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PERSPECTIVES

Effects of Inflammatory Bowel Diseases on Bone Metabolism

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Abstract

Inflammatory bowel diseases (IBDs) are chronic inflammatory conditions that involve the gastrointestinal tract and affect approximately 1.2 million Americans, of whom 25% are diagnosed as children. The incidence of IBD is increasing worldwide. The term IBD encompasses two distinct entities, Crohn's disease and ulcerative colitis. Both diseases are frequently associated with decreased bone mineral mass. This *Perspective* examines the prevalence, mechanisms and optimization of bone health in adults and children with IBD. *IBMS BoneKEy*. 2009 November;6(11):420-428.

Inflammatory bowel disease (IBD) is thought to be caused by an inappropriate immune reaction to resident intestinal bacterial flora triggered by environmental factors in genetically susceptible individuals. Activated T cells drive an inflammatory reaction that releases pro-inflammatory factors in the intestinal mucosa, which may spill over into the circulation and affect bone cell function. In a mouse model of colitis, a pool of effector memory T cells that can induce colitis circulates back into the bone marrow. Consequently, it is possible that these and other cells serve as "inflammatory shuttles" between the intestine and bone. Recently, immune activation of bone marrow cells has been demonstrated in animal models of IBD, which may affect bone cell function. Additional mechanisms, such as malnutrition, inactivity, hypogonadism and reduced lean body mass may also affect bone mass in IBD. These modifiable risk factors can be addressed in patients with IBD to optimize bone mass.

Challenges for Bone Health in IBD

IBD can strike at any age, but it is most commonly diagnosed in adolescents and young adults. During adolescence there is normally rapid linear growth and bone mineral accrual, whereas young adults maintain peak bone mass. Adults and children remodel stressed or damaged bone, a function that is performed by sequential waves of osteoclasts and osteoblasts over 3-4 months. Additionally, in growing children, active bone modeling and endochondral bone formation occur. During these processes, osteoblasts and osteoclasts act on different bone surfaces, changing the length, shape and mechanical properties of those surfaces in weeks. These important physiological differences between adults and children affect the way that bone responds to the multiple challenges posed by IBD.

Crohn's disease and ulcerative colitis are frequently associated with bone mass deficits. The prevalence ranges widely (0-65%) depending on the population studied and the method used to determine bone mass (1). Reduced bone mineral mass can be present from the time of diagnosis (2;3). Peripheral quantitative computed tomography (pQCT) in children with newly diagnosed Crohn's disease reveals decreased trabecular bone mineral density, expanded endocortical surface and reduced periosteal circumference, resulting in mechanically weaker long bones (3). However, it is not known whether this predisposes patients with IBD to fractures. Retrospective population-based cohort studies in adults with IBD show mild-to-moderate increases in fracture risk (4-7), or no increase (8;9). However, the true

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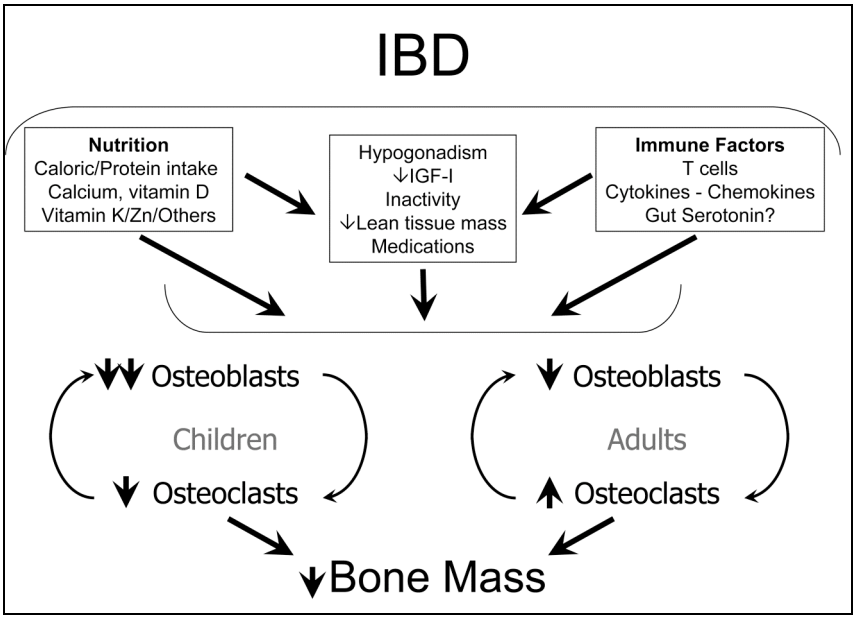

Fig. 1. Multifactorial pathogenesis of bone mass deficits in IBD. Multiple inflammatory, nutritional and hormonal influences can affect bone cell function. Children and adults respond differently to these influences.

prevalence of fractures in IBD patients may be underestimated because these studies did not include clinically silent vertebral fractures, which may be commonly present, at least in adults with IBD (10;11). The only available fracture study in children with IBD used a recall questionnaire and found that fracture rates were similar in patients and their unaffected siblings (12). However, to show a difference in fracture rates between affected and unaffected children would require a much larger sample size, given the high prevalence of arm and leg fractures in children without disease.

In adults and children, bone biomarkers suggest that Crohn's disease is associated with reduced bone formation (13;14). However, bone resorption is increased in adults but not in children (2). Consequently, in children with IBD, bone turnover (modeling and remodeling) is suppressed overall, while in adults bone loss is a consequence of unopposed bone dissolution. Recently published bone biopsy data in children with Crohn's disease at diagnosis, before starting any anti-inflammatory therapy, also suggest decreased bone formation and resorption (15).

Mechanisms by Which IBD May Affect Bone Mass

IBD may impair bone mass accrual and maintenance through multiple mechanisms (Fig. 1). Malnutrition, mainly due to reduced intake of calories and protein, is common and can result in suboptimal bone development (16;17). Obligatory colonic losses of calcium may increase in patients with diarrhea, potentially affecting bone mineralization. Vitamin D deficiency is frequently detected in patients with IBD (18), which may impair calcium absorption and bone mineral deposition. In rodent models of colitis, vitamin D supplementation ameliorates inflammation (19) and a lack of vitamin D receptor exacerbates it (20), suggesting that vitamin D may have an immunomodulatory effect in IBD. Subclinical vitamin K deficiency has been reported in Crohn's disease (21). Vitamin K is a co-factor in the γ-carboxylation of glutamic acid in osteocalcin to form γ-carboxyglutamic acid residues that can bind calcium. Therefore, vitamin K deficiency may decrease the affinity of osteocalcin for calcium in the bone matrix.

Table 1. Mucosal and circulating factors present in IBD affect bone cell function.

Factor	Effects	References
IL-6	↑↓ Bone resorption	(32;50;51)
	↑↓ Bone formation	
	High IL-6 production associated with osteoporosis in adults with IBD	(52)
	IL-6 polymorphisms are associated with increased bone loss	(53)
INF-γ	↓ Bone resorption	(54)
	↓ Bone formation	
TNF-α	↑ Bone resorption (directly and via RANKL)	(55;56)
	↓ Bone formation	
RANKL	↑ Bone resorption	(57)
OPG	↓ Bone resorption	(58)
IL-17	↑ Bone resorption	(59;60)
IL-1β	↑ Bone resorption	(61)
	High IL-1β associated with low BMD in adult IBD	
IL-4	↓ Bone resorption	(62;63)
IL-12	↓ Bone resorption	(64)
IL-23	↓ Bone resorption	(65)
Serotonin?	↓ Bone formation (interference with Wnt signaling in osteoblasts)	(66)

IL: interleukin; INF-γ: interferon-γ; TNF-α: tumor necrosis factor-α; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor κB

Hormonal disturbances associated with IBD can affect bone development and maintenance. Delayed puberty is often a feature of IBD (22) and is associated with a relative estrogen deficiency, which may affect bone mass accrual. Hypogonadism can be seen in adults and may similarly impair bone remodeling (23). Serum insulin-like growth factor-1 (IGF-1), a potent growth factor for bone, is commonly reduced in children with active inflammation. This is due to a combination of malnutrition and growth hormone signaling blockade in the liver and peripheral tissues (24). Low IGF-1 may impair longitudinal growth by chondrocytes, expansion of the outer cortical layer by periosteal osteoblasts, and recruitment of undifferentiated stromal cells into the osteoblast lineage (25;26). Normal bone development is stimulated by weight-bearing exercise. Patients with IBD may have limited endurance and energy and prefer more sedentary activities. Potentially this can decrease mechanical stress on bone that is important to maintain its strength. Crohn's disease is associated with persistent deficits in lean body mass and musculature (27;28), which result in reduced mechanical strain and decreased bone formation (29).

Cytokines, chemokines and other factors released by the inflamed intestine into the circulation can influence the function of bone cells (Table 1). Serum from newly diagnosed

children with Crohn's disease decreases bone formation in bone explants and primary osteoblast cultures (30;31). Antibody neutralization of serum IL-6 reverses in part the effects of Crohn's serum in this model (32). Properly stimulated osteoblasts, osteoclasts and bone marrow cells can also secrete inflammatory factors. Investigators have demonstrated a bone marrow infiltrate that produces TNF-α in an adoptive transfer mouse model of colitis (33), suggesting that locally produced pro-inflammatory factors may also modulate bone cell function. Adequate control of inflammation may restore bone homeostasis in IBD. It has been reported that treatment with infliximab, a TNF-α blocker, is associated with a dramatic increase in biomarkers of bone turnover, especially bone formation, in children (34).

Medications to treat IBD can also impact bone cell function. Corticosteroids primarily inhibit bone formation and secondarily increase bone resorption. Corticosteroids decrease BMD and increase the risk of fractures in adults, an effect that occurs early in the course of therapy and can be observed even with small doses (35). A large case-control study involving children who received four or more courses of oral corticosteroids (mean duration, 6.4 days) found an increased risk of fracture compared with controls (7). However, the effect of corticosteroids on bone mass in IBD remains controversial, because it is difficult to separate disease-related effects from those of treatment (36). The calcium-binding phosphatase calcineurin regulates osteoblast function (37;38), and its substrate nuclear factor of activated T cells (NFAT) is critically important in osteoblast and osteoclast differentiation (39). Calcineurin inhibitors like cyclosporine and tacrolimus used in refractory IBD can inhibit osteoblasts (40;41).

Improving Bone Mass in IBD

Bone mass will increase with adequate disease control and measures that improve general well-being including optimizing nutrition (calories, protein, calcium and vitamin D), weight-bearing physical activity (42), and steroid-sparing anti-inflammatory regimens (43;44).

Bisphosphonates are used to increase BMD in adults with IBD, especially those receiving corticosteroids. In children, reduced BMD alone should not be used as the sole criterion to start these medications. Bisphosphonates increase BMD, but it is not known whether they prevent fractures in this population (45-49). Anabolic agents such as teriparatide have not been tested in patients with IBD. Finally, low intensity vibration is a promising treatment modality aimed at mechanically stimulating bone formation. It is currently being tested in children with Crohn's disease (NCT00364130).

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