

# Osteoporosis, osteopenia, and inflammatory bowel disease: lessons from a real-world study

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Osteoporosis is defined by the World Health Organization (WHO) as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”.<sup>1</sup> Osteopenia is characterized by a decreased bone mass density (BMD), but not to the extent of osteoporosis.<sup>1</sup> In healthy individuals, genetics, physical activity, body mass index (BMI), age, diet, and ethnicity are all known determinants of osteoporosis.

The inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the gut. Although the pathogenesis of IBD, as well as of its extraintestinal manifestations, remains to be elucidated, an increasing interest is focused on the potential role of microbiota in the interaction between the immune system and environmental factors in genetically predisposed individuals.<sup>2</sup>

Osteoporosis has been observed in both types of IBD, Crohn disease (CD) and ulcerative colitis (UC). However, data about its prevalence in different populations of IBD patients showed much variability due to different study designs and sample sizes as well as to diverse geographic locations. A recent meta-analysis has shown that the global risk of fracture, the most severe osteoporosis consequence, was increased in patients with IBD compared with controls (relative risk, 1.38; 95% CI, 1.11–1.73). This increase was confined to vertebral fractures (odds ratio, 2.26; 95% CI, 1.04–4.90), and did not involve other sites. Nevertheless, BMD showed a significant decrease for IBD patients versus controls at all sites.<sup>3</sup> The 3 main pathogenetic factors involved in the association between IBD and osteopenia or osteoporosis are the impaired absorption of nutrients that are essential for the bone, such as vitamin D and calcium, the chronic inflammatory process affecting both the bowel and the bone, and the treatment with steroids. Age, sex, and body weight are important factors in the risk profile of a patient with IBD.<sup>4</sup>

The availability of dual energy X-ray absorptiometry (DEXA) has contributed significantly to the increasing awareness of IBD-associated bone diseases, but considering that BMD is only a surrogate outcome, actually the WHO fracture risk assessment model (FRAX) is considered more appropriate to estimate a patient's 10-year probability of developing a hip fracture or a major osteoporotic fracture. Focusing on historical studies, a survey of the Danish Crohn's and Colitis Association has reported that in IBD patients (383 with CD and 434 with UC), the fracture risk was increased in the case of CD (relative risk, 1.7) but not of UC, compared with the control group (n = 635).<sup>5</sup> A population-based study was performed at the University of Manitoba, Canada, using a specific IBD database, which included files of all 6027 residents with IBD. Fracture risk was found to be approximately 1 per 100 patient-years, with an overall fracture risk of 1.41, when compared with 60 270 controls. Fracture risk was comparable between CD and UC patients, as well as between men and women, and increased significantly above the age of 60 years.<sup>6</sup>

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Krela-Kaźmierczak et al<sup>7</sup> evaluated, in a prospective study, the prevalence of osteoporosis and osteopenia in a cohort of Polish IBD patients, as well as the influence of BMI, disease duration, number of hospital stays, and use of steroids on BMD. By using DEXA, the authors found osteoporosis of the lumbar (L<sub>2</sub>–L<sub>4</sub>) spine (T-score) in 11.7% of the patients with CD and in 3.8% of those with UC, whereas that of the femoral neck (FN), in 5.8% and 2.9% of the patients with CD and UC, respectively. Osteopenia occurred in 35.9% (FN) to 36.9% (lumbar) of CD patients, and in 25.7% (FN) to 29.5% (L<sub>2</sub>–L<sub>4</sub>) of UC patients. In CD patients, BMI was associated with L<sub>2</sub>–L<sub>4</sub> and FN BMD and with L<sub>2</sub>–L<sub>4</sub> T-score, whereas FN T-score correlated with BMI. Among UC patients, the cumulative dose of

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steroids correlated with L<sub>2</sub>-L<sub>4</sub> T-score, FN BMD, T-score, and Z-score, whereas the disease duration correlated with FN BMD, and the FN T-score, with the number of hospital stays and FN BMD. The authors concluded that osteopenia and osteoporosis are frequent in patients with IBD, both in women and in men, and that BMD correlates with BMI in all patients and with the use of steroids (cumulative prednisone dose), as well as with the duration of the disease and the number of hospital stays in patients with UC.

Although the methodology of the study raises some critical concerns (since age and BMI are risk factors for osteoporosis, cases and controls should have been matched using the propensity score matching or performing a multivariate analysis), these data give us a diagnostic and therapeutic lesson.

From a diagnostic point of view, IBD patients should be investigated for osteopenia and osteoporosis, both at baseline and during the follow-up, despite the lack of consensus in this setting. After the diagnosis, the aim should be to understand if the extent and duration of IBD, as well as the features of the patients, are associated with bone damage. During the follow-up, the aim should be to understand the potential influence of steroid treatment on BMD.

From a therapeutic standpoint, several considerations should be made. Since, clearly, it is much easier to prevent bone loss than to rebuild bone mass, the key question is if the normalization of vitamin D and calcium in serum influences BMD and reduces the risk of fractures in IBD patients.

Normal vitamin D metabolism is critical in developing and maintaining normal BMD and, in association with adequate calcium levels, has been shown to prevent fractures in older individuals. In Norway, it has been reported that 27% of CD and 15% of UC patients had subnormal serum levels (<30 nmol/l) of 25-hydroxyvitamin D.<sup>8</sup> Although this suggests that supplementation with vitamin D is necessary in a considerable number of IBD patients, it should be highlighted that other studies performed in the same context have shown a lack of correlation between the levels of serum vitamin D metabolites and BMD.<sup>9</sup>

Another question refers to the impact of steroids on the pathogenesis of bone disease. Although steroid use is a major factor in IBD-associated bone loss, it is difficult to separate the effects of these drugs from those of the disease activity. Steroids have multiple mechanisms on bone metabolism. They impair osteoblast function, reduce intestinal calcium absorption, while increasing renal calcium excretion, induce secondary hyperparathyroidism, enhance osteoclast bone resorption via the production of interleukin 1, and precipitate hypogonadism.<sup>10</sup> This leads to a low bone turnover. The dose-effect relationship of steroid use and fracture rates has been shown by revisiting the Manitoba IBD cohort. CD patients with fractures were significantly more likely to have used steroids in the 2 years prior to

this event than those without fractures. Moreover, steroid use was not more common among UC patients with fractures.<sup>11</sup> These data suggest that when CD subjects are sufficiently ill to warrant steroids, they are at increased risk for fractures. The greatest effects are seen in the initial months of treatment, especially in areas of trabecular bone. Although it has been reported that prednisone doses as low as 2.5 mg/d increase the risk for fracture,<sup>12</sup> it is unclear if this relates to the drug itself or to the disease for which the steroid was given. In fact, it has been hypothesized that it might be the active inflammation or other factors related to disease severity, and not steroids per se, that lead to fractures. In any case, in a large research database covering mixed general practice patient population, subjects who suspended oral steroids showed a rapid decrease in fracture risk towards baseline shortly after stopping them.<sup>13</sup> According to these data, a population-based study determined the BMD among premenopausal women who developed IBD before or after puberty. Surprisingly, the average BMD was no different between the 2 groups and only 4% had BMD in the osteoporotic range.<sup>14</sup> It is possible that, during the periods of disease remission and/or corticosteroid "holiday", there is sufficient opportunity to catch up on bone deposition with normalization in bone mass.

In their consensus on extraintestinal manifestations of IBD, the European Crohn's and Colitis Organisation reported that osteoprotective therapy is advisable in patients with low BMD and/or additional risk factors. The latter include systemic steroid therapy. Vitamin D should be maintained in the recommended range using a dose of ~1000 IU/d or a higher dose in case of vitamin D deficiency. Supplemental calcium should be given only if the dose of dietary calcium is lower than 800 mg/d.<sup>4</sup> This strategy has been shown to be able to increase BMD in patients with IBD of 0.76% over 4 years.<sup>15</sup>

In conclusion, the work by Krela-Kaźmierczak et al<sup>7</sup> offers a real-world picture of the actual association between osteopenia or osteoporosis and IBD. Their findings alert clinicians to the importance of identifying patients with low BMD, with the aim to treat and prevent fractures as a consequence of unidentified bone disease. Future studies should focus on the fracture events or on the FRAX score, comparing IBD patients with a well-characterized control group.

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