatases and serum albumin, and the erythrocyte sedimentation rate, were measured by standard methods. Total parathyroid hormone (PTH(1–84), normal range 10–60 pg/ml) was measured by a commercially available two-site immunoradiometric assay (Intact PTH, Nichols Institute, San Juan Capistrano, CA). Osteocalcin (normal range 2–7 ng/ml) was measured by a radioimmunoassay (Osteocalcin $^{125}$I RIA Incstar, Incstar Corporation, Stillwater, MN), using bovine reagents. Serum 25-hydroxyvitamin D concentration (25(OH)D, normal range 5–30 ng/ml) was measured by a competitive protein binding assay after extraction and chromatographic purification; the coefficient of variation for this method was 9% for low and normal values [9]. Serum 1,25-dihydroxyvitamin D (1,25(OH)$_2$D, normal range 15–60 pg/ml) was measured by a radioreceptor assay involving extraction and purification on C180H cartridges; calf thymus receptor specific for both 1,25(OH)$_2$D$_2$ and 1,25(OH)$_2$D$_3$ was used in a non-equilibrium competitive protein binding assay (Incstar, MN). Within- and between-assay variation is less than 10% [9].

Biochemical markers of bone metabolism were

normal, with no difference between the three groups. The level of 25(OH)D was normal, although lower in the ulcerative colitis group than in the other groups. Patients with IAA differed from the other two groups with respect to erythrocyte sedimentation rate and serum albumin levels (Table 1).

### *Bone Mineral Density Assessment*

Bone mineral density (BMD, in g/cm$^2$) was measured by dual-energy X-ray absorptiometry (DXA; Hologic QDR 1000) at L2–4 and at the proximal left femur. Femoral neck was chosen as representative of cortical bone. BMD values of trochanter and intertrochanteric areas, as well as Ward's triangle, were calculated by the software. BMD results were expressed for each site as the number of standard deviations from normal values corrected for age and sex ($Z$-score). The control population consisted of 397 normal females who have been described previously [10]; normal values for men were supplied by Hologic. All the measurements were performed by the same observer, with strict standardized positioning of the patients. For each patient, the measurements were analyzed with the same region of interest. In our department, short-term precision of BMD measurements in young subjects, calculated from five measurements with repositioning in 10 subjects, is 1% and 1.2% at lumbar spine and femoral neck respectively. Thus, at the individual level, we considered as statistically significant a lumbar spine BMD change of at least 2.8% [11].

### *Statistical Analysis*

Results were expressed as the mean ± SD (range). During the follow-up, the variation in BMD was plotted as a mean annual variation. Differences between groups were analyzed using ANOVA (between three groups) and Student's unpaired $t$-test or the Wilcoxon and Mann–Whitney tests (between two groups). Linear regression analysis and Spearman's rank correlation test were used as appropriate. In all statistical analyses, $p<0.05$ was considered significant.

## Results

### *Study Course*

During the follow-up 14 patients received oral steroids; the total dose was 4436 ± 3870 mg (median 4930 mg) and the daily dose 24.20 ± 14.96 mg (median 18.4 mg). Patients with IAA remained in remission and did not receive steroids between the two evaluations. Surgery was performed in 8 patients with ulcerative colitis: coloproctectomy with ileoanal anastomosis for 2 patients and subtotal colectomy with ileorectal anastomosis for the 6 others.

### *Bone Mineral Density Assessment*

Lumbar bone mineral density at baseline was 1.038 ± 0.147, 0.903 ± 0.146 and 0.974 ± 0.109 g/cm$^2$ ($p=0.06$) in patients with ulcerative colitis, Crohn's disease and IAA respectively. Femoral neck density was 0.854 ± 0.156, 0.768 ± 0.209 and 0.835 ± 0.118 g/cm$^2$ ($p=0.58$) in these groups respectively.

Mean $Z$-scores at baseline in the three groups are reported in Table 1. Fifteen patients (43%) had a $Z$-score below −1 SD, and 7 (20%) had a $Z$-score below −2 SD. Among patients with IAA, there was a positive correlation between lumbar spine or femoral neck $Z$-scores and the time elapsed since coloproctectomy ($r=0.66$, $p=0.003$, and $r=0.5$, $p=0.05$, respectively). In patients who had previously received corticosteroids, there was no correlation between prednisone cumulative or daily dose and lumbar or femoral neck BMD.

During the follow-up, in the whole population, mean annual lumbar BMD change was −2.31 ± 6.14% (−19, +12). These changes were −6.42 ± 7.54%, −3.08 ± 4.91% and +1.96 ± 3.96% in the ulcerative colitis, Crohn's disease and IAA groups respectively ($p$ = 0.007). At the femoral neck, mean annual bone density changes were −6.91 ± 6.57%, −5.59 ± 11.12% and +1.01 ± 6.51% in these groups; this difference

**Table 2.** Comparison between patients with and without significant bone loss (defined as a mean annual decrease of more than 2.8%) at lumbar spine level during follow-up (mean ± SD)

| | No significant bone loss | Significant bone loss | $p$[a] |
|---|---|---|---|
| Number | 23[b] (66) | 12[b] (34) | |
| Diagnosis | | | |
| Ulcerative colitis | 4[b] | 5[b] | |
| Crohn's disease | 7[b] | 7[b] | |
| Ileoanal anastomosis | 12[b] | 0[b] | |
| *Baseline* | | | |
| $Z$-scores | | | |
| Lumbar spine | −1.07±1.24 | −0.36±1.27 | 0.18 |
| Femoral neck | −1.01±1.38 | −0.13±1.67 | 0.24 |
| ESR (mm/h) | 38.2±33.8 | 30.8±23.4 | 0.53 |
| Serum albumin (g/l) | 40.14±6.35 | 34.50±7.28 | 0.10 |
| Osteocalcin (ng/ml) | 3.1±2.4 | 3.2±2.5 | 0.92 |
| 25(OH)D (ng/ml) | 11.53±5.65 | 16.76±14.47 | 0.66 |
| 1,25(OH)$_2$D (pg/ml) | 32.48±9.66 | 24.27±8.83 | 0.05 |
| PTH(1–84) (pg/ml) | 33.05±13.42 | 21.41±10.99 | 0.02 |
| *Follow-up* | | | |
| Variation in weight (%) | 5.8±6.1 | 4.5±7.6 | 0.83 |
| Steroid intake | 6[b] (26) | 8[b] (67) | |
| Steroids | | | |
| Total dose (mg) | 4375±4082 | 4579±3533 | 0.73 |
| Daily dose (mg/day) | 26.01±21.09 | 20.42±8.73 | 0.56 |

ESR, erythrocyte sedimentation rate.
[a] Statistical significance of the difference between groups determined by Mann–Whitney's test.
[b] Number of patients (percentage).

approached statistical significance ($p = 0.058$). At the three other femoral sites there was a wide spread of individual changes, without any significant difference between the three groups. Twelve of 35 (34%) patients had significant lumbar bone loss (>2.8%). Comparisons between these patients and the others are reported in Table 2. There was no difference between these two groups with respect to age, sex, calcium intakes and BMI at baseline. Among the biochemical parameters measured at baseline, only $1,25(OH)_2D$ and PTH levels were correlated with subsequent changes in lumbar BMD ($r = 0.36$, $p = 0.04$, and $r = 0.37$, $p = 0.04$, respectively). No patient with IAA had a significant bone loss. A significant increase in lumbar BMD was observed in 4 patients.

Mean annual lumbar spine density changes were $-6.23 \pm 7.04\%$ in patients with steroids and $+0.87 \pm 3.94\%$ in patients without steroid treatment ($p = 0.002$). At femoral neck level, mean annual bone density changes were $-8.97 \pm 9.57\%$ and $+0.20 \pm 5.78\%$ in these groups respectively ($p = 0.002$). We did not find any correlation between BMD changes and corticosteroid therapy during the follow-up ($p = 0.71$).

## Discussion

Our study suggests an increased rate of bone loss in patients with ulcerative colitis and Crohn's disease, at the lumbar spine as well as the femoral neck. Patients with IAA, cured of the inflammatory disease and without corticosteroid therapy, no longer show decrease in BMD.

The rate of bone loss we observed in our young patients is higher than the reported rates of bone loss in normal premenopausal women. Mean ± SD annual rate of change at the lumbar spine, measured by dual photon absorptiometry in premenopausal women, is $-0.79 \pm 1.5\%$ [12]. In our study, women did not show a difference in bone density changes compared with men, and no premenopausal women had amenorrhea during the follow-up.

No patient in the study had symptoms or signs of osteomalacia. 25(OH)D and alkaline phosphatase levels were normal in our patients. Normal vitamin D metabolites have been observed in patients with Crohn's disease, even after small bowel resection of an average of 105 cm [1]. A reduced plasma level of 25(OH)D has been reported, but in undernourished patients [13]. A recent bone histomorphometric study showed only mild mineralization defect in patients with IBD and osteopenia [14]. We did not find increased circulating levels of PTH, even in corticosteroid-treated patients. Patients with IBD are at risk of decreased bone formation rate and a negative remodelling balance [14]. Low-turnover osteoporosis is considered the most common form of metabolic bone disease in patients with gastrointestinal disorders [15]. Accordingly, osteocalcin levels were low in our patients. However, the importance of BMD change seems to be modulated by the initial bone metabolism, as indicated by the lower levels of PTH and $1,25(OH)_2D$ in patients who subsequently lose more bone. This point needs further study.

The pathogenesis of osteopenia associated with inflammatory bowel disease is incompletely understood, but corticosteroid therapy is a likely contributory factor in some patients. In restrospective studies, lumbar bone density measured by dual photon absorptiometry varied from $-9.6\%$ to $-19.5\%$ in patients treated with corticosteroids compared with controls [16]. These drugs are considered to have a more deleterious effect on trabecular than on cortical bone. However, evidence of bone loss at the femoral neck has been found [17], and our findings suggest that DXA can easily assess bone loss at cortical as well as trabecular sites in patients with IBD. Retrospective studies fail to demonstrate any correlation between the cumulative or daily dose of corticosteroid and a change in BMD. This may be due to the difficulty in retrospective calculation of these doses. On the other hand, low-dose corticosteroids may have no deleterious effect on bone, as shown in patients with rheumatoid arthritis. Lastly, there is the well-known difference in individual effects of corticosteroid therapy [17]. Twenty-six percent of our patients on steroid therapy did not lose bone, whereas 34% with significant bone loss did not receive steroid therapy during the follow-up period.

Initial serum albumin concentration was lower in patients with significant bone loss. In patients with IBD, hypoalbuminemia may result from mucosal protein loss or malnutrition. However, we did not observe any malnutrition in our patients, and hypoalbuminemia is likely to be related to the intestinal disease. Prior investigations have revealed that the mucosa of IBD patients synthesizes a number of inflammatory mediators in increased amounts [18]. It has also been demonstrated that patients with IBD have high circulating levels of inflammatory factors such as interleukin 1, interleukin 6 and tumor necrosis factor [19]. These circulating factors may act on bone, because they are potent stimulators of osteoclasts and bone resorption. Cells of the monocyte–macrophage series serve as local regulators of bone turnover, and interleukin 1 secretion by peripheral blood monocytes is increased in osteoporosis [20]. In our study, no patient with IAA showed bone loss. Coloproctectomy with ileoanal anastomosis was performed in patients with the most severe or longest duration of ulcerative colitis. However, removal of risk factors such as steroid therapy and inflammatory disease activity may have stopped bone loss in these patients.

An increased rate of bone loss can be observed in patients with IBD at clinically relevant sites. Our results in patients with IAA suggest that better control of the inflammatory process, and the use of newer corticosteroids with reduced effects on bone metabolism, may help prevent skeletal deterioration. Concomitant use of hormone replacement therapy has been shown to be effective in postmenopausal women with IBD [21].

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