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REVIEW PAPER

Bone Metabolism in Inflammatory Bowel Disease and Celiac Disease

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Abstract
Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitecture deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Several gastrointestinal disorders have been associated with osteoporosis including inflammatory bowel disease and celiac disease. Different factors can explain low bone density and fractures in these patients.

Keywords Inflammatory bowel disease · Celiac disease · Bone mineral density · Fractures · Osteoporosis

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitecture deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Several gastrointestinal disorders have been associated with osteoporosis including inflammatory bowel disease (IBD) and celiac disease.

Inflammatory Bowel Disease

IBD and Osteopenia/Osteoporosis

The incidence and prevalence of IBD is increasing worldwide. Crohn's disease (CD) and ulcerative colitis (UC) are the principal types of inflammatory bowel disease. The exact cause is unknown, but IBD is the result of a defective immune system. IBD is characterized by chronic inflammation in the gastrointestinal tract. The inflammatory process can affect several organs, including bone. Several studies conclude that patients with IBD, are at an increased risk of osteoporosis (20–50%) and fractures (1.3 to 2.5 times) [1–3]. IBD is associated with a decreased bone mineral density (BMD) [4]. Recommendations regarding osteoporosis screening by DXA in IBD patients according to current guidelines do not differ from those for the general population and are based on risk factors [5–7]. The prevalence of osteoporosis and osteopenia in patients with IBD is variable. Some studies consider up to 70% of patients have low BMD [8–10], others find a lower prevalence (19.4%) [11]. Patients with CD had a significantly lower bone mineral density than patients with UC [12]. A recent meta-analysis of BMD changes in 1338 patients with IBDs and 808 controls showed a significant decrease in BMD and Z-scores for IBD patients compared to controls at all sites (mean difference of -0.06 g/cm^2 at lumbar spine, -0.04 g/cm^2 at femoral neck and -0.08 g/cm^2 at total femur) [9].

IBD and Fractures

The reduction in BMD is associated with an increased risk of fractures. In a study with 6027 subjects with IBD (mean age 36 and 42 years for CD and UC, respectively) and 60,270 controls, the rate of fracture among people with IBD was 40%. People with IBD had a significantly increased incidence of fractures at spine (incidence rate ratio [IRR], 1.74 [95% CI, 1.34 to 2.24]; $p < 0.001$), hip (IRR, 1.59 [CI, 1.27 to 2.00]; $p < 0.001$), wrist/forearm (IRR, 1.33 [CI, 1.11 to 1.58]; $p = 0.001$), and rib (IRR, 1.25 [CI, 1.02 to 1.52]; $p = 0.03$) [13]. A case-control analysis conducted in the British General Practice Research Database showed a 40% increased risk of hip fracture in patients with IBD after adjustment for the use of corticosteroids [14]. In a study with 231,778 fracture cases and 231,778 age- and sex-matched controls, the patients with

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IBD had an increased risk of vertebral fracture (OR 1.72; CI 1.13–2.61) and hip fracture (OR 1.59; CI 1.14–2.23) [15]. In a meta-analysis (9 studies with 203,193 healthy controls and 42,568 IBD patients) the global risk of fracture was increased for patients with IBDs compared to controls (RR = 1.38, 95% CI 1.11–1.73; $p = 0.005$). The risk of vertebral fractures was significantly increased with IBDs (OR 2.26, 95% CI 1.04–4.90; $p = 0.04$). The risk of hip fractures was increased but not significantly in IBDs (OR 1.29, 95% CI 0.84–1.96; $p = 0.24$). Fractures in IBD developed in relatively young people (ranged from 33.4 to 48.9 yrs. old). This fact is especially important because fractures in patients with IBD worsen their quality of life prematurely [9]. Also, the higher the age the higher risk of fractures (1.3-fold mayor for with every 10-yr increment of age) [16]. Patients with CD seem especially vulnerable to fractures, both vertebral and hip [17, 18].

Contributors to Bone Loss in IBD

Different factors can explain low bone density in patients with IBD like nutritive deficiency, malabsorption (deficiency in vitamin D, calcium and vitamin K), low body mass index (BMI), chronic inflammatory state, limited physical activity, decreased skeletal muscle mass, extensive small-bowel disease or resection, treatments (especially corticosteroids), coexisting comorbidities and genetic abnormalities [19–23].

There is a relationship between systemic inflammation and bone fragility. Mucosal inflammation and the underlying inflammatory process in IBD lead to bone loss [24]. Intestinal chronic inflammation leads to the activation of T lymphocytes and production of pro-inflammatory cytokines, including tumor necrosis factor (TNFα) that activates the RANK-RANK-ligand pathway which leads to the promotion of bone resorption and a decrease in bone formation [25]. Activity indexes (CDAI and MTWAI) in IBD are predictors of osteoporosis in some works [11]. Several studies analyzed different polymorphism of genes that may be involved in the pathogenesis of IBD and the decrease in bone mass [26–28] among them Nucleotide-binding Oligomerization Domain-containing protein (NOD)2 [19]., cytokine IL-6 [29], osteoprotegerin (OPG) [30], TNF-α [31] and vitamin D receptor (VDR) [32].

Male patients with IBD have a trend towards lower BMD [19]. The reasons for this difference across gender in IBD are unclear but glucocorticoid-induced hypogonadism has also been proposed as a possible mechanism in males with IBD [33].

Vitamin D deficiency is common in IBD patients. Up to 91% of patients with IBD have a vitamin D3 deficiency (< 30 ng/ml). The prevalence is similar in CD and UC [34]. Also, pregnant women with IBD are at an increased risk of vitamin D insufficiency [35].

The relationship between vitamin D deficiency and IBD may be bidirectional. On one hand, the active inflammation of the terminal ileum leads to a decreased reabsorption of secreted bile salts and reduces the absorption of vitamin D, above all in CD [36]. On the other hand, the deficiency of vitamin D could have an influence on the pathogenesis and activity of IBD [37], given that vitamin D has immunomodulatory actions, above all on patients with CD [38]. Levels lower than <20 ng/ml of 25OHD have been associated with increased IBD activity scores and lower quality of life scores [39]. Vitamin D receptors (VDRs) can be protectors of colonic mucosa by regulating the intestinal homeostasis [40].

Risk factor for osteoporosis in IBD
- Nutritive deficiency
- Malabsorption
- Deficiency in vitamin D, calcium and vitamin K
- Low body mass index
- Chronic inflammatory state
- Limited physical activity
- Decreased skeletal muscle mass
- Extensive small-bowel disease or resection
- Treatments (especially corticosteroids)
- Comorbidities
- Genetic abnormalities

Impact of IBD Treatments on Bone

The risk of osteoporosis is high in patients who use corticosteroids [41]. The use of glucocorticoids plays a major role on bone loss in IBD [19]. Inflammation is one of the factors that contributes to osteoporosis in these patients. The increase of proinflammatory cytokines, such as the TNF-α and the interleukins (IL), also appear to be involved in the pathogenesis of bone loss [42]. Treatments with anti-TNF are frequently used in patients with IBD. Some works have studied the effect of anti TNF in BMD and fractures. A recent longitudinal prospective cohort study (7 yr. of follow-up), with 71 IBD patients (23 with anti-TNF-α and 48 received conventional treatment) showed that the increase of bone mass was significantly higher in the group treated with anti-TNF-α (lumbar spine 8% and femoral neck 7%). However, this treatment did not reduce the risk of new vertebral fractures [43]. Another prospective study in patients with active IBD (UC and CD) showed that bone mineral density remained stable during one year with TNF-α inhibitor treatment (41% infliximab and 59% adalimumab) with a small increase in the percentage of change in BMD (g/cm^2) with respect to baseline but which was not significant either in lumbar spine or hip. There were no changes in bone microarchitecture with trabecular bone score either (TBS: 1439 ± 157 vs. 1453 ± 136; $p = 0.23$) [44].

TNF-alpha antibody could therefore have a significant positive effect on BMD, although some studies find a similar prevalence of osteoporosis and osteopenia in patients with CD treated as well as untreated with anti-TNF (16% vs. 18% for osteoporosis and 53% vs. 57% for osteopenia) [45].

On the other hand, TNF blockers also have a positive effect on bone markers [46]. A prospective study involved 17 patients with active IBD (4 with UC and 13 with CD) showed that bone formation marker P1NP (type-I procollagen N-terminal propeptide) and parathyroid hormone (PTH) increased in week 8 by 18% and 21% respectively after anti-TNF [44]. In a prospective study in 71 CD patients treated for the first time with infliximab, after 8 weeks there was an increase in bone formation marker (P1NP 30%) and a decrease in resorption marker (CTX: C-telopeptide of type-I collagen 38%) [47]. Another study with 37 anti-TNFα-naive IBD patients and 20 healthy controls described that osteocalcin and P1NP increased significantly after infliximab (at 6 weeks and 30 weeks respectively) [48]. Also, with adalimumab in CD patients there was a significant increase in bone formation markers (osteocalcin and P1NP) at 1 and 3 months post-treatment [49]. It seems that anti-TNF could have certain effects in bone remodeling, increasing bone formation and decreasing resorption. On the other hand, the effect of cessation of anti-TNF-α therapy on bone metabolism is unknown.

Few studies assess short-term changes in vitamin D-related mineral metabolism in IBD after anti-TNF-α induction therapy. 1.25 $(OH)_2D$ concentrations increase after induction with anti-TNFα (41.7 vs. 48.1 pg/mL 10 weeks later; $p = 0.014$), but there are not concomitant changes in 25OHD [50]. Others authors find no changes in levels of 25OHD after treatment [44].

Treatment of Osteoporosis in IBD

It is important to identify the population at risk and initiate treatment strategies early. Bisphosphonates have a positive effect on BMD in patients with IBD. On the basis of a meta-analysis in 2014, bisphosphonate is effective and well tolerated for the treatment of low BMD in patients with IBD and reduces the risk of vertebral fractures [51]. In other recent meta-analysis (13 randomized controlled trials and 923 patients) bisphosphonates decreased BMD loss at the lumbar spine (p = 0.0002) and reduced the risk of new fractures (p = 0.01) [52]. Eleven randomized clinical trials were included in a meta-analysis demonstrating that bisphosphonate therapy has an effect on bone loss (LS and TH) in patients with IBD [53]. However, only 29% of patients with IBD and osteoporosis receive treatment with bisphosphonates [54]. There is not enough evidence that other treatments (teriparatide and denosumab) are effective in IBD.

Supplementation calcium (1000–1200 mg/day) and vitamin D supplementation (600–800 UI/day) are recommended in patients with IBD because they increase bone density [55, 56] . Also, it is advisable not to smoke, do physical activity, use the lowest possible dosage of corticosteroid and for the shortest possible time, use corticoids with few systemic effects (budesonide), and propose the use of infliximab [57].

Celiac Disease

Celiac Disease and Osteoporosis

To investigate the epidemiology between celiac disease and osteoporosis we should differentiate two aspects: on the one hand, recent studies described a prevalence of osteoporosis of 20%–30% and osteopenia in 40%–50% of patients with celiac disease measured by a bone densitometry depending on other factors like age, gender or gluten free diet (GFD) [58, 59]. It is especially remarkable in patients older than 50 [60]. Although there are not randomized case-control studies about diet; GFD seems to increase the BMD and hence, reduce the risk of bone fracture [61, 62]. On the other hand, the prevalence of celiac disease in patients with osteoporosis is similar to the general population [63]. Screening celiac disease in patients affected by osteoporosis remains controversial even though European Guidelines still recommend it [64, 65].

A higher prevalence of osteoporosis in patients over 45 years, being male and related to the degree of villous atrophy was recently described in a meta-analysis [66]. Regarding gender, there are disparities between studies about the risk of osteoporosis. A prospective study of 260 patients with celiac disease showed an association between low BMD with being female, reduced BMI and the risk of previous fractures. However, women in the same study showed a non-significant increase of osteoporosis measured as having T-score ≤-2.5 [67]. Other studies observed a higher risk of osteoporosis in women especially in the postmenopausal period [68]. Osteopenia measured by a bone densitometry was also recorded in premenopausal women and men albeit more case-control studies are necessary to investigate the different prevalence between both genders [59]. The degree of villous atrophy and the lack of adherence to GFD was also related to low densitometry with an increase in the values after a GFD [69–71]. Satenga-Guidetti et al. described a significant improvement in the lumbar Z-score from −1.45 to − 0.97 after a year under GFD and higher values of bone density from 1.034 g/cm^2 to 1.057 g/cm^2 after 5 years under GFD [72, 73]. Measurements of bone densitometry were evaluated in celiac disease patients describing normal values of bone density in the long term which supports the idea that the recovery occurs during the first years after the diagnosis and highlights the efficacy of the GFD [74].

Therefore, screening in celiac disease is recommended in patients with low adherence to GFD or with risk factors associated to osteoporosis. Recent studies suggest performing a densitometry every 2 years in patients with low bone density at the diagnosis of celiac disease until normalization of the values [75, 76].

Celiac Disease and Fractures

The risk of fractures in celiac disease was evaluated in several studies. Most of the results were obtained from retrospective case-control data. One of the studies with more than 13,000 patients identified a risk of hip fracture of 2.1 (95% CI = 1.8–2.4) and a HR of 1.4 (95% CI = 1.3–1.5) for any fracture [77]. Hekkila et al. reported in a meta-analysis a risk of fracture of 1.30 (IC 95%: 1.14–1.50) albeit great heterogeneity was reported in this study [78]. The same group showed in a prospective study a risk of hip fracture of 1.54 (IC 95%: 1.17–2.12) in those patients in which transglutaminase antibodies were positive [79]. Nevertheless, there is no detail about the adherence of GFD in many of these studies [80]. More discussion exists with regard to the risk of fractures in children. Some studies stated that there was no risk associated to children while others observed that the risk was double the controls [77, 81]. In any case, osteoporotic fractures in children are the exception due to the evolutive course of the disease.

As previously mentioned, a reduction in BMD is described in celiac disease in 50% of the patients at the point of diagnosis [82]. This parameter is modified after GFD so we should consider the real risk of fracture of these patients. Concerning the diet, 12% of fractures at 5 years-time were observed in a retrospective study despite the improvement in BMD secondary to GFD [70]. Due to the limitations of the study, more data is necessary to evaluate the real risk of fractures and the effect of the GFD.

Contributors to Bone Loss in Celiac Disease

Celiac disease is an immune-mediated disease (IMID) characterized by inflammation of intestinal mucosa after gluten intake in people who are genetically predisposed [83, 84]. Nowadays, a global prevalence of celiac disease is estimated between 0.5 and 1.5% in the general population depending on the geographical area [85]. A prevalence of 0.5% in Asia was reported meanwhile in Europe or North America it reaches a prevalence of 1.5% [86, 87].

Celiac disease is an underdiagnosed condition, asymptomatic in most of the patients whose prevalence has been growing the last few years as a result of deeper knowledge of the disease and worldwide access to upper endoscopy [88, 89]. Practitioners should take into account that described previous prevalence could be influenced by the diagnostic criteria established in each study [90]. Although biopsy criteria are used more often, exclusive serological criteria studies still exist [91, 92]. The presence of osteoporosis in celiac disease depends on several factors. The classic risk factors associated to osteoporosis are low BMI, malabsorption and history of osteoporotic fractures [93].

To understand the relationship between celiac disease and BMD, the pathophysiology of calcium should be known. The bowel is the main source of external calcium while the duodenum, jejunum and ileum are responsible for the absorption of this mineral through cellular and paracelullar transport [94, 95]. Calcium absorption depends on several factors which will regulate the absorbed amount such as 1,25 dihydroxyvitamin D and PTH [96]. Depending on calcium levels, an autoregulation between the bone and the renal system occurs in order to maintain the calcium balance [97]. When hypocalcemia is identified, there is a stimulation of osteoclasts although when calcium is high, there will be a bone resorption [98].

Both villous atrophy and lymphocytes infiltration in intestinal mucosa appear in celiac disease [99, 100]. Over time, diarrhea and secondary symptoms result from nutrient malabsorption [101]. Ionic alteration such as calcium deficiency, hydroxyvitamin D, vitamin B12 and folic acid are present during this period [102]. The lack of these elements is a consequence of dietetic restriction due to diarrhea, lactase deficiency, the conjugation of calcium with no absorbable fatty acids and the decreased exposure to sunlight [103–105]. Hypocalcemia and vitamin D deficiency induce alterations in bone homeostasis, activation of osteoclasts and therefore a reduction in BMD [106]. Ludvigsson J et al. described a Hazard Ratio (HR) to primary hyperparathyroidism of 1.91 (95% CI = 1.44–2.52) in celiac patients with respect to the control cohort during the early years after the diagnosis [107]. Secondary hyperparathyroidism was also associated to suffering lower BMD in 20–28% of patients with celiac disease [108, 109]. Moreover, the levels of PTH are reduced and even returned to normal levels in those patients under GFD [110].

Concerning inflammatory pathways, an increase of proinflammatory cytokines such as IL-1, IL-8, IL-15 IL-17F, IL-22 and tumor necrosis factor alpha (TNF-α) has been described in celiac disease [111, 112]. Some of these inflammatory cytokines have been associated to intestinal mucosa damage within the bowel measured by Marsh Classification which indicates the importance of the inflammatory charge in the disease [113, 114]. In vitro studies showed the differentiation of the osteoclast by the activation of TNF-α, not related to the receptor activator of nuclear factor kappa beta ligand (RANKL) [115]. The activation of the osteoclast is promoted by RANKL whereas bone destruction is preserved by OPG [116]. Additionally, TNF-α and other interleukines activate nuclear factor kappa beta (NFKB) that modulates RANKL [117, 118]. RANKL/OPG ratio is increased in celiac disease, then reduced after GFD and it is also correlated with BMD [119, 120]. Awareness has to be drawn to the fact that an enhancement of OPG in celiac disease patients under long-term GFD has been described by an Italian group attributing those levels to a compensatory effect of the reduced activity of osteoclasts therefore limiting bone destruction [121].

Treatment of osteoporosis in celiac disease.

Good GFD adherence is paramount to avoiding osteoporosis in celiac disease due to histologic remission of mucosa

which is associated with a recovery of BMD and the regeneration in bone microarchitecture [122, 123]. GFD enhances BMD in the first year after the diagnosis of celiac disease so supplements during this period are not recommended [124]. The treatment with calcium or vitamin D afterwards increase the parameters of bone density in celiac disease despite the fact that calcium and vitamin D absorption in those patients is reduced [125, 126]. Guidelines recommend regular exercise to prevent osteoporosis in the general population but in celiac disease this action has a minor role [127, 128].

With respect to bisphosphonates, only a prospective study evaluated the effectiveness of these treatments. Passananti V. et al. examined BMD in patients with celiac disease under zolendronic acid treatment comparing this bisphosphonate to conventional treatment based on calcium, vitamin D and GFD. No improvement in BMD was observed in the group under zolendronic acid [129]. Hence, there is no recommendation concerning bisphosphonates in celiac disease so general measures will be followed for these patients.

Conclusion

The IBD and celiac disease are illnesses prevalent in the general population. As we have commented, both have risk factors related to the loss of bone mineral density, either due to the illness with the inflammatory process and malabsorption of nutrients, partly because of specific complications or due to the treatments received as what happen with the use of corticoids in IBD. The development of fractures in these patients worsens their quality of life, frequently already diminished. It therefore, seems important to evaluate the risk of osteoporosis and fractures in both illnesses, as well as the necessity to start a treatment. More studies are needed in the future to analyze the effects of both illnesses in the bone.

Compliance with Ethical Standards

Conflict of Interest Carmen Valero and Mª José García declare that they have no conflicts of interest.

Informed Consent It is a review article in human's studies Informed consent, It is not necessary, It is a review article.

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