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Bone, Inflammation, and Inflammatory Bowel Disease

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Abstract Osteoporosis is a leading cause of morbidity in patients with inflammatory bowel disease (IBD). Bone loss is an early systemic process and occurs even before clinical disease manifests. Bone disease is attributed to vitamin D deficiency, steroid use, and/or systemic inflammation. In this review, we discuss the molecular pathways of bone loss mediated by inflammatory cytokines and other mediators. Further research will hopefully clarify the mechanisms of inflammation-induced bone loss in IBD and guide effective treatment modalities.

Keywords Osteoblast · Osteoclast · Inflammatory bowel disease · Bone loss · Cytokines · Bone · Inflammation

Introduction

Osteoporosis is the microarchitectural deterioration of bone and loss of bone mineral density (BMD) that increases fracture risk. Osteoporosis is a leading cause of morbidity and affects over 75 million people worldwide [1]. There were over 2 million osteoporosis-associated fractures in 2005 costing the health care system over $17 billion, estimated to increase to $25 billion by 2025 [2]. Glucocorticosteroid (GCS) use is the most common secondary cause of bone loss; 30% to 50% of those on GCS are likely to develop fractures [3]. Several other risk factors have been identified for bone loss, including post menopause, age, family history, sedentary lifestyle, malnutrition, smoking, and gastrointestinal factors (GI; inflammatory bowel disease [IBD], celiac disease, pancreatitis, and bypass surgery) [4]. The purpose of this review is to describe the mechanisms by which IBD affects signaling pathways involved with osteoblast (OB)–osteoclast (OC) crosstalk that leads to decreased BMD and osteoporosis.

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Epidemiology of Bone Loss in GI Diseases

The incidence of osteopenia in IBD is 32% to 36% and osteoporosis is 7% to 15% [5]. In patients with ulcerative colitis (UC) following ileal pouch-anal anastomosis, the prevalence of low BMD is 32.1%. The risk of fragility fractures is 10.5% in the low BMD group and 5.9% in the normal BMD group [6]. The prevalence of fragility fractures in patients with chronic pancreatitis is 4.8%, Crohn's disease (CD) 3.0%, celiac disease 5.0%, post gastrectomy 5.4%, versus controls 1.1%. The odds ratio (OR) of fractures in each group is significantly higher than in the control group ($P<0.0001$) [7]

Children with IBD, even at the time of diagnosis, have mild cortical bone loss [8]. Similarly, children with celiac disease have a high prevalence of low bone mass at diagnosis [9]. On histomorphometric analysis, subjects with clinically dormant CD are found to have low BMD, trabecular thinning, and decreased mineral apposition rate, OC number, and surface

area [10••]. Undiagnosed celiac disease is also associated with bone loss [11]. Even after being on a long-term gluten-free diet and calcium supplements, osteopenia associated with celiac disease is not completely reversed [12].

Based on our current understanding of osteoimmunology, it is evident that the mechanism of osteoporosis in inflammatory GI diseases is similar with other inflammatory systemic diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis, systemic lupus erythematosus, dermatomyositis, and systemic sclerosis. In a population-based case–control study with a cohort comprising of 53,108 patients and 370,602 age-matched controls, the fracture risk was highest for patients with RA (OR, 3) and IBD (OR, 1.6) [13].

Mechanisms of Bone Loss in GI Diseases

Bone is a dynamic organ in a state of continuous bone formation and resorption responding to mechanical stress, microfractures, and various circulating factors. The main bone cell types are the OB, the bone-forming cell, and the OC, the bone-resorbing cell. OBs are derived from mesenchymal stem cells and OCs from hematopoietic stem cells. The bone loss in GI disease is multifactorial and complex, requiring an integrated management approach that targets the primary disease and mechanisms of bone loss. With respect to IBD, this strategy addresses systemic inflammation, malnutrition, malabsorption, and steroid therapy. This review focuses on the inflammatory mechanisms of bone loss in IBD.

Interleukin/RANK-RANKL-OPG Axis

Receptor activator of nuclear factor-κB ligand (RANKL) is a circulating cytokine secreted by mature OB and T cells, interacts on the receptor activator of nuclear factor-κB (RANK) receptor located on the mature OC cell membrane, and activates bone resorption. RANKL is an absolute requirement of the OC to initiate bone resorption. The OB also secretes osteoprotegerin (OPG), a decoy receptor of the RANKL. Thus, the balance between RANKL and OPG determines if there will be net bone formation or resorption. Ashcroft et al. [14] demonstrated that in the interleukin (IL)-2–deficient mouse model of autoimmunity, bone loss was mediated via activated T cells secreting RANKL. Interestingly, they found that both the transcription and plasma levels of the decoy OPG were also increased but were not sufficient to reverse the increased RANKL-mediated bone loss [14]. This effect was supported by the increase in BMD seen with exogenous OPG administration, which also reversed colitis [14]. Moschen et al. [15] studied 180 patients with IBD and found that OPG plasma levels were elevated 2.4-fold in CD and 1.9-fold in UC, whereas soluble RANKL (sRANKL) levels were not significantly different in IBD patients compared with healthy controls. These findings corroborated the results from the IL-2–deficient murine models of colitis and suggested the role of OPG-RANK-RANKL axis in the decreased BMD associated with IBD [15]. Miheller et al. [16] showed that in patients treated with infliximab (a tumor necrosis factor [TNF]-α inhibitor) there was a statistically significant decrease in OPG levels and increase in osteocalcin and sRANKL, thus supporting the hypothesis that there is a counter-regulatory increase in serum OPG levels in patients with IBD [16••].

Several studies have shown elevated levels of circulating proinflammatory cytokines in IBD including TNF-α, IL-1β, IL-6, and IL-17. These cytokines have been implicated in OC-mediated bone resorption in experimental models through p38 mitogen-activated protein kinase (MAPK) pathways [17–20]. IL-1β is a key mediator of bone resorption in inflammatory conditions, such as RA and IBD. IL-1β promotes osteoclastogenesis by inducing RANKL expression on stromal cells and synergizing with RANKL to promote later stages of OC differentiation. IL-1β is also a potent inducer of nuclear factor (NF)-κB. High concentrations of IL-1β are found in both CD and UC [21]. Nemetz et al. [22] showed that in IBD patients, carriers of allele 2 of the *AvaI* gene (IL-1β-511*2 polymorphism), characterized by IL-1β hypersecretion, have a higher risk of diminished BMD (OR of 3.63 at the femoral neck) than healthy controls [22]. Apart from IL-1β, studies have shown that IBD patients exhibit significantly elevated IL-6 activity both locally in the lamina propria mononuclear cells and colonic epithelial cells [23] as well as in circulating monocytes [24].

CD patients with antibodies to Cbir1 (a flagellin that mediates mucosal inflammation) have a more complicated course [25]. Although IL-6 is significantly increased in monocytes from IBD patients, anti-CBir1(+) and IL-6 are inversely correlated. Anti-CBir+ antibodies are associated with decreased activation of NF-κB, which inhibits OC activation. [24]. IL-6 receptor blockade strongly reduces OC formation and bone erosion [26]. Humanized antibody against the IL-6 receptor (tocilizumab) has shown benefit in inflammatory arthritis seen in RA [27].

TNF-α appears to be the master regulator of bone loss in patients with IBD. It promotes osteoclastogenesis in conditions such as inflammatory osteolysis, by inducing OC differentiation, a function that requires the presence of RANKL, as evident from studies on RANK-deficient mice [28, 29]. Once differentiated, TNF-α can activate the OCs and this action is independent of RANK signaling [29]. TNF-α and RANKL markedly potentiate NF-κB and stress-activated protein kinase/c-Jun NH_2-terminal kinase activity, two signaling pathways essential for osteoclastogenesis [30].

In addition to osteoclastogenesis, the effect of TNF-α on OBs is critical in the pathogenesis of reduced BMD seen with IBD. In the noninflammatory state, OB maturation is dependent on Wingless-Int signaling pathway (Wnt) and the genes regulated through the pathway such as Dmp1 (dentin matrix protein 1), Phex (phosphate-regulating gene with homologies to endopeptidases in the X chromosome), and Bsp (bone sialoprotein). The key regulator of this pathway appears to be a secreted factor termed Rspo2 (R-spondin 2) (Fig. 1). Knockout of Rspo2 abrogates Wnt-mediated OB maturation [31].

The cause and effect relationship with TNF-α is established by several studies, which demonstrated the increase in BMD seen with infliximab, the monoclonal antibody against TNF-α. The REACH (A Pediatric Trial in Moderate to Severe Crohn's Disease) study group showed that in 112 pediatric patients with CD (ages 6–17 years), infliximab induction at 5 mg/kg/dose and maintenance every 8 to 12 weeks showed statistically significant improvement in serum bone-specific alkaline phosphatase, N-terminal propeptide of type 1 collagen (P1NP), urine C-telopeptide of collagen cross-links (CTX-1), and deoxypyridinoline. The increases in CTX-1 and deoxypyridinoline likely reflect coupling of bone formation and resorption as increases in linear growth were seen (54-week increases in height z-score; $P<0.001$) [32]. Results from prospective studies in adults have also shown the benefits of infliximab in improving BMD in patients with CD. Bernstein et al. [33•] showed improvement in BMD of the lumbar spine (L2–L4) and proximal left femur (neck and trochanter) in 46 CD patients treated with infliximab (5 mg/kg) at 6- to 8-week intervals for 1 year. Thirteen patients received concurrent prednisone

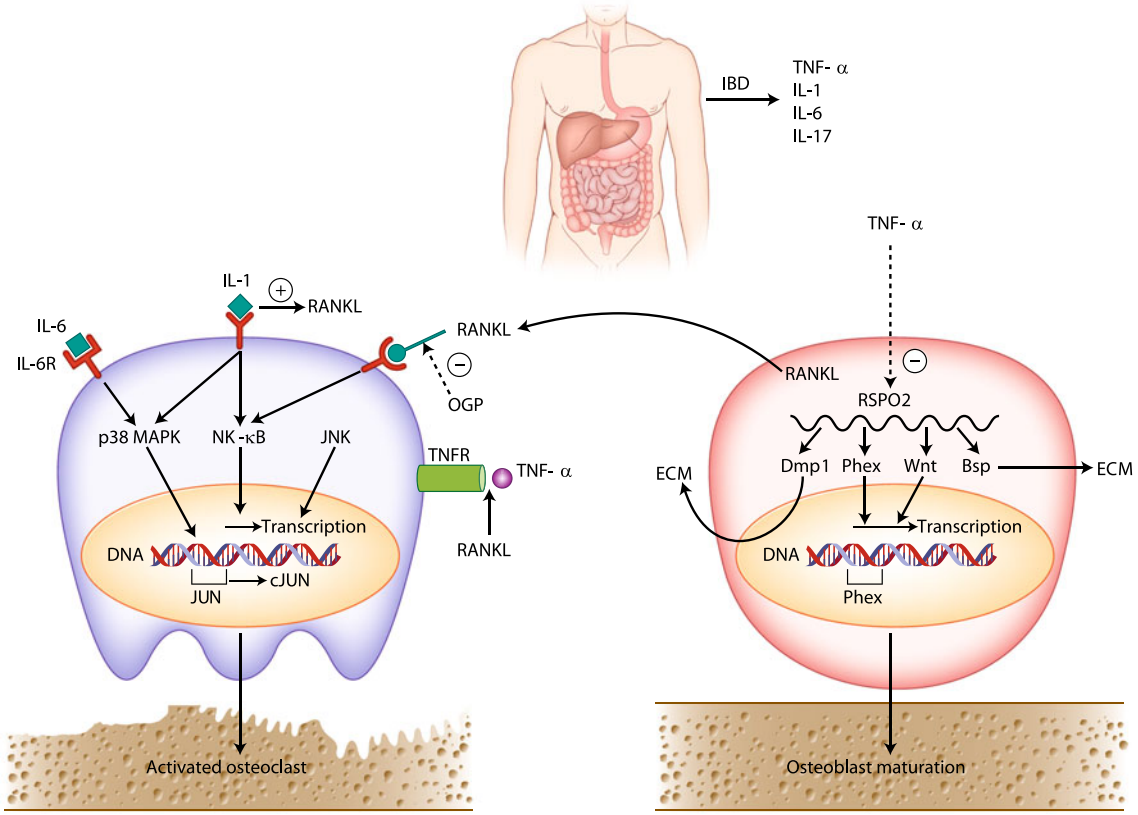

Fig. 1 Mechanism of bone loss in IBD. Under normal conditions, osteoblasts secrete RANKL, which binds to RANK receptor and activates NF-κB pathway, and in turn it controls DNA transcription necessary for osteoclastogenesis. OPG, a decoy receptor, blocks the interaction between RANKL and RANK causing decreased osteoclast activation. During inflammatory conditions, release of various cytokines such as IL-1, IL-6, and TNF-α and binding to its respective receptors cause increased activation of p38 MAPK, NF-κB, and JNK pathways causing excessive bone loss reducing BMD, seen in IBD. Osteoblast maturation is dependent on RSPO2, which controls several pathways responsible for osteoblast differentiation such as Wnt, Phex, Bsp, and Dmp1. TNF-α inhibits the activation of RSPO2 causing decreased bone mineralization. BMD—bone mineral density; Bsp—bone sialoprotein; Dmp1—dentin matrix acidic phosphoprotein 1; ECM—extracellular matrix; IBD—inflammatory bowel disease; IL—interleukin; IL-1R—interleukin-1 receptor; IL-6R—interleukin-6 receptor; JNK—c-Jun N-terminal kinases; NF-κB—nuclear factor-κB; OGP—osteoprotegerin; p38 MAPK—p38 mitogen-activated protein kinase; Phex—phosphate-regulating neutral endopeptidase; RANK—receptor activator of nuclear factor-κB; RANKL—receptor activator of nuclear factor-κB ligand; RSPO2—R-spondin-2; TNF-α—tumor necrosis factor-α; TNFR—tumor necrosis factor receptor; Wnt—Wingless-Int signaling pathway

at a mean dose of 10 mg/day (range: 5–15) [33•]. BMD increased at the lumbar spine by 2.4%±0.7% (P=0.002), at the femoral trochanter by 2.8%±1.2% (P=0.03), and at the femoral neck by 2.6%±0.7% (P=0.001) [33•]. Interestingly, in a retrospective analysis on 61 patients with CD [34], patients with concurrent infliximab and bisphosphonate treatment exhibited a greater increase in BMD compared with those on bisphosphonates alone (+6.7%/year vs +4.46%/year; P=0.045).

Because GCS remain the mainstay therapy for patients with IBD, does infliximab increase BMD through neutralization of steroid-mediated bone loss? This question was addressed in a study on 56 pediatric patients with IBD (35 CD, 21 UC) and an inverse correlation was found between bone marrow apparent density (BMAD) and IL-6 in patients with UC (r=−0.65); no correlation was found between BMAD and serum levels of TNF-α, IL-10, and IL-12 [17]. Disease activity indices inversely correlated with BMAD (r=−0.62 in patients with CD; r=−0.64 in patients with UC). Cumulative dose of GCS and duration of therapy did not correlate with BMAD. Patients treated with infliximab had a higher BMAD. It appears that at least in pediatric IBD, GCS appear to play a lesser role in the pathogenesis of decreased BMD [17].

Insulin-Like Growth Factor Axis

The catabolic state and growth retardation seen in patients with IBD led to investigations exploring the growth hormone (GH) axis. In a retrospective analysis in 28 pediatric patients with IBD (25 CD, 3 UC), four children showed functional GH deficiency (decreased GH and decreased insulin-like growth factor-1 [IGF-1]) and 11 children showed GH resistance (increased GH and increased IGF-1). One child showed an impaired hepatic response to GH (increased GH and decreased IGF-1) [35]. Results were slightly more skewed in an analysis from 37 patients with IBD (N=17 with CD and 20 with UC) in which total IGF-1 was reduced in 36% of CD patients and 41% of UC patients. Moreover, free IGF-1 increased significantly in patients with UC when treated with GCS; no change was seen in patients with CD [36].

Alteration of the IGF axis by inflammation was suggested by studies showing IGF-1 levels are inversely proportional to systemic inflammatory markers such as erythrocyte sedimentation rate, and C-reactive protein and that the alteration of IGF-binding protein-3/IGF-binding protein-2 ratio is altered in a manner that would reduce IGF-1 action [37, 38]. In vivo data from experimental colitis murine models (trinitrobenzenesulfonic acid [TNBS] colitis) showed that with normal stimulated GH secretion, the IGF-1 levels were reduced with reduced IGF mRNA expression, and this effect was reversed by neutralizing IL-6 [39]. TNF-α has been shown to inhibit GH-stimulated IGF-1 secretion in cultured rat liver cells [40]. There is evidence to suggest that anti TNF-α therapy (adalimumab) improves IGF-1 levels at least in RA with an improvement in the muscle wasting component of IBD [41].

The Role of Phex

Phex encodes a neutral (zinc) endopeptidase that regulates phosphate metabolism. Inactivating mutations of Phex leads to X-linked hypophosphatemic rickets with mineralization defects and renal phosphate wasting independent of vitamin D and phosphate levels [42]. Phex is expressed in the OB (and odontoblast) and is downregulated by TNF-α in IBD [43••, 44]. Uno et al. [45] demonstrated that animal models of chemically induced colitis demonstrated a 40% to 50% decrease in the Phex mRNA expression that was reversed with dietary curcumin, which has a potent anti-inflammatory effect in animal models of colitis [46•, 47–49] and human studies [44]. Anti-TNF-α antibody also restored Phex expression, further substantiating the role of TNF-α in its modulation. In vitro, OB-like osteosarcoma cells demonstrated a decrease in Phex mRNA on exogenous TNF-α administration in a concentration-dependent manner, associated with significantly decreased mineralization. OBs, derived from Hyp (Phex knockout) mice cultured in vitro, failed to mineralize [50]. Children with CD were found to have deranged OB function [51]; in vitro OBs also showed abnormal function when cultured in sera from patients with CD [52]. Thus, bone loss due to inflammation in IBD is mediated in part by the suppression of Phex, giving us a clearer insight into inflammatory bone disease.

TNF-α downregulates Phex transcriptionally with no effect on mRNA stability [45]. Majewski et al. [43••] identified that TNF-α induces poly (ADP-ribose) polymerase 1 (PARP-1), for enzymatic PARylation of the p65 (Rel A) subunit, increasing the affinity of NF-κB for the Phex promoter region and leading to decreased expression of Phex. Furthermore, in PARP-1–deficient mice and when PARP-1 is inhibited, downregulation of Phex is not seen.

In animal studies, inhibition of inhibitor of κB kinase (IκK) and NF-κB results in increased bone mass and density with no change in bone resorption [53••]. The increase in bone formation is mediated by an increase in the expression of Fos-related antigen-1 (Fra-1) [51], an indispensible transcription factor in bone formation [54, 55]. NF-κB is upregulated by inflammatory cytokines including TNF-α, IL-1, IL-6, and IL-7 [51], which are chronically elevated in systemic inflammatory conditions, including IBD.

Mapping of the IκK–NF-κB and PARP-1 pathways in bone loss characterizes them as potential targets for therapeutic intervention in bone loss of inflammatory diseases.

The Role of Klotho

Klotho encodes an anti-inflammatory protein with widespread actions, including regulation of calcium and phosphate metabolism. It has been demonstrated that Klotho expression is downregulated in animal models of colitis, mediated by TNF-α and interferon (IFN)-γ [56••]. The extent of Klotho suppression was directly related to the severity of colitis and was reversed by anti-TNF-α antibodies. IFN-γ amplifies the effect of TNF-α and mediates the downregulation of Klotho by transcriptional repression of its promoter [57]. As Klotho maintains calcium and phosphate homeostasis, loss of Klotho mediated by TNF-α and other modulators of inflammation aggravates bone disease. An in vitro study on human umbilical vein endothelial cells showed that Klotho protein attenuated TNF-α–induced expression of adhesion molecules and activation of NF-κB [57], substantiating the involvement of Klotho in bone loss due to systemic inflammation.

Conclusions

Bone loss remains a major extraintestinal cause of morbidity in IBD, leading to impaired quality of life and productivity. It is clear that systemic inflammation and chronically high levels of circulating cytokines interact with bone through multiple pathways, synergizing to produce profound net bone loss, independent of other theoretically modifiable causes of bone loss. Even in pediatric IBD and clinically dormant IBD, osteopenia is manifest. The pathways leading to inflammatory bone disease are still inadequately understood and we need more studies to fill in the gaps. However, many factors have been identified as possible points of therapeutic manipulation, including TNF-α, RANKL, Phex, NF-κB, and PARP-1, among others. Using a multipronged approach to prevent and treat bone disease will likely be more successful because it is evident that no one factor in isolation can be implicated.

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