Bone Disease In the Inflammatory Bowel Disease Population

Jeanette Smith, MD, and Sheldon Lidofsky, MD

Bone disease, an under-diagnosed manifestation of Inflammatory Bowel Disease IBD, warrants special consideration. Osteoporosis/osteopenia commonly affects 30-50% of IBD patients. The quiescent nature of this disease makes it extremely challenging to diagnose and treat. Patients with osteoporosis and osteopenia are asymptomatic unless they suffer a fracture. In the past, bone health has been overlooked due to the other pressing issues and complications that arise in this population. However, screening, preventive efforts and active treatment are essential. Because bone disease can significantly reduce health and quality of life, clinicians should be aware of bone disease in all patients with IBD.

Definition and Epidemiology of Osteoporosis.

The **World Health Organization (WHO)** defines osteoporosis as a "systemic skeletal disease characterized by low bone mass and architectural deterioration of bone, with a consequent increase in bone fragility and susceptibility to fracture." [1] It has often been thought of as an older person's disease. However, in the IBD population it can occur at any age. Studies have shown that approximately 30% of patients with inflammatory bowel disease have low bone density, with a mean bone density on average 10% lower than normal age matched controls.[2,3] The overall relative risk of fracture is 40% greater in IBD patients compared to the general population.[4]

The prevalence of bone disease in patients with **Crohn's disease (CD)** or **Ulcerative Colitis (UC)** is thought to be equal.[4] Thus, patients with UC and CD should be evaluated and treated similarly.

Normal Bone Development

Normal adult bone is comprised of metabolically active cells (osteoblasts and osteoclasts) along with a non-living extracellular matrix of collagen and calcium salts.[5] Bone strength is determined by these collagenous proteins and mineralized osteoid. It has been accepted that bone mass is the single best predictor of in vivo bone strength and fracture risk.[1] Adult bone is constantly being remodeled to maintain strength. Osteoclasts direct the timing and location of bone resorption, whereas osteoblasts secrete, mineralize and form the new osteoid. The osteoclasts require weeks to resorb bone, whereas the osteoblasts need months to produce new bone. Therefore, any process that increases the rate of bone remodeling results in a net bone loss over time. Furthermore, in periods of rapid remodeling, bone is at an increased risk for fracture because the newly produced bone is less densely mineralized.[5]

Bone mass peaks by the third decade of life and slowly decreases afterward. The failure to attain optimal bone strength by this point is one factor that contributes to osteoporosis. Therefore, nutrition and physical activity are important during growth and development. Genetic factors play a principal role in determining an individual's peak bone strength. Ethnicity and gender also have an influence on the development of osteoporosis. The risk of developing osteoporosis is higher in Caucasian women compared to other groups.[1]

Development of Bone Disease in IBD

The pathogenesis of bone disease in IBD is multifactorial. Patients are at increased risk for development of bone disease due to nutritional deficiencies in Vitamin D and calcium, decrease in gonadal function, disease-related inflammatory activity and most commonly as a result of medications, especially glucocorticoid therapy. Glucocorticoid-induced bone disease is such a significant component of osteoporosis and osteopenia in the IBD population that it will be discussed separately (see next article by Lidofsky and Smith).

Vitamin D, calcium and parathyroid hormone help to maintain normal bone homeostasis. Insufficient dietary calcium or impaired intestinal absorption of calcium due to small bowel disease can lead to secondary hyperparathyroidism. Parathyroid hormone is secreted in response to low serum calcium levels and increases calcium resorption from bone, decreases renal calcium excretion, and increases renal production of 1,25-dihydroxyvitamin D all in an attempt to raise the serum calcium level. This active hormonal form of vitamin D optimizes calcium and phosphorous absorption from the gut, inhibits parathyroid hormone synthesis, and plays a minor role in bone resorption. Vitamin D deficiency has been estimated to occur in 30-60% of patients with CD and can result in secondary hyperparathyroidism via decreased intestinal calcium absorption.[6] In CD, Vitamin D and calcium deficiency are the result of malabsorption from uncontrolled small bowel inflammation, malabsorption secondary to significant bowel resection, poor nutritional intake and patient's avoidance of dairy products.

Amenorrhea and hypogonadism are also very common in IBD patients and can contribute to decreased bone mineral density. They occur due to the inhibitory effects the chronic inflammatory illness has on the pituitary gonadal axis and the use of glucocorticoids.

Bone mineral density (BMD) is still significantly reduced in many patients in the absence of nutritional deficiencies, gonadal dysfunction or treatment with glucocorticoids implying that there are other causes of bone disease in these patients.

Inflammation has emerged as the principal pathophysiological mechanism responsible for bone loss in IBD. It is be-

TABLE 1. Criteria for Osteoporosis/Osteopenia

T-score of -1 to -2.5 SD indicates osteopenia
T-score of less than -2.5 SD indicates osteoporosis.
T-score of less than -2.5 SD with fragility fracture(s) indicates severe osteoporosis

Adapted from WHO.

lieved that bone resorption may be increased in IBD patients without a compensatory increase in bone formation. The cause of excess bone resorption is not fully understood. One possibility is increased intestinal production of cytokines that stimulate bone resorption. In CD, the main inflammatory cytokines are interferon gamma, TNF alpha and IL-6. In particular, TNF alpha and IL-6 have been shown to stimulate osteoclast activity, leading to increased bone resorption and net bone loss. Maintenance treatment with TNF alpha antagonists, such as infliximab, is associated with improvement in bone mineral density, thus implicating a role for TNF alpha in bone loss.[7, 8]

Detection of Bone Disease

Bone disease can be evaluated by diverse modalities including blood, urinary testing and bone imaging. All patients with IBD should be screened for osteoporosis with a complete blood count, serum alkaline phosphatase, creatinine, calcium, 25-OH vitamin D, testosterone level and protein electrophoresis. This testing will screen for the other causes of low bone density. There are specific biochemical markers of bone formation (bone-specific alkaline phosphatase, osteocalcin, and type I procollagen peptides) and bone resorption (urinary deoxypyridinoline, cross-linked N- and C-telopeptide).[9] These markers of bone turnover may be elevated in high bone turnover states and may be useful for monitoring and predicting response to therapy. However, currently these markers are used by bone disease specialists. Their clinical utility in osteoporosis management needs further study before recommendations are made to include them in routine testing.

Dual-energy x-ray absorptiometry (DEXA), a radiological study used to establish or confirm a diagnosis of osteoporosis/osteopenia, is considered the gold standard for bone mineral measurement. The measurement depends on the ability of bone to block the transmission of energy. DEXA is used to calculate BMD at the hip and spine. Measurements at these sites are the best predictors of fracture risk. DEXA measurements are reported as T-scores and Z-scores. T-scores represent the number of **standard deviations (SD)**s from the mean bone density values in healthy young adults, whereas Z-scores represent the number of SD from the normal mean value for age- and sex-matched controls. Z scores should be used in place of T scores when evaluating pre-menopausal women and men younger than age 50. The WHO defines a normal T-score value as within 1 SD of the mean bone density value in a healthy young adult. For each SD reduction in BMD, the relative fracture risk is increased 1.5-3 times.[1] It is important to interpret these tests with caution. A DEXA scan cannot differentiate low bone mineral density as osteopenia or osteoporosis from metabolic bone disease or osteomalacia (Vitamin D deficiency).

Insufficient dietary calcium or impaired intestinal absorption of calcium due to small bowel disease can lead to secondary hyperparathyroidism

Alternative imaging modalities for diagnosis of bone disease include conventional radiographs, quantitative CT scanning, peripheral DEXA and quantitative ultrasonography. Plain radiography is not sensitive. Approximately 30-80% of bone mineral must be lost before radiographic lucency becomes apparent on radiographs.[10]

The 2003 Guidelines from both the **American College of Gastroenterology (ACG)** and **American Gastroenterological Association (AGA)** recommend the selective screening of IBD patients with DEXA scanning. They specify the use of DEXA in patients in the postmenopausal state, ongoing corticosteroid treatment, cumulative prior use of corticosteroid exceeding 3 months, history of low trauma fracture and age over 60.[4,11]

Prevention and Treatment of Bone Disease in IBD

All patients with IBD should utilize preventive measures to ensure bone health, including low impact exercise regimens, institution of adequate calcium and vitamin D, and education regarding smoking cessation and minimal alcohol consumption.

Physical activity is very important to bone health. The benefit of a low impact exercise program on bone mineral density has been shown in patients with CD after a one year intervention. Patients who exercised 2 times per week demonstrated an increase in their bone mineral density compared to controls.[12] Patients can be referred to a physical therapist to assist in developing an exercise regimen and for instruction on proper technique.

It has been accepted that calcium and vitamin D are essential, but frequently not sufficient for prevention and treatment of osteoporosis. The supplementation of calcium and vitamin D has been shown to have a modest effect on reducing fracture occurrence.[13] The AGA recommends Vitamin D 800 IU/day and calcium 1000-1500mg/day to minimize bone loss.

Patients with IBD who are receiving appropriate vitamin D and calcium supplements should have measurement of bone density every two years. Patients who continue to lose bone on this regimen should be considered for antiresorptive therapy.[4]

Antiresorptive agents, including bisphosphonates (both oral and intravenous), the **selective estrogen-receptor modulator (SERM)** raloxifene, calcitonin, and the anabolic agent teriparatide, are currently used for osteoporosis treatment.[10, 13] There are no comparative data on the relative efficacy of the different antiresorptive drugs in patients with IBD.

Bisphosphonates are stable analogs of inorganic pyrophosphate that have a high affinity for hydroxyapatite crystals. They bind to sites of active bone resorption and inhibit osteoclastic resorption. Bisphosphonates are approved in the United States for the prevention and treatment of postmenopausal osteoporosis, osteoporosis in males, and steroid-induced osteoporosis. They include etidronate (Didronel), pamidronate (Aredia), aledronate (Fosamax), risedronate (Actonel), ibandronate (Boniva) and clodronate (not available in US). A systematic review of randomized controlled trials evaluating alendronate and risedronate revealed that both increase bone mineral density in the spine

and hip and reduce risk of fracture by 30-50%.[14, 15] There are scant data evaluating the effectiveness of bisphosphonate therapy in IBD patients.

Hormone replacement therapy has been shown to increase bone mineral density in postmenopausal women with IBD. However, in the Women's Health Initiative trial hormone replacement therapy was associated with an increased risk of breast cancer, myocardial infarction, stroke and venous thromboembolic events and is no longer recommended as a treatment of osteoporosis in postmenopausal women. Bisphosphonates should be used instead of estrogen and progestin in postmenopausal women.

SERMs act as weak estrogens in some organ systems, while acting as estrogen antagonists in others. Raloxifene (Evista) is approved for the prevention and treatment of postmenopausal osteoporosis. It was shown to reduce spinal fracture rate, but not effective in prevention of hip fracture.[10, 13]

Calcitonin (Micalcin) acts directly on osteoclasts to inhibit bone resorption. It is available as a subcutaneous injection and an intranasal spray. It has been reported to reduce spinal fractures, but not hip fractures.[10, 13]

Teriparatide is a biological product that contains a portion of the human parathyroid hormone. It is the first approved agent for the treatment of osteoporosis that stimulates bone formation. Teriparatide is approved in the United States for postmenopausal osteoporosis and primary or hypogonadal osteoporosis in men. The major limiting factors are its subcutaneous administration and its cost. There are concerns with prolonged use (>24months) and development of osteosarcoma.[10, 13]

Conclusion

Bone disease in IBD is preventable and warrants investigation. It is the role of both the gastroenterologist and the primary care physician to evaluate for bone disease in IBD patients and to refer to a specialist when appropriate (endocrinologist or rheumatologist) to ensure adequate prevention and treatment of this silent disease.

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Jeanette G. Smith, MD, is an Instructor in the Department of Medicine, The Warren Alpert Medical School of Brown University.

Sheldon Lidofsky, MD, is a Clinical Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

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Discussion of off-label or investigational drug: Miacalcin

Correspondence

Jeanette G. Smith, MD
University Medicine Foundation
Department of Gastroenterology
110 Lockwood Street, Suite 116
Providence, RI 02903
phone: (401) 444-3575
e-mail: jsmith9@lifespan.org