Metabolic Bone Disease in Inflammatory Bowel Disease

Chronic inflammatory bowel diseases (IBD) affect bone metabolism and are frequently associated with decreased bone mineral density (BMD) and increased risk of fractures. Experimental models of IBD and as well as data from pediatric and adult IBD patients do not provide a uniform answer whether the changes in bone metabolism leading to decreased mineral density are the result of decreased bone formation, increased bone desorption, or both. New studies continue to unravel a complex network of interactions leading to the inflammation-associated loss of BMD, and may help direct treatment of IBD toward more bone-sparing strategies. Nutritional interventions (dietary calcium and vitamin D supplementation) are of limited efficacy in IBD patients. Therefore, appreciating the extent of the problem and understanding the pathophysiology of osteopenia and osteoporosis in Crohn’s disease and ulcerative colitis are critical for the correct choice of available treatments or the development of new targeted therapies.

INTRODUCTION

Inflammatory bowel diseases (IBD), which include Crohn’s Disease (CD) and Ulcerative Colitis (UC) affect more than 1.5 million people in the United States. A major extraintestinal manifestation of IBD relates to osteopenia and osteoporosis, which occur in 22-77% and 17-41% respectively, resulting in higher risk for bone fractures. Vertebral fractures are seen in 22% of adults with IBD. In children, the risk of fracture is twofold with each standard deviation (SD; Z-score unit) of decrease in areal bone mineral density (BMD). Pediatric onset IBD is expected to decrease peak bone accrual and accelerated bone loss into later adulthood, while adult onset IBD may similarly accelerate progressive loss of BMD, especially in women. Therefore, it is important to manage patient’s long term risks for poor bone health, abnormal bone development, osteoporosis and, ultimately, greater risk for fractures which may have a significant impact on mortality later in life. This may require a concerted and coordinated effort on the part of the patient’s primary care physician, gastroenterologist, and endocrinologist. This multidisciplinary care is of particular importance since the mechanisms for bone loss in IBD are multifactorial and include many factors exemplified in Table 1.
We have previously reviewed the current concepts explaining the effects of inflammation, inflammatory mediators and their signaling effectors on calcium and phosphate homeostasis, osteoblast and osteoclast function, and the potential limitations of vitamin D use as an immunomodulator and anabolic hormone in IBD. In this article, we will provide a brief summary of these aspects, and focus on more clinically relevant approaches to managing metabolic bone disease in IBD.

**Physiology of Bone Formation and Remodeling**

Bone has multiple functions. It provides support for the body, protects underlying soft tissues, allows movement through muscle, tendon, and ligament attachment, it is a site for hematopoiesis and blood cell storage, works as an endocrine and immune organ, and stores calcium and phosphorus, the two most abundant minerals in the body. Bone is a dynamic structure in a continuous state of bone formation and remodeling. Ninety percent of adult bone mass is gained during the first two decades of life. Almost 10 percent of total bone content is replaced every year.

Osteoblasts and osteoclasts are the major players of bone formation and remodeling. Osteoblasts are derived from mesenchymal stem cells which secrete bone matrix proteins and promote mineralization with deposition of calcium and phosphate in type 1 collagen. The proliferation and differentiation of osteoblasts depends on RunX2 (runt-related transcription factor) and osterix. Osteoblasts express RANKL (receptor activator of nuclear factor -kappa B ligand). Binding of RANKL to RANK, its receptor on osteoclasts, is inhibited by its decoy receptor osteoprotegrin (OPG) (Fig. 1). Osteoclasts are involved in bone resorption which takes three weeks, whereas the repair phase takes about three months. Therefore, coupling and synchronization of osteoblast and osteoclast activities are of paramount importance in preventing bone loss.

RANKL is also secreted by stromal cells and activated T cells. The balance between RANKL and OPG, controlled by many factors including 1,25(OH)₂ vitamin D₃ and inflammatory mediators, determines the net outcome of bone formation or resorption (Fig. 1).

Clinically utilized markers for bone formation include bone alkaline phosphatase (b-ALP), osteocalcin (OC), and procollagen type 1 amino-terminal propeptide (P1NP). Bone resorption markers include collagen cross-links (urinary pyridinoline and deoxypyridinoline), and serum or urinary cross-link-containing peptide fragments (NTx - N-telopeptide of collagen type I; SCTx C-terminal telopeptide). Other markers of bone turnover, such as serum tartrate-resistant acid phosphatase (TRAP) 5b, serum cathepsin K, leptin, adiponectin, RANK, RANKL, and OPG may eventually be used as markers of bone metabolism, albeit with limited specificity. A number of factors determine

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**Table 1. Risk Factors for Bone Loss in Inflammatory Bowel Disease**

- Malnutrition
- Malabsorption of vitamin D, calcium, and vitamin K
- Low body mass index (BMI)
- Low bone mineral intensity peak in IBD patients with pediatric onset
- Chronic inflammatory state
- Type of IBD (CD vs. UC; small intestinal involvement)
- Increasing age
- Female gender
- Immobilization
- Chronic use of corticosteroids
- Previous fragility fracture
- Hypogonadism
- Smoking
- Family history of osteoporosis
reliability of bone turnover marker assays, including diurnal and day-to-day variability, food consumption, sample handling, patient age and puberty/menopause status. These have been well reviewed by Singer and Eyre.2

Pathophysiology of Bone Disease in IBD Patients
The pathogenesis of osteopenia and osteoporosis is multifactorial and can be divided into three major categories. First, inflammation associated cytokine release resulting in disruption of bone formation and remodeling. Second, inflammation induced decreased intake of nutrients, malabsorption, and loss of nutrients essential for bone formation via the gastrointestinal tract and renal tubules. Third, iatrogenic effect induced by glucocorticoids used on a continuous basis. The interrelationship of some of these events is shown in Figure 2. The role of the RANK-RANKL-OPG axis in osteoporosis has been studied and reviewed extensively [e.g.3] and will not be reviewed here. Since the supply of calcium and phosphate are essential for building bone matrix comprised primarily of hydroxyapatite (Ca_{10}(PO_{4})_{6}(OH)_{2}), we will focus on the role of inflammation in mineral homeostasis and bone metabolism, as pertinent to IBD.

The Role of PHEX During Inflammation
Our laboratory has been involved in the study of PHEX, which is mutated in the X-linked hypophosphatemic vitamin D resistant rickets. PHEX encodes a neutral zinc endopeptidase expressed primarily on osteoblasts and osteocytes. PHEX regulates phosphate homeostasis, and is critical for intrinsic mineralizing activity of osteoblasts. PHEX is downregulated by TNFα in the course of experimental colitis at the transcriptional level.4 Anti-TNFα antibodies restore PHEX expression. Further work from our laboratory has shown that in osteoblasts, TNFα induces poly(ADP-Ribose) polymerase 1 (PARP-1)-dependent post-translational modification (poly-ADP-rybosylation) of the p65(RelA) subunit of NF-κB which then acts as a transcriptional repressor of PHEX gene.5 Interestingly, in animal studies, NF-κB inhibition resulted in increased bone formation and BMD. Since PARP-1 deficiency or inhibition is also protective in experimental colitis, it is conceivable that inhibition of this enzyme may become an attractive strategy for the treatment of inflammation and bone loss in IBD.

The Role of Klotho During Inflammation
Klotho encodes an anti-inflammatory protein with multiple functions including regulation of vitamin D and phosphate metabolism. Indeed, serendipitously obtained Klotho hypomorphic mice exhibited symptoms typical of human aging, short life span, infertility, arteriosclerosis, skin atrophy, severe osteoporosis, and emphysema. Klotho encodes 130-kDA single pass transmembrane protein with beta-glucuronidase activity
and it’s primarily expressed in epithelial cells of renal distal tubules, choroidal plexus and parathyroid glands. We have demonstrated transcriptional downregulation of renal Klotho expression by TNFα and INFγ in multiple models of IBD (TNBS colitis, SPF-associated germ free IL-10−/− mice, and T cell transfer colitis).6

**Intestinal And Renal Calcium Transport**

Calcium absorption in the gastrointestinal tract occurs mainly in the duodenum and proximal jejunum. It is estimated that under conditions of limited dietary intake and low luminal Ca²⁺ concentrations, active transport mediated by TRPV6 accounts for approximately 80% of the total calcium absorption. However at a high Ca²⁺ supply (>50mM), the contribution of the active transport diminishes to below 10%. Both renal TRPV5 and intestine-predominant TRPV6 channels are regulated at the transcriptional level via 1,25 (OH)₂ D₃, parathyroid hormone, and estrogens. The importance of these two channels has been verified in knockout mice, which have significant defects in Ca²⁺ homeostasis. Following the entry of Ca²⁺ into the cells, it is shuttled via calbindins D₉ or D₁₀, as well as via an alternative vesicular transport. Ca²⁺ transport at the basolateral membrane occurs via sodium-calcium exchanger, NCX1, and via a calcium extrusion pump PMCA1b.

Although not systematically studied, it is conceivable that in IBD patients, malnutrition and dairy avoidance increases the contribution of active Ca²⁺ transport, therefore alterations of both intestinal and renal Ca²⁺ (re)absorption is likely to contribute to negative Ca²⁺ balance and ultimately to BMD loss. Indeed, in mouse model of Crohn’s-like ileitis (TNFα-overexpressing TNFΔARE mice), both duodenal and renal Ca²⁺ absorptive epithelia showed significant downregulation of TRPV6, calbindin D₉K, PMCA1b, as well as calbindin D₁₀K and NCX1, respectively.7 Klotho, through its enzymatic activity, also participates in stabilization of a key renal Ca²⁺ channel TRPV5 (transient receptor potential vanilloid 5) at the apical membrane in the epithelium of the renal distal convoluted tubules, thus facilitating active Ca²⁺ reabsorption. In the used experimental IBD models, decreased Klotho expression is accompanied by increased fractional urinary Ca²⁺ excretion and dramatic decrease of TRPV5 protein expression (Kiela and Ghishan, unpublished observations).

**Intestinal and Renal Phosphate Absorption**

Hypophosphatemia is the hallmark of rickets. Although phosphate is a widely abundant dietary constituent, the homeostatic Pi regulation largely depends on the intestinal type llb Na⁺/Pi co-transporter (SLC34a2) and renal type IIa and IIc Na⁺/Pi co-transporter (SLC34a1 and SLC34a3, respectively) in renal tubules. In animal model of colitis as well as in vitro, TNFΔ downregulates phosphate transport and SLC34a2 expression via a transcriptional mechanism. FGF23, a phosphaturic hormone, is upregulated in IBD and in animal models of colitis (Kiela and Ghishan; unpublished data). 1,25(OH)₂ D₃ also increased in a subset of IBD patients dramatically increases FGF23 levels. Therefore, although there are no studies investigating phosphate (re)absorption in IBD patients, it appears that vitamin D₃ and FGF23 may play a major role in phosphate homeostasis during inflammation.

**Methods for Assessing Bone Health and Special Considerations for Pediatric IBD Patients**

Dual energy x-ray absorptiometry (DXA) is the most widely used method for diagnosing osteoporosis in adults. DXA is not a true volumetric measurement of bone density, but rather a 2D representation of a three-dimensional structure which provides an estimate of the amount of bone mineral density and bone area. Bone mineral density is then calculated as the bone mineral content BMC / bone area (G/cm²) and often referred to as an areal BMD (aBMD). The advantages of DXA are its wide availability, short scan times, and relatively low radiation exposure. Measurements of aBMD are influenced by bone size, with larger bones having inflated aBMD measurements. This observation has relevance to measurements of bone mineral density in pediatric patients because of the differences in bone size at different ages. The bone mineral density results are often presented as T and Z scores. The world health organization criteria for diagnosis of osteoporosis in adults are based on aBMD, T scores defined as the standard deviation score of the observed aBMD compared to that of a normal young adult. A T score of less than -1 SD indicates osteopenia, and a T score of -2.5 SD indicates osteoporosis. In pediatric patients, rather than a T score, Z score is calculated and defined as the SD score based on gender specific norms. This is definitely a more appropriate method for comparison of aBMD in pediatric patients. The
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Figure 2. Factors and mechanisms associated with bone mass loss and increased risk of fractures in patients with inflammatory bowel diseases. IBD, inflammatory bowel disease (adapted from Ghishan and Kiela, Am J Physiol Gastrointest Liver Physiol 300:G191-G201, 2011)

Major limitations of DXA are its dependence on areal rather than volumetric bone density which clearly results in underestimation of bone density in shorter individuals, such as pediatric patients with stunted growth. Moreover, DXA does not differentiate between cortical and trabecular bone. Furthermore, there is no evidence that aBMD is predictive of future fracture risks. Because DXA provides little data on measures of bone geometry and trabecular microarchitecture of the bone, other methods have been proposed. Those include a peripheral quantitative computed tomography (pQCT) which assesses bone in three dimensions and allows for separation of cortical and trabecular bone. Therefore, pQCT allows the determination of bone size, geometry, and quality of bone. However, pQCT also has some problems in regards to its use in pediatrics due to insufficiency of reference data included in the software, which would take into account children representative of the population, with adequate representation of age, and gender. Furthermore, the standardization of scan acquisition and analysis including a consensus where to mark the end of bone in children with large growth plates could be a problem. Furthermore, CT scans require radiation. Another method is using quantitative ultrasound (QUS) which assesses bone by measuring the speed of sound of an ultrasound wave along the bone. The advantages of QUS are no radiation exposure, and that it has been shown to be comparable to DXA in adults in identifying multiple fractures. It is clear that it has an appeal to Pediatric patients due to the lack of radiation exposure, low cost, and portability. While this test is still in its infancy in Pediatric patients, the likelihood of gaining a wide application is appealing.

Concerns and Alternatives to Bone Densitometry

Some studies in post-menopausal women and in general population indicate that vast majority of fractures occur in patients with T-scores >-2.5, therefore in the osteopenic rather than osteoporotic range, thus suggesting that factors other than BMD should be considered when estimating fracture risk and determining the need for regular screening and treatment. Moreover, although IBD patients are certainly at increased risk of fractures,
low BMD by itself is believed to confer only a modestly increased risk. Therefore routine screening with DEXA were not viewed as justified by guidelines issued by the British Society of Gastroenterology\textsuperscript{10} or the American Gastroenterological Association.\textsuperscript{11} Recently, based on data from population-based cohorts, and using guidelines of the National Osteoporosis Guidelines Group (NOGG), World Health Organization (WHO) developed an online tool to assess the need for DEXA screening, treatment, and lifestyle changes. The tool named FRAX (WHO Fracture Risk Assessment Tool) is available at http://www.shef.ac.uk/FRAX/tool.jsp and recent retrospective study with CD and UC patients suggests that this tool can accurately predict the risk of fractures in IBD patients without DEXA.\textsuperscript{12} This tool requires further development and validation. The accuracy of prediction may be increased by including femoral neck BMD value, while the interpretation of the prediction data or the recommendations appears limited due to inclusion of circular reference to a known T score, and needs to be verified in pediatric patients. Further development of additional criteria, particularly for pediatric IBD cases, may be required for a better tool performance.

**A Clinician’s Dilemma: To Screen or not to Screen**

In 2003 American Gastroenterological Association released a position statement and guidelines on osteoporosis in gastrointestinal diseases.\textsuperscript{11} At that time, AGA took a stance that “osteomalacia and vitamin D deficiency are not common in IBD (including Crohn’s disease) and are unlikely to be important causes of most cases of diminished bone mineral density in IBD.” The guidelines recommended that DEXA scans should be selectively ordered in IBD patients based on a thorough risk factor assessment. This publication was later followed by a more detailed report and guidelines by the British Society of Gastroenterology.\textsuperscript{10} Although later evidence from multiple IBD populations suggested much stronger association of IBD with metabolic bone disease, risk of fractures, and 25(OH) D3 deficiency, lack of awareness, associated radiation exposure, additional cost and insurance coverage are frequently the reasons for underutilization of DEXA in IBD patient population. As an example, a recent study on the VA patient population\textsuperscript{13} found relatively low rates of DEXA use to screen for osteoporosis in patients with IBD, although the prevalence of osteoporosis in the tested IBD population was high, with over one-fourth of patients meeting WHO osteoporosis criteria. Importantly, as individual criteria, the guidelines did not identify patients with higher prevalence of osteoporosis. Also, testing for and treatment of secondary causes of low BMD were suboptimal. On the other hand, opponents of routine bone screening IBD may argue that DEXA should be used only if it guides the strategy for the treatment of the primary disease. To this end, diagnosis of osteopenia and osteoporosis in IBD patients would be a counter-indication for chronic steroid therapy.

**IBD TREATMENT VS. BONE DISEASE**

**Glucocorticoids**

Although loss of BMD in IBD has been demonstrated in steroid-naïve patients, and no significant correlation between steroid use and IBD-associated osteopenia and osteoporosis has been found, iatrogenic effects of glucocorticoids cannot be neglected. Glucocorticoids impair osteoblast function, induce osteoblast apoptosis, reduce intestinal calcium absorption, and increase renal excretion of calcium. Patients on prolonged glucocorticoids regimen are at increased risk for fracture, although studies show a decrease in fracture risk upon glucocorticoid cessation. On the other hand, we have demonstrated that glucocorticoids induce expression of Phex gene in osteoblasts, suggesting a mechanism potentially mitigating bone loss. While prolonged use of systemically acting steroids (prednisone, prednisolone, and or methylprednisolone) is likely a contributing factor to IBD-associated bone loss, locally acting corticosteroids, such as budesonide, may represent a more bone sparing strategy.

**Treatment of the Underlying Disease**

Treatment of the underlying inflammation and induction of remission in Crohn’s disease and ulcerative colitis should be the primary goal. Immunosuppression utilizing mesalamine, immunomodulators, and biologicals appear to be the most important factor in restoring bone density. The evidence from our data and others suggest that inflammatory cytokines negatively impact calcium and phosphate absorption, and downregulate genes involved in bone formation. Reversing this effect requires halting the inflammatory cascade in IBD patients.

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Life Style Modification
All IBD patients should be advised on the importance of lifestyle changes. A balanced diet with optimal amounts of nutrients is essential. Patients with IBD should not smoke and should use alcohol with caution. Physical activity, especially regular weight-bearing exercise, is important in maintaining bone density.

Vitamin D & K, Calcium, Phosphate, and Magnesium
Classically, vitamin D₃ deficiency has been described in IBD patients. Therefore, supplementation of vitamin D₃ seems an intuitive choice for patients with active disease to increase Ca²⁺ absorption, and as a potential immunomodulator. However, studies in pediatric IBD patients failed to show that supplementation with vitamin D₃ and calcium had a significant effect on bone mineral density accrual. Moreover, a significant subset of IBD patients shows elevated levels of 1,25(OH)₂D₃ likely secondary to upregulation of 1α(OH)ase, during uncontrolled inflammation. In experimental settings of established murine T- cell transfer colitis, switching from “low” (730IU/day human equivalent dose, HED) to high dietary vitamin D₃ intake (3,650IU/day HED) for only 12 days resulted in relative decrease in serum osteocalcin and OPG, and loss of trabecular bone (Kiela & Ghishan, unpublished data). Therefore, we believe that high-dose vitamin D₃ supplementation in IBD patients with active inflammation or flare-up may be detrimental to the bone. However, once the inflammatory activity is suppressed, the patient should be supplemented with Vitamin D₃ at 2,000-5,000 IU/day with measurement of 25(OH)D₃ to be maintained between 30-80 ng/ml. Calcium intake should be between 1,000-1,500 mg/day. Optimal phosphate intake in adults is approximately 700 mg/day and magnesium to 400 mg/day. Vitamin K intake of 80-100 µg/day is adequate.

Bisphosphonates
These compounds inhibit bone osteoclastic activity, and are commonly used in postmenopausal women with osteoporosis. Bisphosphonates may be used for the prevention and treatment of proven osteoporosis in IBD patients, patients with atraumatic fractures,
and patients unable to withdraw from corticosteroids after 3 months of use. Clinical evidence suggests effectiveness of bisphosphonates in patients with steroid-induced bone loss. In postmenopausal osteoporotic women with IBD, long-term treatment with risedronate was effective in increasing BMD and reducing vertebral and nonvertebral fracture risk. Although bisphosphonate therapy has been beneficial in general in Crohn’s disease or ulcerative colitis, potential complications such as osteonecrosis of the jaw and paradoxical increased risk of fractures, suggest a more careful approach. Rheumatoid arthritis has been suggested as a relevant risk factor for bisphosphonate-related osteonecrosis of the jaw. Whether with increased use of this class of drugs IBD will result is similar risk association is not known. However, until more clinical data is accumulated, use of bisphosphonates should be limited to steroid-dependent patients with proven osteoporosis and postmenopausal osteoporotic women with IBD.

References


