

Osteoporosis and Gastrointestinal Disease

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Abstract: Gastrointestinal disease is often overlooked or simply forgotten as a cause of osteoporosis. Yet, the consequences of osteoporotic fractures can be devastating. Although the bulk of the published experience regarding osteoporosis is derived from the postmenopausal population, this review will focus on gastrointestinal disorders implicated in osteoporosis, with an emphasis on inflammatory bowel disease and celiac disease. The unique aspects of gastrointestinal diseases associated with osteoporosis include early onset of disease (and, therefore, prolonged exposure to risk factors for developing osteoporosis, particularly with inflammatory bowel disease and celiac disease), malabsorption, and maldigestion of nutrients necessary for bone health and maintenance (eg, calcium, vitamin D), as well as the impact of glucocorticoids. These factors, when added to smoking, a sedentary lifestyle, hypogonadism, and a family history of osteoporosis, accumulate into an imposing package of predictors for osteoporotic fracture. This paper will review the identification and treatment strategies for patients with gastrointestinal disorders and osteoporosis.

Osteoporosis is a common complication of a variety of bowel diseases. This review will highlight the epidemiology of osteoporosis in gastrointestinal (GI) diseases, as well as the pathophysiology of osteoporosis, which includes systemic inflammation, malnutrition of calcium and vitamin D, secondary hypogonadism, and medication-induced bone loss. This review will also address the diagnosis and treatment of osteoporosis, including features of bone physiology as well as the relevance to GI disease.

Epidemiology: Why Should Gastroenterologists Be Concerned About Bone Disease?

Osteoporosis is generally considered to be a disease of the elderly, yet it may present in a bowel disease patient of any age. Osteoporosis may also be the initial sign of bowel disease in otherwise asymptomatic patients, who then may be referred to a gastroenterologist for further evaluation and management.

Osteoporosis-related fractures are a major public health burden, estimated at 1.6 million fractures per year.¹ This figure outweighs

Table 1. Fracture Risk in Gastrointestinal Disease

Gastrointestinal disease	Low bone density*	Fracture risk
Celiac disease ¹⁰⁻¹⁹	40% increased risk vs controls	1.4 × normal
Postgastrectomy ²⁰	32–42%	55%
Crohn's disease ^{19,21-31}	Osteopenia: 22–55% Osteoporosis: 3–6%	40–60% vs controls 1.3–14 × that in ulcerative colitis Greatest risk: the elderly with inflammatory bowel disease
Ulcerative colitis ^{19,25-31}	Osteopenia: 32–67% Osteoporosis: 4–50%	Risk for men slightly higher than that for women Overall, same as Crohn's disease vs no increase
Orthotopic liver transplant/ primary biliary cirrhosis ³²⁻³⁴	46% (17% in the first year)	36.7%

*Femoral neck and L-S spine.

the incidence of stroke (420,000), myocardial infarction (365,000), or breast cancer (250,000) per year.^{2,3} Despite public perceptions, osteoporosis is not only a disease found in women; approximately 20% of hip fractures in the elderly occur in men.⁴

Fractures have significant associated morbidity and mortality. Hip fractures in elderly women are associated with a 15% excess mortality in the first year compared to that of age-matched controls (particularly men).⁵⁻⁷ Multiple vertebral fractures and the associated kyphosis increase long-term mortality, presumably due to restrictive lung disease and decreased activity.⁸

Permanent disability occurs in 30% of the elderly with fractures, the inability to walk without assistance in 40%, or to maintain independent daily living in 80%, with a health cost of 13 billion dollars per year. It is important to note that these morbidity and mortality data are based mainly upon elderly individuals with postmenopausal and “senile” osteoporosis, and may not apply to younger individuals with secondary diseases, such as GI diseases.

Osteoporosis in Gastrointestinal Diseases

Osteoporosis is common in GI diseases, particularly those associated with malabsorption and maldigestion (celiac disease, postgastrectomy, short gut, pancreatic insufficiency); inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis); chronic liver disease (cholestatic and hepatocellular diseases); or may be secondary to therapy for GI disease (liver and small bowel transplant, total parenteral nutrition, gastric bypass, or medications such as proton pump inhibitors [PPIs] in gastroesophageal reflux disease [GERD] patients).

Osteoporosis may also be the only presenting finding for a GI disease in an otherwise asymptomatic patient. For example, the frequency of celiac sprue in asymptomatic osteoporotic patients presenting to a metabolic bone clinic was 3%, compared to 0.3% in a general medicine clinic in the same institution (Table 1).⁹⁻³⁴

The prevalence of osteoporosis is quite varied in different IBD populations, ranging widely from 13% to 50%, in part due to variation in patient characteristics, dual energy x-ray absorption (DEXA) methodology, age, disease duration, and the size of the study.^{20,21} Low body mass index (BMI; <22 kg/m²) has been shown to be frequently associated with low bone mineral density (BMD), along with use of glucocorticosteroids (GCS), smoking, hypogonadism, calcium, vitamin D deficiency, and disease activity. Change in lean body mass correlated better with BMD at the hip than with fat tissue.³⁵

A Cleveland Clinic study revealed that 32% of 327 patients with ileal pouch anal anastomosis (IPAA) who were followed for a median of 4 years had low BMD. Bone fragility was documented in 11 patients (10.5%) of the low BMD group and 13 of 222 patients (5.9%) of the normal BMD group. Low BMD was associated with advanced age, low BMI, and failure of calcium supplementation. IPAA factors alone were not associated with bone loss.³⁶

Celiac patients are prone to vitamin D and calcium malabsorption, reduced calcium intake, secondary hyperparathyroidism, and neutralizing antibodies to osteoprotegerin (OPG), all leading to an increased fracture risk^{9,37} with a hazard ratio of 1.4, according to documentation. Low BMI, insulin-like growth factor (IGF-10), and leptin levels also contribute to a reduced

BMD, which improves with therapy. Asymptomatic celiac patients may present only with low bone density. Overall, risk factors for osteoporosis include disease activity, age, gender, menopausal status, and GCS.¹⁰

Understanding Bone Physiology

Remodeling of Bone

A review of normal bone physiology is needed to understand the pathophysiology and treatment strategies for osteoporosis in GI patients. The normal bone remodeling cycle includes metabolically quiet bone covered by resting lining cells with osteocytes buried within the bone itself. In response to signals that have not yet been uncovered, bone remodeling begins with osteoclasts resorbing bone. Osteoclasts are multinucleated giant cells of hematopoietic origin and are highly polarized cells. The portion of the cell touching the bone surface forms a tight seal around its edge. The membrane facing the bone forms a ruffled border, allowing a high surface area. The cells secrete both hydrogen ions to resorb the mineral component and cathepsins or proteases to digest the protein matrix. The osteoclastic phase lasts for 2–3 weeks before bone resorption ceases, presumably due to apoptosis of the osteoclast.

Bone-forming cells—the osteoblasts—then migrate onto the newly resorbed bone surface. Osteoblasts are derived from multipotential mesenchymal cells, which can differentiate into osteoblasts or adipocytes. This pathway is affected by gut hormones such as serotonin, and by pharmacologic therapy such as thiazolidinediones. The osteoblast lays down new bone, first in the form of protein matrix, including type 1 bone collagen, and non-collagenous proteins such as osteocalcin. The osteoid, or protein matrix, is then mineralized with hydroxyapatite. The osteoblastic anabolic stage is significantly longer, lasting months. The osteoblast is eventually buried within the newly made bone and becomes an osteocyte.³⁸

Many factors control bone remodeling rates, including sex hormones, vitamin D, parathyroid hormone (PTH), and a variety of cytokines, including interleukin (IL)-1 and IL-6. One of the most important factors is the receptor activated nuclear factor kappa β (RANK)/RANK-ligand (RANKL) system (which will be discussed later on in this review).

Bone remodeling is best measured by histomorphometry of transiliac bone biopsy specimens with labeling of the bone with tetracyclines. However, this is not a practical option for routine clinical care. Noninvasive measures of bone remodeling include biochemical markers of bone turnover (eg, serum or urine assays measuring osteoclastic bone resorption such as urinary n-telopeptides, a measure

of type 1 bone collagen degradation). Markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and the procollagen extension product P1NP. Although markers are accepted as validated research tools, their utility in individual patients is more controversial, due to intra- and interpatient variability.^{39,40}

Adult bone mass, as measured by BMD, peaks in the second to third decades of life and then declines. Bone mass is commonly measured by DEXA.⁴¹ Because of machine and skeletal site differences, the results are noted by a derived statistical value, the T score, which is not the absolute value, but the number of standard deviations above or below the BMD average value in young healthy adults (ages 20–29). The Z score, or score of age-matched controls, is less commonly used, except for research studies. The World Health Organization (WHO) divides bone density into the following categories: a T score of -1.0 and greater is normal; a T score between -1.0 and -2.5 signifies osteopenia; and a T score of -2.5 and below signifies osteoporosis.⁴² It should be noted that these cutoffs were defined for postmenopausal women and have not been validated for men or premenopausal women. The WHO has also recognized other risk factors for predicting future fractures, using a model known as FRAX, which estimates the absolute risk of fracture using age, BMI, prior fractures, family history, use of steroids, and comorbid diseases.⁴³

Pathophysiology of Gastrointestinal-related Bone Diseases

Factors contributing to bone loss in GI disease include malabsorption, systemic inflammation, secondary hypogonadism, and anti-inflammatory medications, particularly GCS. Other possible mechanisms include metabolic acidosis and, possibly, the effects of PPIs in GERD.

Women have the highest risk of fracture because of a genetically lower peak bone mass than men and more rapid bone loss after menopause. However, bone fragility and susceptibility to fracture may occur in both men and women in many different scenarios, such as the following: failure to achieve peak bone mass (eg, celiac sprue in childhood); normal peak bone mass but either early bone loss (premature ovarian failure) or rapid bone loss (drug-induced); high-turnover osteoporosis, in which bone resorption exceeds bone formation (ie, most forms of osteoporosis) seen with chronic inflammation; low-turnover osteoporosis, in which bone resorption is normal but osteoblastic activity is reduced, including bone collagen production and mineralization, as is typical of GCS-induced osteoporosis⁴⁴; and abnormal mineral properties such as osteomalacia (eg, low vitamin D in malabsorptive diseases).

Malabsorption

Malabsorption occurs in many small-bowel disorders (such as celiac sprue) and can be iatrogenic, as in gastric bypass surgery. Affected nutrients include calcium, phosphorous, and vitamin D, though vitamin K and protein deficiency can also be critical in select circumstances. Poor absorption of vitamin D and calcium results in secondary hyperparathyroidism, which increases rates of bone loss. Low vitamin D levels or hypocalcemia can lead to osteomalacia (rickets), in which the new protein matrix, osteoid, remains unmineralized. The standard recommended daily allowances (RDAs) of nutrients are often inadequate, and GI patients require much higher intakes. Secondary hyperparathyroidism is initiated when vitamin D is less than 30 ng/mL. Vitamin D deficiency occurs most frequently from a lack of sunlight exposure, as dietary vitamin D supplies only 5–10% of total vitamin D requirements. Bowel resection patients absorb vitamin D poorly, even with oral supplements. Low vitamin D levels may be partly due to enterohepatic recirculation and loss, even with adequate sunlight exposure.⁴⁵

Vitamin D deficiency is common in patients with IBD, and may not only contribute to bone disease, but also worsen the underlying inflammatory bowel disorder.⁴⁶ In a Scandinavian study of 182 CD patients versus 62 healthy patients, vitamin D deficiency (low serum 25-OH vitamin D <25 nmol/L) was associated with increased CD activity (increased Crohn's disease activity index [CDAI] and C-reactive protein [CRP] levels). Patients on vitamin D supplementation had lower CDAI and CRP levels.⁴⁷ Smokers had lower vitamin D levels. While in remission, CD patients have a normal response to vitamin D, which enhances calcium absorption. However, concomitant GCS use, the extent and location of the inflammation, and prior resections may still impact such absorption.⁴⁸

In a study by Binion and colleagues, 50% of 504 Wisconsin IBD patients were deficient in vitamin D, with 11% having had a severe deficiency. Vitamin D may be independently associated with IBD activity, particularly in CD patients with a worsened quality of life. This was not true for ulcerative colitis, and vitamin D levels did not correlate with hospitalization or surgical rates.⁴⁹

Vitamin D deficiency contributes to activation of a T-cell mediated immune response, which lessens the integrity of intestinal mucosal barriers with a higher risk of microbial infection.⁵⁰ Vitamin D is necessary for upregulating tight junction and adherent junction proteins.⁵¹ When given to IL-10 knockout mice, vitamin D ameliorated active disease.⁵²

Inflammation

Inflammatory cytokines such as serum IL-1 β , tumor necrosis factor (TNF)- α , IL-6, and IL-1 are increased

in IBD, with direct effects on bone turnover.⁵³ Severe osteoporosis can be the presenting symptom in children with CD before treatment has been initiated.⁵⁴ Patients with symptoms lasting over 6 months have a lower bone density than that of age-matched controls.

TNF- α inhibits differentiation of osteoblasts from pluripotent progenitor cells, as well as expression of a critical transcription factor required for osteoblast differentiation.⁵⁵⁻⁵⁷ TNF- α also induces osteoclast differentiation and increases osteoclastic bone resorption.⁵⁸ Mature osteoclasts are relatively short-lived cells, but TNF- α dramatically increases their survival and protects them against apoptosis.⁵⁹ TNF- α also inhibits bone collagen synthesis in vitro.⁶⁰ TNF- α and IL-1 β contribute further to bone resorption. They also sensitize osteoblasts to Fas-mediated apoptosis, thus diminishing bone formation.^{61,62} Finally, TNF- α inhibits the action of 1,25 (OH) vitamin D through activation of a nuclear inhibitor that antagonizes the effect of vitamin D.⁶³ In contrast, IL-12 and IL-18 have been shown to potently inhibit osteoclast formation.⁶⁴ Transforming growth factor- β has both positive and negative effects on osteoclast differentiation.⁶⁵ Expression of IL-18 is increased in CD patients.⁶⁶ Although local cytokine production has the greatest effect on bone metabolism, systemic IL-12 and IL-18 may also protect against negative bone balance.

The Role of the RANK/RANKL System

RANK is a cell-surface receptor on osteoclasts and osteoclast precursors. The ligand for RANK is simply known as RANKL and is produced by the osteoblast. Binding of RANKL to the receptor RANK leads to osteoclast differentiation and subsequent bone resorption. This process is self-regulated by the production of the soluble antagonist OPG, which essentially acts as a decoy for RANKL, preventing its binding to RANK. Local ratios of RANKL:OPG determine net bone resorption. This system has been identified as a key regulator of bone remodeling.⁶⁷⁻⁷¹

Denosumab (Prolia, Amgen), a fully humanized monoclonal immunoglobulin (Ig)G antibody to RANKL, has been produced and acts like OPG in reducing RANKL binding to RANK and thereby decreasing bone resorption. In clinical practice, denosumab has been highly effective in clinical trials of a variety of human bone diseases, including osteoporosis and bone metastases.^{72,73}

In IBD, celiac disease, and, now, chronic liver disease, increased OPG production provides a continuous homeostatic defense against RANKL-driven osteoclastogenesis.⁷⁴ There has been a proven increase in such levels in osteopenic and osteoporotic IBD patients. Yet, IBD patients still suffer from reduced BMD of neck and lumbar spine, suggesting very active (ie, not completely controlled) RANKL production.

Interferon- γ and T Cells in Bone Resorption

Macrophage colony stimulating factor and RANKL stimulate osteoclast renewal. The net effect of interferon (IFN)- γ is bone loss by upregulating antigen presentation and thereby stimulating osteoclastogenesis with further T-cell activation.⁷⁵ This overcomes the initial suppressive effect of IFN- γ on osteoclast precursors, thereby resulting in bone loss. Future therapy may use agents that inhibit IFN- γ to reduce inflammation and bone loss.⁷⁶

Glucocorticoid-induced Osteoporosis

Early studies emphasized that the effects of GCS on calcium balance were decreased calcium absorption and increased urinary calcium excretion, leading to secondary hyperparathyroidism.⁷⁷ More recent studies suggest that these are not the primary mechanisms of bone loss due to GCS. More important are the direct effects of GCS on bone remodeling, which increases RANKL and decreases OPG even at low doses (<10 mg prednisone per day), thereby increasing osteoclast activity.⁷⁸

Steroids suppress osteoblast function, exaggerating the mismatch of bone resorption versus bone formation. There is a qualitative defect in bone strength, as well as a quantitative loss of bone density, as the risk of fracture is increased at any level of bone density versus postmenopausal osteoporosis. GCS suppresses adrenal and gonadal sex-hormone production in both genders. The loss of adrenal testosterone and dehydroepiandrosterone may be particularly critical to bone loss in women.

GCS-induced osteoporosis is dose- and duration-dependent.⁷⁹ Higher doses and longer exposure are associated with increased risks of bone loss and fracture. There does not appear to be a completely safe dose. A British study found that even doses of 2.5 mg daily of prednisone or its equivalent were associated with an increased risk of fracture.⁸⁰ As expected, higher doses were associated with a higher risk. Even as little as 3 months of therapy increases the risk of fracture. However, bone loss can generally be recovered and fracture risk restored to normal if GCS therapy is stopped at 3 months. Longer duration of therapy is associated with irreversible bone loss.⁸¹ Adverse effects may be limited by using first-pass metabolism oral steroids, which have mucosal effects and less systemic absorption. All steroids have similar adverse bone effects when used at equivalent anti-inflammatory doses. The development of selective GCS receptor ligands may allow organ-specific effects with less systemic adverse effects.

Acidosis

Although acid-base abnormalities contribute to bone loss, they have not been extensively studied. Acidosis occurs in diarrheal syndromes or in patients with urinary diversion procedures using colonic segments. The

Table 2. A Summary of Risk Factors for Osteoporosis Related to Gastrointestinal Disease

Risk factor	Diseases
Mucosal disease and decreased transit time	CD, PGx, SBS (malabsorption)
Steatorrhea impairs vitamin D absorption	All diseases
Inflammation alters bone metabolism	CD, IBD, CLD
Secondary hyperparathyroidism	All diseases
Metabolic acidosis	SBS (diarrhea), CLD (RTA)
Abnormal gonadal axis	CD, IBD, CLD

CD=celiac disease; CLD=chronic liver disease; IBD=inflammatory bowel disease; PGx=postgastrectomy; RTA=renal tubular acidosis; SBS=short bowel syndrome.

hydroxyapatite of the skeleton serves as a vulnerable buffer for the extra acid load.⁸²

Protein Pump Inhibitors

Epidemiologic studies suggest an association between the use of PPIs, low bone density, and fractures.^{83,84} The proposed mechanism of action is decreased gastric pH causing a decrease in absorption of calcium, though this theory has been questioned.⁸⁵ The available data require a risk-versus-benefits assessment of long-term usage of PPIs, particularly in patients at risk for osteoporosis.⁸⁴

Screening

A baseline BMD test by DEXA is recommended in most patients with significant inflammatory or malabsorptive diseases and repeated every 2 years.^{86,87} However, DEXA should be repeated at 1 year in higher-risk patients or those beginning GCS treatment for osteoporosis.⁸⁶ Particular care is required when interpreting DEXA in pediatric patients, as scanning is age- and stature-dependent.⁸⁸ In addition to bone density, the standard risk factors for osteoporosis (such as age, previous fractures, family history of osteoporosis, rheumatoid arthritis (RA), excessive alcohol use, and smoking; Table 2) must also be considered when interpreting fracture risk.⁴²

25-hydroxyvitamin D should be measured in patients at risk for malabsorption with a goal of blood levels of 30 ng/dL. Serum levels of the active metabolite 1,25 dihydroxyvitamin D do not correlate with nutritional stores and should not be measured. Measuring serum PTH

levels and 24-hour urine calcium collections may be useful in selected patients. Secondary hyperparathyroidism and low urinary calcium levels may be seen in patients with severe malabsorption or low vitamin D and may be useful to monitor with replacement. Measurement of testosterone should be considered in men.⁸⁹

Management

The first goal in managing osteoporosis is to treat the underlying disease. Improvement in the underlying active disease improves BMD in IBD.⁹⁰ GCS use improves the disease state but requires both an exit strategy and use of the lowest dose for the shortest duration. GCS use may suppress disease activity, but its influence on bone loss and overall risks, particularly in CD (not ulcerative colitis), presents a greater fracture risk.⁹¹ Less bone loss is seen with budesonide in GCS-naïve CD patients.

Calcium and vitamin D supplements are generally required, as the standard RDAs are rarely met with diet only. The RDA for calcium is 1,000 mg per day for men and premenopausal women and 1,000–1,500 mg per day for postmenopausal women.^{92,93} As the average daily calcium intake is less than 500 mg daily, most patients will need 500–1,000 mg daily as a supplement. The current RDA of vitamin D 400 IU per day is clearly inadequate.⁹⁴ The National Osteoporosis Foundation recommends routine supplementation with 800–1,000 IU daily.⁹⁵ Many patients have vitamin D malabsorption and require even higher doses. If the baseline 25-vitamin D level is less than 15 ng/mL, most recommendations are to give 50,000 units per week for 8–12 weeks and then to re-evaluate. The goal is to maintain the serum level of 25-OH vitamin D at 30 ng/mL or higher, with higher levels possibly having additional health benefits.⁴⁰ It is particularly important to replace calcium and vitamin D in patients beginning antiresorptive therapy such as bisphosphonates, as treatment can induce hypocalcemia. Exercise improves bone density in IBD patients and should be recommended for all patients, though long-term studies on compliance and fracture effects are lacking.⁹⁶

The decision to add pharmacologic therapy, in addition to calcium, vitamin D, exercise, and control of underlying disease, is based upon fracture risk. Medical therapy is recommended for GCS-induced osteoporosis patients if their T score on DEXA is less than –1.0, but this may not apply to all women of child-bearing potential.⁷⁸

Medical therapy options for treatment or prevention of osteoporosis include antiresorptive and anabolic therapies. Antiresorptives approved by the US Food and Drug Administration (FDA) include bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), denosumab, and calcitonin. The only FDA-approved

Table 3. Therapeutic Options for Osteoporosis

<p>Nonpharmacologic therapy</p> <ul style="list-style-type: none"> • Diet (eg, gluten-free diet in celiac disease) • Exercise • Discontinuation of smoking • Minimization of glucocorticosteroids • Calcium • Vitamin D
<p>Pharmacologic therapy</p> <ul style="list-style-type: none"> • Bisphosphonates • Selective estrogen receptor modulators (eg, raloxifene) • Estrogen/progestin • Calcitonin • Calcitriol • Vitamin K • Denosumab • Teriparatide

anabolic agent is teriparatide (Forteo, Lilly). Table 3 lists the therapeutic options.

Bisphosphonates

Bisphosphonates are the most commonly used class of drugs for the prevention and treatment of all forms of osteoporosis.⁹⁷ They share a common structure (P-C-P), which is similar to that of pyrophosphate; the central carbon replaces oxygen and prevents rapid metabolism. The PCP backbone is responsible for binding to hydroxyapatite in bone. Bisphosphonates differ in side-chain binding to the central carbon (Table 4).⁹⁸ The earliest drugs, such as etidronate (Didronel, Warner Chilcott), had simple side chains. More potent drugs have nitrogen on the side chain (aminobisphosphonate).

Mechanism of Action Bisphosphonates attach to bone undergoing resorption. They enter active osteoclasts and adhere to bone (via failure of “ruffled” border formation); the osteoclasts then fail to produce the protons necessary for continued bone resorption and undergo apoptosis, or programmed cell death.^{98,99} Aminobisphosphonates have a different mechanism of action and are more potent inhibitors of bone resorption than simple bisphosphonates. They inhibit farnesyl pyrophosphatase, an enzyme involved in the production of long-chain fats from the mevalonate pathway (which is critical for cholesterol biosynthesis). This disrupts protein prenylation and alters the traffic of key regulatory proteins in the cell membrane. Simple bisphosphonates such as etidronate are metabolized by osteoclasts that exchange with the

Table 4. Types of Bisphosphonates

Non-nitrogen-containing bisphosphonates	Nitrogen-containing bisphosphonate alkyl	Nitrogen-containing bisphosphonate heterocyclic
Etidronate	Pamidronate	Risedronate
Clodronate	Alendronate	Zoledronate
Tiludronate	Ibandronate	

terminal moiety of adenosine-5'-triphosphate, inactivating it as a source of energy and resulting in apoptosis of the osteoclast.⁹⁸

Etidronate can inhibit mineralization leading to osteomalacia with prolonged use, which is not the case for aminobisphosphonates. However, etidronate has not yet been approved for osteoporosis in the United States.

Pharmacokinetics Approximately 0.6% of bisphosphonates given orally are absorbed when taken on an empty stomach; 50% of the absorbed bisphosphonate is cleared by the kidney, and 50% enters the bone (though this number will increase with high bone turnover). Although the plasma half-life is 1 hour, bisphosphonates persist in bone for the life of the patient (ie, for at least 10 years), which raises concerns about use in young patients or those considering pregnancy.¹⁰⁰ Factors affecting skeletal retention of bisphosphonates include the rate of bone turnover that controls the binding site availability; renal function, which clears unbound bisphosphonates; and the particular potency of that bisphosphonate for bone matrix incorporation.¹⁰¹

Reduction in markers of bone resorption can be anticipated within 3 months of onset of oral bisphosphonates and will remain so with continued use. More rapid suppression of bone resorption will occur with intravenous (IV) bisphosphonates. The duration of that suppression varies with the particular product's potency (eg, 2 years of suppression after IV zoledronic acid).⁹⁹

Clinical Trial Results Bisphosphonates are highly effective at reducing fracture risk in postmenopausal and GCS-induced osteoporosis; the trial data have been extensively reviewed and will not be repeated here.⁹⁹ The study and use of oral bisphosphonates in patients with gut disorders has lagged due to fears of either inadequate absorption or GI safety, but several studies have demonstrated safety and efficacy. Oral bisphosphonates are well absorbed even in Crohn's patients.¹⁰² Efficacy trials have studied changes in bone density and biochemical markers of bone

turnover, but they have not been powered to demonstrate fracture outcomes. Alendronate (Fosamax, Merck), risedronate (Actonel, Warner Chilcott), pamidronate (Aredia, Novartis), and clodronate, but not etidronate, have been shown to reduce turnover and increase bone mass.¹⁰³⁻¹¹⁰ For example, 40 postmenopausal women with IBD who were given risedronate over a 3-year study period revealed significantly higher BMD, reduced bone turnovers, and a trend toward a reduction in vertebral and nonvertebral fracture rates compared to 41 placebo-treated female controls.¹¹⁰

Despite fears of increased GI risks such as gastritis or worsening IBD, oral therapy has been well tolerated from a GI perspective. In an animal model, ibandronate (Boniva, Roche) was shown to have a potential benefit on the gut disease itself, decreasing the potential for carcinogenesis in a murine model of ulcerative colitis.¹¹¹

Adverse Events A variety of adverse events have been reported with bisphosphonates. Esophageal ulcerations have been reported with prolonged contact, particularly if dysmotility exists. Twenty-three cases of esophageal cancer were identified between 1995 and 2008 by the FDA Office of Surveillance and Epidemiology. Thirty-one cases have been reported in Europe and Japan using alendronate, and 10 other cases had suspected associations with risedronate, ibandronate, and etidronate. These carcinomas occurred with Barrett esophagus. The median duration of exposure was 2.1 years (range, 0.5–10 years), with 8 deaths; most patients were women (n=18; 78%), with an average age of 74 years. Six deaths occurred in women in Europe and Japan (n=22; 71%), with a median age of 68.5 years.¹¹² However, these associations have been challenged.¹¹³

IV bisphosphonates can cause an acute-phase reaction or flu-like syndrome in up to 20–22% of patients. The incidence is much lower with repeated doses. This reaction is most common during the first week and can last for 3–5 days with lymphopenia, which will resolve.⁹⁹ The reaction can be prevented or treated with acetaminophen.

Hypocalcemia can occur if the patient has pretreatment calcium or vitamin D deficiency, or renal insufficiency with secondary hyperparathyroidism. Hypocalcemia should be managed with 1,000 mg calcium and 800–1,000 IU vitamin D daily before bisphosphonates.

Rapid infusions of IV pamidronate or zoledronate can alter renal function and cause rare cases of renal failure. This risk is reduced by slowing the infusion rate and ensuring that the patient is adequately hydrated. Monitoring of renal function is required. The FDA has approved therapy only for patients with a creatinine clearance of greater than 35 cc/min.

Osteonecrosis of the jaw is a nonhealing ulcer of the jaw with exposed bone that presents after 8 weeks in the

absence of radiotherapy. It was first seen with IV aminobisphosphonates in cancer patients and has a frequency of 1% in breast cancer patients and 3% in multiple myeloma patients. The frequency is much lower in osteoporosis patients (ie, approximately 1–10/100,000 per year).^{114,115} Osteonecrosis did not appear to be an issue in clinical trials (most trials had no cases of this adverse event). For example, in the zoledronate HORIZON trials, which randomized 10,000 patients to zoledronate or placebo annually for approximately 3 years, there were 2 cases of osteonecrosis, 1 on placebo and 1 on active drug.¹¹⁶ The mechanism of action of osteonecrosis is not known. Suppression of bone turnover remains unproven and would not explain why the jaw is the only site presenting with this problem.

It is advised that patients undergo routine dental examinations (including a discussion regarding the risks and benefits of bisphosphonates prior to initiation of therapy) and that they are reassured that osteonecrosis is rare. An active prevention protocol should be initiated before dental procedures.^{117,118} Dental surgery may still be performed in oral bisphosphonate patients.

Unusual subtrochanteric fractures of the femoral shaft have been reported (but in small numbers) in patients on long-term bisphosphonates.¹¹⁹ These patients have an unusual pattern of simple transverse or oblique fractures of the femur below the lesser trochanter, with “beaking” of the cortex on one side and thickened cortices. There is a pain prodrome, and the fractures can occur in the absence of trauma. Contralateral pain with mirror-image abnormal findings detected on bone scans and magnetic resonance imaging has also been described. The mechanism of action is not known but may represent an inability to heal microfractures with accumulated damage in a highly stressed skeletal site.

The incidence of atrial fibrillation was 1.3% in a pivotal IV zoledronic trial versus 0.5% in controls.¹¹⁶ Although first suspected with oral bisphosphonates (alendronate), this association was not substantiated in larger studies of this drug or with risedronate.^{120,121} An FDA statement dismissed the possibility of atrial fibrillation being a consequence of bisphosphonate use.

Ocular findings with bisphosphonates (uveitis, pain episodes, and photophobia) are rarely seen with either oral or IV bisphosphonates. This is an unpredictable and idiosyncratic reaction.

Prolonged skeletal half-life of bisphosphonates permits a continued effect (eg, 5 years after initial use). The optimum dose and duration of bisphosphonates remains unclear when continued beyond that seen in clinical trials. Some physicians offer stable or moderate-risk patients a 1-year holiday after 5 years of alendronate therapy based upon the results of the cessation arm of

the FLEX study.¹²² As of yet, there is no consensus on this issue.

Calcitonin

Calcitonin interacts with osteoclast receptors, thereby reducing bone resorption. A 5-year trial in postmenopausal women showed a reduction of vertebral fractures at a dose of 200 IU daily intranasally, but not at a dose of 400 IU daily, and no effect on BMD or nonvertebral fractures.¹²³ This drug has not been studied in GI disorders. Calcitonin is used infrequently, due to the availability of more potent alternatives.

Teriparatide

Teriparatide or the 1-34 amino acid fragment of human recombinant parathyroid hormone (rhPTH 1-34) is the only directly anabolic agent approved for the treatment of osteoporosis. Daily subcutaneous dosing of PTH is anabolic on osteoblasts compared to continuous endogenous hyperparathyroidism, which causes bone loss. In the pivotal fracture trial, teriparatide therapy significantly increased BMD and reduced fractures compared to placebo.¹²⁴ rhPTH was more effective on BMD in osteoporosis in high-risk patients for fracture than alendronate. When compared to alendronate for the treatment of GCS-induced osteoporosis, teriparatide resulted in larger increases in BMD.¹²⁵

Strontium Ranelate

Strontium ranelate is partly anabolic to bone increasing bone formation and lessening resorption in postmenopausal osteoporosis. The exact mechanism of action remains unclear. Strontium has not been approved for use in the United States.

Hormonal Replacement Therapy and SERMs

Hormonal replacement therapy (HRT) and SERMs have not been studied specifically in GI diseases. Estrogen can significantly decrease the fracture rate by 24–34%, but the increased risks of cardiovascular disease and breast cancer reported in the Women’s Health Initiative has virtually derailed any further use of HRT as first-line therapy.¹²⁶ Raloxifene (Evista, Eli Lilly) is approved for treatment of postmenopausal osteoporosis and has been shown to reduce spine (but not hip or nonvertebral) fractures. Newer SERMs may offer improved fracture protection.¹²⁷

Denosumab

Denosumab has not been formally studied in GI disorders. It was highly effective in postmenopausal osteoporosis⁷¹ and has recently been approved by the FDA for treatment of postmenopausal women at high risk for fractures. Ongoing studies in oncology patients include

the use of denosumab to treat the effects of androgen deprivation therapy for prostate cancer⁷² and for treatment of skeletal metastases.

Anti-Tumor Necrosis Factor Therapy

IBD patients who achieve remission in response to medical therapy have significantly better BMD (ie, Z scores) than those with active disease, particularly with a longer duration of remission. This response to therapy was seen for azathioprine and, now, anti-TNF therapy. A positive bone remodeling effect was reported with infliximab (IFX; Remicade, Centocor) monotherapy but only in bone formation markers; BMD and fracture rates were not studied, nor was there any correlation with clinical activity.¹²⁸ Abreu and associates¹²⁹ noted that in 38 IBD patients, IFX increased bone alkaline phosphatase as a marker of bone formation but did not affect N-telo peptide of type I collagen as an indicator of bone resorption. Similar results in another study of bone markers still did not show correlation with clinical disease activity (ie, response).¹³⁰

RA studies using anti-TNF agents did show an increase in bone formation markers and lessened bone resorption (decreased deoxypyridinoline).¹³¹ A prospective IFX study over 1 year in 102 RA patients revealed lessened bone loss but in only the spine and hip, and not the metacarpals.¹³² A third study also conducted over 1 year in 26 RA patients showed a beneficial trend in BMD in the femoral neck and spine.¹³³

An Israeli study showed that the use of IFX in IBD patients improved BMD according to DEXA in 18 patients when compared to 16 controls. The mean ages were 25.6 years and 28.1 years, respectively. After 21 months (for treated patients) or 28 months (for nontreated patients), T scores improved in the femoral neck in the IFX group, whereas they deteriorated in the control group.¹³⁴

A marked improvement in biomarkers of bone formation was recorded in a pediatric study (REACH) during IFX therapy. An impressive increase in bone-specific alkaline phosphatase and N-terminal propeptide of type I collagen (PINP) occurred with an associated increase in height Z scores. PINP improvements correlated with a decreased pediatric CDAI. Increased C-telopeptide of collagen cross-links and deoxypyridinoline mirrored bone formation and the resorption process with the increase in linear growth.¹³⁵

In CD patients from the University of Pennsylvania who were given IFX alone (n=23) or both IFX and bisphosphonate therapy (n=36), dual therapy patients had greater improvement in BMD (+6.7%) than bisphosphonates alone (+4.46%), though GCS use

inhibited this effect. Bisphosphonate patients improved lumbar spine BMD compared to those not on bisphosphonates (+3.97% T score vs -3.68% not on bisphosphonates).¹³⁶ It can be thus concluded that IFX and bisphosphonates are additive in their benefits on BMD and that bisphosphonates are beneficial in CD, but are inhibited partially by GCS use.

Body Mass Index, Fat, and Bone Health

Initially thought to be an improbable theory, it has become clear that fat and bone cells derived from the same stem cells are linked to the process of bone remodeling. Bone growth is dependent upon energy derived from fat cells. Hypothalamic stimulation of fat cells regulate bone mass by controlling energy utilization and insulin secretion.

Treatment of obesity is intimately involved with skeletal (bone) dynamics. Given the low BMI as an index of osteoporosis, it would appear counterintuitive that obesity is a factor as well, yet osteoporosis and obesity coexist in Cushing syndrome, adult onset diabetes, and thiazolidine-treated diseases, with an increased fracture risk. Fat deposition in bone marrow increases fractures and is inversely related to BMD.^{137,138}

GCS use contributes to bone loss by shifting stem cell differentiation toward fat cells. BMD in anorexia nervosa increases only with weight gain. Fracture risk is greater in the obese metabolic syndrome patient. Bariatric surgery produces a decrease in bone mass, as well as weight reduction. Composition of total body mass values and BMD in IBD patients revealed that lean tissue mass determinations have a greater correlation than fat tissue with bone density, particularly for total hip and total body bone measurements. An increase or decrease in hip bone density was best correlated with an increase or decrease in all body mass variables, respectively.^{138,139}

A gluten-free diet will benefit BMD scores in celiac patients, but the mechanism remains unexplained. It is worrisome that even after years of a gluten-free diet, sprue patients remain at an increased risk for hip fracture, though this has been disputed by some observers.

Conclusion

It is essential to recognize the nexus between chronic GI diseases and bone inflammatory disorders mediated by TNF- α , IL-1, IL-6, and IFN- γ . The interweaving of bone remodeling factors such as RANK, RANKL and OPG are in continual flux. Control of inflammatory disease activity and nutritional support play a key role, among the other risk factors for osteoporosis. Aggressively providing the necessary global therapies by the treating physician remains a daunting problem.

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