Chapter 13
Osteoporosis in Gastrointestinal Diseases of Malabsorption and Inflammation

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Chronic conditions affecting the gastrointestinal tract and its functions can have profound long-term effects on bone. Pathological conditions resulting in malabsorption of key vitamins and minerals, as well as altered metabolism of essential components of bone, can have lasting effects on bone health. Individuals with Crohn's disease, ulcerative colitis, pancreatic insufficiency, celiac disease, and restrictive forms of bariatric surgery, as well as gastric bypass or partial small bowel resection, are at significant risk for osteoporosis. This chapter will cover the above topics and offer strategies for clinician awareness and monitoring, diagnosis, and treatment approaches, both nonpharmacologic and pharmacologic in nature.

Inflammatory Malabsorption Disorders

Inflammatory Bowel Disease

Definition and Pathophysiology

Inflammatory bowel disease (IBD) is an umbrella term that combines both Crohn's disease and ulcerative colitis. Both disorders are characterized by fatigue, abdominal pain, diarrhea, GI bleeding, and structural tissue damage to the intestine [1]. Crohn's disease involves periodic or unremitting inflammation of the gastrointestinal tract anywhere along the alimentary pathway (esophagus to anus), whereas ulcerative colitis affects primarily the large bowel which is less involved in nutrient absorption. Fever, nutrient malabsorption, and anemia are common among persons with Crohn's disease [2]. Frequently, those with Crohn's experience reduced levels of vitamin B12, vitamin D, and folate, as well as low prealbumin. If the disease is mild to moderate, medical management of the condition includes antibiotics such as

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metronidazole or fluoroquinolone. However for those with severe disease, emergent hospitalization and initiation of corticosteroids or agents that act against tumor necrosis factor alpha (TNF-α), such as infliximab or adalimumab, are the standard of care.

Osteoporosis and IBD

Osteoporosis has been associated with IBD particularly in the advanced stages. It has also been linked to an increased risk of fragility (low trauma) fractures, but the cause and effect of this is less well known. The pathophysiology of bone loss in IBD is secondary to inflammatory processes and their consequences; inappropriate absorption of nutrients, calcium, vitamin D and trace minerals, and ongoing use of osteotoxic medications that may harm bone yet benefit the overall management of IBD. The process of bone loss begins when increased T-cell activity accelerates cytokine production which, in turn, stimulates osteoclasts [3]. These cytokines include IL-1α, IL-1β, IL-6, IL-11, IL-17, TNF-α, and prostaglandin E-2 [4]. Upregulation of IL-6 is particularly problematic because it reduces levels of male and female sex hormones which support osteoblastic activity [5].

Additional bone loss occurs through a receptor ligand pathway identified on osteoblast and osteoclast precursor cells. A surface ligand known as the receptor activator of nuclear factor kappa B ligand (RANKL) can bind to either an osteoclast precursor, called the receptor activator of nuclear factor kappa (RANK), or to a decoy receptor known as osteoprotegerin (OPG). The osteoblast cell produces the soluble decoy receptor OPG. The process of RANKL binding to RANK promotes a cascade of events that matures osteoclasts and causes osteoporosis. The decoy receptor is the key to blocking this process of bone loss by attempting to have RANKL bind to OPG instead; unfortunately the activity of OPG is inadequate to balance the bone loss of the RANKL-mediated osteoclastogenesis. In the setting of prolonged inflammation, OPG levels continue to remain elevated so there is an ongoing attempt by the body to limit further bone loss [6]. In an investigation by Moschen et al. [7], levels of OPG were 2.4 times normal in Crohn's and 1.9 times greater than normal levels in ulcerative colitis. Despite this counter attempt, a negative bone balance results.

Corticosteroids (also known as glucocorticoids) are traditionally utilized in the treatment of IBD, particularly in the more advanced forms of the disease. Not only do glucocorticoids promote osteoblastic apoptosis, but they also impair calcium absorption and promote renal excretion of calcium [4]. They are associated with increased fracture risk, with the greatest detriment in the initial months of treatment, but adverse effects are reduced in the long term if steroids are discontinued [8]. Another encouraging development in recent years is the introduction of budesonide for the treatment of IBD. This corticosteroid has low systemic bioavailability and does not lead to bone loss associated with traditional steroids [4].

Bone Density and Fracture Risk with IBD

The prevalence of osteoporosis and IBD is estimated to range from 42 to 70 %. These estimates are derived from studies generated by tertiary care centers rather than from population-based studies. A more accurate estimate of 5–6 % can be found by looking at a reasonable cross section of the population [1, 9]. Vestergaard found that 32–38 % of persons with Crohn's and 23–25 % of those with ulcerative colitis experience osteopenia [10]. However the relative risk (RR) of fractures is only modestly increased: RR of 1.2 for any fracture and 2.2 for spine fractures for those with Crohn's; 1.1 for any fracture and 1.5 for spine fractures for those with ulcerative colitis.

The American Gastroenterological Association (AGA) has developed a position statement on guidelines for osteoporosis management in a number of gastrointestinal diseases, including IBD [11]. According to this report, IBD has a modest effect on BMD, with a *Z*-score of −0.5. The prevalence of patients with osteoporosis and IBD is 15 %, but increasing age significantly influences results in terms of both prevalence of osteoporosis and fracture incidence, estimated at one per 100 patient years. According to the committee's findings, corticosteroid use was the variable most likely responsible for osteoporosis, but use was difficult to calculate in terms of magnitude of effect due to variability of the disease itself. Also unlike other studies which demonstrated males are more likely than females to be affected by Crohn's disease-related osteoporosis, the AGA stated that the risk of developing osteoporosis in males and females was equivalent. In addition, while other reports [10] found the risk of bone loss to be higher in Crohn's than in ulcerative colitis, the AGA maintained that the risks were comparable.

In terms of prevention of osteoporosis for those with IBD, the AGA recommends the vitamin and calcium supplementation, noted below, as well as periodic assessment by DXA for any patient with IBD who has more than one additional risk factor for osteoporosis including chronic corticosteroid use (defined as three months or longer [1]), hypogonadism, male gender, postmenopausal status if female gender, age greater than 50, or prior history of fracture. Moreover it advises that DXA scans be repeated every 2–3 years for patients with established osteoporosis (*T*-score <2.5) [12].

As described in the early chapters of this text, peak bone mass varies by sex and skeletal site. The degree of bone mineralization increases gradually to a maximum level in the third decade for both genders [13]. The inability to achieve peak bone density by age 25–30 and maintain it until ages 30–40 for women and 40–50 for men places individuals at risk for developing osteoporosis. Since Crohn's disease affects children and teenagers, early efforts to attain maximal BMD by participating in weight-bearing exercise during early life and by optimizing vitamin D and calcium intake should be undertaken. Despite relatively inactive inflammation and disease activity, Laakso et al. found that over a prospective 5-year period, when pre- and postpubertal children should be increasing BMD, children with IBD either maintained their current bone density or, even worse, lost bone over the observa-

tion period [14]. This same study found that 25 % of subjects were deficient in vitamin D. Wingate et al. [15] compared the effects of supplemental vitamin D3 in dosages of 400 IU versus 2000 IU in 83 subjects from ages 8–18 with mean BMD of 24 ng/ml. Both groups were able to increase BMD to a mid-range threshold of 20 ng/ml over a duration of six months. However, the desired serum vitamin D25OH level of 30 ng/ml was achieved by only 35 % of subjects receiving supplementation of 400 IU cholecalciferol daily, compared with 79 % of the group that received 2000 IU daily.

Irritable Bowel Syndrome

Irritable bowel disease or syndrome (IBS) is a condition involving chronic abdominal pain and altered bowel habits in the absence of a defined pathology of the GI tract [16]. It is a functional bowel disorder characterized by alternating bouts of constipation and diarrhea, painful defecation, and increased levels of inflammatory cytokines [17]. This condition, highly prevalent in the US population with estimates now at 10–20 %, is more common in young adult or middle-aged females. An early epidemiologic study by Whitehead et al. [18] examined a number of comorbid conditions among IBS patients and noted an increased incidence of osteoporosis among IBS subjects relative to control subjects.

Using the National Emergency Department Sample (NEDS) database, which is comprised of emergency room visit data from 20 % of the hospitals in the United States, Stobaugh et al. [19] found that of 317,857 visits, 752 or 5.6 % carried a simultaneous diagnosis of osteoporosis, with 0.6 % also having a diagnosis of either a pathologic or traumatic fracture of spine or extremities. The odds ratio (OR) was 4.28 for a concurrent diagnosis of osteoporosis and 2.36 for diagnosis of an osteoporosis-related fracture. The authors carefully controlled for common comorbidities that would lead to false elevations in prevalence, including family history of osteoporosis, vitamin D deficiency, various forms of cancer, renal disease, thyroid disease, and eating disorders.

Authors compared prevalence of osteoporosis and osteoporosis-related fractures in IBS with Crohn's disease, ulcerative colitis, and celiac disease. The OR for fractures was greater for IBS than either Crohn's (1.98) or UC (1.72) but was not as high as that of celiac disease (OR of 3.21). The increased risk of osteoporosis in IBS is unclear, but several experts believe it may be linked to elevated levels of serotonin found among IBS patients [20]. In addition, the elevated serotonin levels are associated with heightened states of IBS and its ongoing pathogenesis [21]. Additional causes of osteoporosis may be related to a reduced intake of milk and other calcium products since patients with IBS frequently report intolerance to such food sources [19]. Studies on treatment for bone disease in IBS are lacking. Of note, steroids can decrease the intensity of bouts of IBS, but their use may have adverse effects on bone if prescribed for over three months [16].

Treatment for Inflammatory Malabsorptive Disorders (IBD and IBS)

Pharmacologic Interventions

The strategies for pharmacologic intervention involve a reduction in medications causing bone loss and an initiation of those that build or maintain bone. Corticosteroids and immunomodulating agents have been significant factors in furthering bone loss in IBD and related conditions. If an individual's inflammatory level permits, reducing corticosteroids in the form of prednisone or methylprednisolone should be considered. Frequently, this is not possible. Vestergaard et al. [22] found that doses as small as 6.7 mg daily increase fracture risk in a dose-dependent manner. However, other steroids, specifically hydrocortisone and oral budesonide, did not increase overall fracture risk. Several years prior to the Vestergaard study, a similarly favorable outcome on preservation of bone mass was published by Schoon et al. [23]. Even though a 3.35 % loss of BMD for the group treated with methylprednisolone seems unsubstantial compared with budesonide loss of 0.9 %, the findings are significant ($p = 0.002$). For a follow-up time of six months, a 3.35 % bone loss is concerning.

Azathioprine-treated patients as well as those with anti TNF-α therapy may experience benefits in terms of maintaining or increasing BMD [4]. The theory behind treatment with an agent directed against TNF-α is based on the upregulation of osteoclastic function by cytokines including TNF. Reducing the inflammation component of IBD would help maintain bone but may not actually increase BMD. However, one retrospective study of subjects, conducted at an outpatient Crohn's disease clinic, examined the use of infliximab with simultaneous use of alendronate or risedronate and compared BMD findings to those with infliximab alone. This investigation revealed improved overall BMD with a combination of infliximab and bisphosphonate relative to infliximab alone. However, the use of infliximab alone did result in a preservation of existing BMD but not an increase in density [24].

The British Society of Gastroenterology (BSG) advises that all patients over age 65 with IBD receive bisphosphonates at the start of steroid treatment [25]. The FDA has approved bisphosphonates for patients with known osteoporosis, history of traumatic fractures, or use of steroids for more than three months due to a high risk of developing osteoporosis. Because bisphosphonates are not without their own set of side effects, particularly in the elderly, the BSG advises obtaining a DXA before starting a patient on a bisphosphonate and deferring start of medication unless the DXA has a *T*-score of <1.5.

In terms of clinical trials focused on subjects with IBD, one double-blind trial involving 61 patients, each of whom received either 12 months of 5 mg risedronate plus 600 mg calcium or placebo and calcium, yielded a 2.0 % increase in BMD in the spine and 1.9 % at the hip for those on risedronate [26]. Favorable

BMD outcomes at one, two, and three years at the spine, trochanter, and femoral neck were seen in a second study of risedronate [27]. Studies on the benefits of alendronate, ibandronate, and zoledronic acid have also been conducted [28]. A meta-analysis of five large clinical trials involving 423 participants found that, as a class of drugs, bisphosphonates improved hip BMD but not spine BMD at 12 months. No differences between subjects receiving bisphosphonates and those taking placebo were found at 24 months for either spine or hip BMD, and no differences were found for rates of new vertebral fractures or incidence of side effects. Nevertheless, individual trials have found some positive trends for BMD outcomes for focused groups of patients.

A small trial of 32 subjects using low-dose alendronate 10 mg daily was published by Haderslav et al. in 2000, prior to the widespread acceptance of IV bisphosphonates for management of chronic osteoporosis. Authors found a 4.6 % increase in lumbar spine BMD among patients who received alendronate in comparison to a 0.9 % decline in control subjects [29]. The study was not powered sufficiently to detect a fracture rate difference, and with a follow-up time of only 12 months, large differences would be unlikely. No significant differences in GI adverse effects were seen. Since a weekly dosage of alendronate at 70 mg has become available, dosages of 10 mg daily have gone out of favor due to patient choice and low compliance. However, symptoms of GI burning, pain, and nausea, to which patients with Crohn's disease are predisposed, are less likely to occur with a 10 mg tablet as opposed to a 70 mg tablet.

Other investigations of subjects with postmenopausal osteoporosis have suggested that compliance with oral regimens is limited by GI intolerance and lifestyle inconveniences [30]. A recent soluble formulation of alendronate may be better tolerated in persons prone to GI symptoms. Coaccioli et al. [31] found that after one year of use of a 70 mg soluble weekly alendronate, 92.4 % of subjects were still taking the soluble form, but only 65.4 % of those using the tablets were still adhering to their medication. No subjects after three months and only 5 % after six months had chosen to discontinue treatment with soluble alendronate in comparison to 5 % at three months and 23 % at six months for those using traditional oral alendronate, risedronate, or ibandronate tablets.

Siffledeen and colleagues explored the use of etidronate 400 mg on BMD in patients with Crohn's disease [32]. All subjects received daily calcium of 500 mg and vitamin D3 of 400 IU but only half received etidronate, with the remaining 50 % receiving placebo. Based on BMD outcomes at both 12 and 24 months, both groups demonstrated improved BMD values of similar degrees. No benefit was realized by the addition of etidronate to calcium and vitamin D.

Bartram et al. conducted the first clinical trial examining the effects of an IV bisphosphonate in patients with Crohn's disease. The group receiving both calcium and IV pamidronate increased BMD significantly more than the subjects receiving calcium alone [33]. Their comparison of IV ibandronate versus sodium fluoride on 66 patients with Crohn's disease showed both groups had improved BMD at the spine but not the femur [34].

Nonpharmacologic Interventions

Individually tailored rehab programs should be initiated for patients with IBD and other malabsorptive disorders including celiac disease and conditions involving ileal dysfunction, due to malnutrition and potentially to proprioceptive and sensory deficits involving low levels of key vitamins. Those with critically low levels of pyridoxine (vitamin B6) may experience proprioceptive deficits. In addition individual case reports of neuropathic sensory changes in the form of absent or impaired light touch, vibration, and pinprick have been reported for patients who have undergone gastric bypass and have experienced critically low vitamin D levels as a result [35]. In the case described by Guanche and Oleson, the patient experienced no clinical symptoms for several months after surgery. Rather, symptoms appeared at the end of winter when vitamin D levels are typically at their nadir and followed a gastrointestinal virus involving intractable nausea and vomiting. Therapists need to focus not only on strengthening management and fall prevention but also on compensatory techniques for patients who lack sensory feedback. These patients must learn to rely on vision or other means of adaptation to compensate for sensory proprioceptive deficits.

Bariatric Surgery and Related Procedures

Patients who have undergone gastric bypass or partial small bowel resection for cancers, volvulus, or ischemia are at increased risk of osteoporosis. Any area that is resected or dysfunctional and involves the proximal small bowel will necessarily compromise the absorption of vitamin D and other key nutrients [11]. Postgastrectomy is a general term that would describe any resection of the GI tract, but specific portions that are resected or circumvented are more harmful than others in terms of malabsorption states. Resection may occur for a deliberate purpose such as weight loss through one of several types of bariatric surgery. Alternatively, resection of a portion of the GI tract may be performed to remove a mass with the purpose of debulking a malignant tumor, thereby limiting further metastases or preventing obstruction. In this chapter, we will focus on resections for the purpose of weight loss, since oncologic resections have considerable variation and individual patient responses are unique.

Surgical Options and Definitions

In 2011, over 340,000 bariatric surgeries were performed worldwide. Currently, these procedures are indicated for those with a BMI greater than 40 without obesity-related health issues or greater than 35 with specific obesity-related health

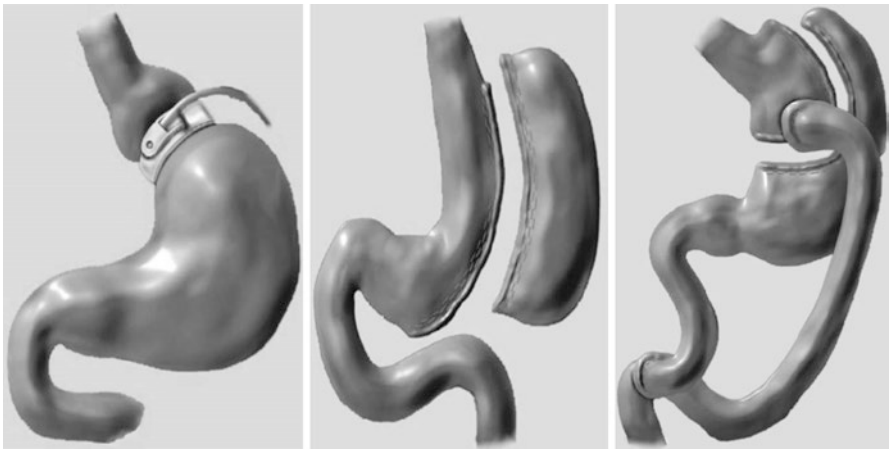

Fig. 1 A comparison of laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB). From *left* to *right*: LAGB, SG, and RYGB (*Source*: Smith et al. [41]. Reprinted with permission)

conditions of diabetes mellitus, hypertension, and obstructive sleep apnea [36]. Several common procedures have been used to generate weight loss. They can be divided into those that induce weight loss by mechanical restriction of food passage through the digestive tract and those that induce more substantial weight loss through malabsorption in combination with some elements of restriction. There are also newer theories concerning neurohormonal pathways that appear to contribute to weight loss [37]. The laparoscopic adjustable gastric band (LAGB) and Roux-en-Y gastric bypass (RYGB) were the most common procedures undertaken in 2008, but by 2011, the number of patients undergoing RYGB had declined, and a less aggressive procedure known as the sleeve gastrectomy (SG) had increased [38, 39]. Numbers issued by the American Society for Metabolic and Bariatric Surgery in 2014 indicate that of the 179,000 surgeries performed the previous year, 34.2 % were RYGB as opposed to 37.5 % in 2012, while SG surgeries increased from 33 % in 2012 to 42.1 % in 2013 [40]. (The specifics of each procedure are illustrated in Fig. 1 [41].)

Restrictive Bariatric Procedures

The LAGB constricts the initial portion of the stomach, slowing down the transit of food and thereby inducing a feeling of early satiety [37]. In this fully reversible procedure, a saline-filled band is inserted around the proximal stomach and reduces the stomach cavity to 10–20 ml [42]. While the LAGB can result in 30–50 % excess body weight reduction, proximal slippage of the band necessitates revision surgery within 5–7 years of the initial operation for 25–50 % of patients. This complication, in combination with recently developed, equally effective alternatives, has made LAGB a less popular option in recent years [43, 44].

A newer surgical option known as the gastric sleeve or sleeve gastrectomy (GS) involves resection of a large section of the lateral stomach, with the remainder stapled shut. The mechanism of weight loss is primarily through reduction of gastric capacity to approximately 120 ml [45] and decreased appetite. Weight loss is gradual over 12–18 months, and significant nutrient malabsorption does not occur because there is no involvement of the small intestine. Appetite attenuation is closely related to the elimination of a portion of the abdomen responsible for the secretion of ghrelin, an anti-satiety hormone which signals the desire to continue eating.

Although initially developed as the first stage of the combined restrictive and malabsorption procedure, SG alone has successfully resulted in a 55–60 % weight loss in some studies and is now offered as a primary procedure [46]. The elimination of ghrelin and other neurohormones including glucagon-like peptide-1 may contribute to the success of GS through continued dietary compliance of patients. One benefit of all restrictive bariatric surgeries is the sparing of the proximal small bowel where many essential vitamins and nutrients are absorbed [47]. The absence of this portion of the small intestine may lead to osteoporosis in part because of lack of vitamin D. Despite the above benefits, postoperative development of gastric reflux or exacerbation of preexisting reflux after SG can be as high as 40 %. Many patients require a surgical solution to the reflux because medications, including proton pump inhibitors, are helpful yet insufficient to overcome the functional problem created by the surgery [48].

Malabsorptive Bariatric Surgeries

In contrast to the adjustable gastric band and GS interventions, the RYGB and duodenal switch circumvent moderate to large portions of the small intestine. Weight loss occurs by redirecting digested food from the stomach to distal gut, bypassing proximal portions of the small intestine that function in key nutrient absorption. Both procedures result in a “common channel” that is shared by both digested food and pancreatic enzymes; their combined action is required for nutrient absorption. The pancreatic enzymes travel through an independent pathway and link up with the food channel further along the path. Not until they come together in the common channel is any food (particularly protein) absorbed [37]. The shorter the channel, the greater the likelihood of insufficient absorption, especially if the length is less than 120 cm from the start of the channel to the ileocecal valve [47]. Certain procedures carry a higher risk of side effects than others. A summary of the complications with the three most common types of procedures is given in Table 1 [49].

RYGB is synonymous with the term “gastric bypass” and results in as much as a 65 % excess body weight loss. The sleeve gastrectomy–duodenal switch combined procedure offers the greatest loss, up to 80 % of excess body weight. This is a modification of earlier versions of the biliopancreatic diversion [50–53]. Even in revised form, patients can become severely malnourished, particularly in vitamin

Table 1 Complications associated with bariatric surgery procedures

Procedure	Complications
Laparoscopic Roux-en-Y gastric bypass	Leaks
	Anastomotic narrowing and strictures
	Marginal ulcers
	Jejunal ischemia
	Small bowel obstruction
	Internal hernias
	Intussusception
	Recurrent weight gain
	Gastrogastric fistula
Laparoscopic adjustable gastric banding	Stomal stenosis
	Malpositioned band
	Pouch dilation
	Distal band slippage
	Perforation
	Gastric volvulus
	Intraluminal band erosion
	Port-related and band-related complications
Laparoscopic sleeve gastrectomy	Gastric leaks
	Gastric strictures and gastric outlet obstruction
	Gastric dilation
	Gastroesophageal reflux

Source: Levine and Carucci [49]

B12 levels, and must be closely followed with blood tests of fat- and water-soluble vitamins and trace elements like zinc and copper [54].

Many considerations go into the decision for surgery. The desired amount of weight to be lost for medical reasons, the risks of a given procedure to the individual patient, and the patient's prior history with weight loss attempts must all be carefully balanced. The patient's own commitment to preparing for the surgery medically and psychologically and their commitment to follow-up care and ongoing nutrition are as important if not more important than the actual surgical procedure chosen. Table 2 describes important selection criteria [55].

Nutritional Deficiencies After Surgery

Malabsorption arises in both macro- and micronutrients following bariatric surgeries. Deficits in many of the key nutrients serving to support bone structures serve as major contributing factors to the development of postsurgical osteoporosis [47]. The major macronutrient affected is protein. When reduced length of the small intestine results in inadequate time for pancreatic enzymes to act on ingested dietary protein, insufficient protein absorption occurs. Anemia and hypoalbuminemia are observed

Table 2 Selection criteria for bariatric surgery

Factor	Criteria
Weight: adults	Body mass index ≥35 kg/m^2 and obesity-associated comorbidity
	Body mass index ≥40 kg/m^2
Weight: children	Severe comorbidity and >95th percentile of weight for age
Weight loss history	Failed attempts of nonsurgical weight loss, including profit-making commercial programs
Commitment	Expectation that patient will adhere to postoperative care including follow-up visits, recommended medical management, and recommended tests or procedures
Exclusion	Current drug or alcohol abuse
	Severe, uncontrolled psychiatric illness
	Reversible endocrine disorders that may lead to obesity
	Inability to comprehend bariatric surgery details (benefits, risks, expected outcomes, alternatives, lifestyle changes, etc.)

Source: Mechanick et al. [55]

in gastric bypass and duodenal switch [47]. Generalized edema that leads to mobility deficits and severe muscle wasting may require physical therapy, in addition to nutritional correction measures such as liquid protein supplementation, to aid functional recovery. As muscle wasting progresses, patients shift stress from their muscles to their bones for ambulation and transfers. In addition, profoundly weak proximal muscles may make activities such as sit to stand transfers more challenging and an increased fall rate is predictable. If BMD is low, falls and altered stress on bones during weight-bearing activities may lead to fractures.

Micronutrients include water-soluble B and C vitamins; fat-soluble vitamins A, D, E, and K; and trace minerals such as copper and zinc. Another key mineral of concern is calcium. In assessing risk of developing bone disease, any nutrient that results in weakness, alters proprioception, causes myalgias, compromises awareness, or results in functional deficits that increase fall risk or reduce mobility warrants discussion. Vitamin B12 deficiency occurs in patients who have undergone procedures that bypass the lower stomach [37] with findings indicating inadequate B12 in 40 % of patients after the first year following traditional RYGB [56, 57]. Vitamin B12 deficiency results in pernicious anemia, affecting both the dorsal tracts of the spinal cord responsible for proprioception and vibration as well as the corticospinal tracts responsible for motor function. A severe form of Vitamin B12 deficiency compromises safety in cases of weight-bearing, ambulation, and transfers, leading to self-care deficits and an increased risk of falls.

Vitamin B1 (thiamine) deficiency arises from bypass of the jejunum where absorption occurs or from recurrent emesis, caused by reduced gastric size or stomal stenosis. Loss of thiamine can present after either gastric banding or gastric bypass [36]. Seen in 49 % of patients after RYGB [58], thiamine deficiency induces Wernicke's encephalopathy involving nystagmus, ophthalmoplegia, confusion, and ataxia [59]. Polyneuropathy has been reported after gastric bypass [59–61]. Nakamura et al. [60] emphasize that a single dose of supplemental thiamine may

correct a lab reading for serum levels of vitamin B1, but if neurological deficits have occurred because the patient has gone untreated in previous months, functional deficits in the form of ataxia and gait dysfunction will remain. Electrodiagnostic studies often confirm a distal axonal sensory polyneuropathy and support the need for physical therapy to educate patients in compensatory measures that improve safety during ambulation and prevent falls [60].

Both calcium and vitamin D are absorbed from portions of the gastrointestinal tract that are bypassed in RYGB and similar malabsorptive bariatric procedures. Due to vitamin D malabsorption, calcium metabolism is compromised through a physiologic mechanism apart from the absence of absorption from the missing region of gastrointestinal tissue. A hypocalcemic state ensues and secondary hyperparathyroidism follows [47]. After gastric bypass, calcium deficiency is seen in 10–25 % of patients after one year and 25–48 % after two years. Vitamin D deficiency one year after a malabsorptive surgery ranges from 17 % to 52 % and becomes significantly worse as years pass unless treatment is initiated. In a series of investigations by Brolin, vitamin D deficiency was seen in 50 % of patients five years after surgery if they had a short common channel 75 cm from the ileocecal valve [56]. Although aggressive supplementation will be helpful in preventing further metabolic disease, this alone may be insufficient in patients with malabsorptive procedures, and dosages of 50,000 IU ergocalciferol weekly may be needed.

Although vitamin D and calcium deficiency are far more common after malabsorptive procedures than after restrictive GI surgeries, deficits in both bone density and individual nutrient deficiencies may occur nonetheless. A study of 73 adolescent patients found that four subjects (5.5 %) had vitamin D deficiency. Restrictive food intake may play a role, but because this study involved teenagers, dietary compliance may be challenging, although physician follow-up in this study was 90 %, far exceeding statistics in most adult bariatric follow-up clinics. Aarts et al. found that in a study of 60 patients who were consuming a daily multivitamin containing 400 IU vitamin D, 39 % were deficient following SG procedures [62]. In this same study, 5 % of patients had vitamin B12 deficiency and 15 % had folic acid deficiency, but what is more remarkable are the chronically *elevated* levels of vitamin A, B1, and B6. Findings highlight the need for comprehensive and frequent postoperative metabolic monitoring coupled with a more aggressive nutritional approach, similar to that offered to restrictive surgery patients. A simple multivitamin is far from adequate and may have an inappropriate mixture of too little vitamin D and too much vitamin A or B6. Table 3 gives suggestive preoperative nutritional assessment measures which should be reviewed with each patient prior to planning surgery [63].

Epidemiology of Osteoporosis After Bariatric Surgery

Scibora et al. [37] have conducted comprehensive reviews of retrospective and prospective studies of osteoporosis and bone density changes related to bariatric surgeries. Because bone loss is a well-established outcome of gastrectomy for

Table 3 Suggested preoperative nutrition assessment

General	Specific
Weight history	Recent weight loss attempts
	Weight gain and loss trends
	Personal weight loss goals
Medical history	Comorbidities
	Medications and supplements
	Food allergies and intolerances
	Body fat distribution
	Available lab values
	Dentition problems
	Eyesight problems
Psychiatric history	Eating disorder history
	Psychiatric diagnoses
	Alcohol, tobacco, drug use
Nutrition and food	Food, mood, and activity log
	Eating patterns
	Restaurant meal intake
	Food cravings
	Cultural and religious dietary considerations
Physical activity	Current activity level
	Physical conditions that limit activity
	Previous enjoyment of physical activities
	Time spent sedentary daily
Psychosocial	Confidence in ability to maintain weight loss
	Support system, family dynamics
	Motivations and reasons for wanting surgery
	Willingness to comply with protocol
	Emotional connection with food
	Stress level and coping mechanisms
Education	Literacy level
	Language barrier

Source: Allied Health Sciences Section Ad Hoc Nutrition Committee, Aills L et al. [63]

non-weight loss purposes, clinicians have long been aware of the risk of osteoporosis following bariatric surgeries [64]. Data from cross-sectional and retrospective studies of BMD in the hip, radius, and lumbar spine have been difficult to interpret due to a number of confounding issues. Obese patients typically have higher BMD than normal weight controls due to the presence of estrogen content in fat cells; thus, comparing postoperative yet still overweight gastric bypass patients to normal weight controls may present challenges. Moreover, many of the cross-sectional studies were unable to separate pre- and postmenopausal women, resulting in a heterogeneous population and compromising any conclusions for specific groups.

Prospective studies examining changes in BMD within the same individual at preoperative and postoperative time points have proven to be more valuable. Overall these investigations support decreases in BMD following malabsorptive as opposed to restrictive surgeries, with the greatest reduction seen in BMD at the hip relative to the lumbar spine or radius [37]. After restrictive surgeries in which the weight loss is less than that achieved from malabsorptive procedures, bone loss at the hip is found to vary by site and is inconsistent among studies. The femoral neck BMD declined by approximately 2.3 % one year after LAGB in a study of premenopausal women [65]. In restrictive procedures where weight loss is accomplished through constriction-forced dieting due to limited abdominal size, weight loss and bone loss continue into the second and subsequent years after surgery. A two-year study demonstrated that femoral neck BMD declined 3.5 % [65, 66]. Although vertical gastric banding is a restrictive procedure done far less frequently today, studies did find that it results in greater bone loss at the proximal hip of 10–14 % [65]. Patients now have other options which may be more favorable from a number of medical perspectives. Bone turnover markers were elevated following SG in one small-scale investigation of 15 patients indicating ongoing effects of bone loss [67].

Greater bone loss is consistently observed with malabsorptive procedures. A number of reports estimate that total bone loss at the femoral neck following either RYGB or the more aggressive biliopancreatic diversion (also now rarely performed) ranges from 9–10.9 % at the femoral neck and 8–10.5 % at the total hip. Postoperative care in the majority of bariatric surgical centers includes vitamin supplementation with vitamin D. But teams caring for patients in a postoperative setting lack a standard protocol, and the amounts that each patient receives vary by institution. In the setting of 800 IU vitamin D3 and 1200 mg daily calcium supplementation [68], femoral neck BMD one year after surgery declined by 10.9 %; in another investigation with even greater supplementation of vitamin D and calcium, BMD of the femoral neck declined by 9.2 % while the total hip saw an 8 % decrease. Since most of the weight loss occurs in the first year following RYGB, findings of stability of BMD in the second and third years following surgery are conceivable [65].

Fleischer et al. [69] assert that the degree of bone loss following restrictive procedures parallels the degree of weight loss. Their prospective study of 23 patients one year following RYGB demonstrates bone loss at the total hip of 8 % and at the femoral neck of 9.2 %. In addition, elevated markers of bone loss in the form of N-telopeptide confirm an active bone loss process. This finding is further supported by a simultaneous increase in PTH and a reduction of urinary calcium, even in patients who increased calcium and vitamin D intake postoperatively to 2400 mg and 1600 IU, respectively. This study is only one of a number of investigations [70, 71] demonstrating increases in markers of bone loss and of PTH. Bruno et al. [70] did show that supplementing patients with 1200 IU vitamin D, more than the Fleisher investigation that prescribed 600 IU for subjects under 50 and 800 IU for those over age 50, prevented development of postoperative vitamin D deficiency. However, even 1200 IU was insufficient to prevent elevation of bone turnover markers.

Bone loss in the lumbar spine is again seen more commonly in patients undergoing malabsorptive rather than restrictive bariatric procedures. After LAGB surgery, one study [66] showed a 3.5 % and 1.6 % increase in BMD, respectively. Several other investigations [72–74] demonstrated either no change or a small increase that was not statistically significant. In SG, Hsin et al. [74] found no change in lumbar spine BMD between L1 and L4 after one year. In contrast, RYGB and similar malabsorptive procedures result in a reduction of lumbar BMD by 3.6–8 % in premenopausal patients, even in those who are supplemented proactively with calcium and vitamin D, the amounts of which vary by study [37, 68, 75]. More aggressive supplementation is unable to help preserve BMD in more aggressive malabsorptive procedures. Tsiftsis et al. [75] noted a 7–8 % decline in lumbar BMD after biliopancreatic diversion in 26 premenopausal women who were given 2 g of calcium daily. This group was also supplemented with vitamin D.

Quite often, bone loss and fractures can occur in nontraditional osteoporotic sites following bariatric surgery, but many of the fractures are not observed until years after surgery. In a large prospective study of 258 subjects, representing 2286 person-years, 79 individuals experienced 132 fractures. Conducted between 1989 and 2004, this investigation has one of the longest follow-up periods of published works to date. In total, 56 % of subjects experienced only one fracture, while 26.5 % reported two or more fractures. The cumulative incidence of fracture after 15 years was 58 %, with the most common mechanism of injury being a fall. However, many fractures occurred in nontraditional osteoporotic sites: 22 % in the feet or toes, 7.6 % in the ribs, and 15 % in hands or fingers [76].

Treatment for Bariatric Surgery Patients

Pharmacologic Interventions

Nutrition Supplementation

The Endocrine Society has developed specific recommendations for treatment of deficiencies anticipated after bariatric surgery, especially after malabsorption procedures, with the expectation of preventing major instances of malnutrition if supplementation is done at the beginning of postoperative care. These recommendations include taking two multivitamin tablets daily, preferably separated in time, as well as consuming 1200–2000 mg of elemental calcium and at least 1000 IU of cholecalciferol (Vitamin D3), if the individual is replete in vitamin D25OH at the time of surgery. Those with greater deficiencies would understandably need higher doses of vitamin D3 or a 50,000 IU capsule of vitamin D2 (ergocalciferol) [36]. These clinical practice guidelines further advise that if aggressive supplementation of nutrients is attempted and fails, revision surgery may be needed to avert severe malnutrition [36].

As illustrated in the prior section, supplementation with various nutrients is helpful but not sufficient in the more aggressive forms of bariatric surgery, particularly in malabsorptive procedures but also in some restrictive procedures such as SG involving the rapid and substantial loss of ghrelin. Gjessing et al. [77] found substantially elevated PTH levels and hypocalcemia one year after SG. The resultant malabsorption of calcium, in conjunction with ongoing hyperparathyroidism, contributes to osteoporosis. Through the above mechanism, supplementation with additional calcium and vitamin D appears unlikely to help. Reduction in PTH and downregulation of osteoclasts or upregulation of osteoblasts may need to be approached from a different direction. Interestingly, Hsin et al. [74] used the guidelines developed by the AGA in his study, and with the exception of the lumbar spine BMD, many regions of the skeleton nonetheless experienced extensive bone loss following bariatric procedures.

Emerging Concept of Bariatric Osteomalacia

A number of studies looking at postmenopausal osteoporosis rarely find that vitamin D or calcium alone can have a singular impact on the development of osteoporosis. However, the situation is very different for those who have experienced malabsorptive bariatric procedures, with results demonstrating the positive impact of aggressive supplementation with calcium citrate and cholecalciferol. Williams [78] describes a case of one female who originally had low BMD in her radius but after eight months of aggressive supplementation achieved a 55% improvement of BMD. Following treatment, she experienced no further development of calcium oxalate stones and reported less muscle and bone pain together with better endurance and strength.

The pattern of bariatric osteomalacia can be so profound that myopathy as well as peripheral neuropathy can develop. A number of case reports describe these events, which can have a devastating effect on a patient's level of independence. Such cases require astonishingly large doses of vitamin D (in one case 1200 IU orally daily plus 400,000 IU intramuscularly every month) to realize improvement in lab values following SG and RYGB [79–81].

Medications

Because oral bisphosphonates carry a high risk of gastrointestinal reflux, these agents are largely contraindicated after bariatric procedures. In fact, reflux is one of the most common adverse effects following SG and a number of malabsorptive procedures. Bisphosphonates and NSAIDs are two classes of drugs that have been specifically reported to worsen symptoms [78]. Intravenous bisphosphonates, subcutaneous denosumab, or other oral medications without side effects of gastric reflux are worth discussing, but few reports examining these alternatives have been published outside of limited case studies. Oral alendronate was used successfully in

one small investigation of 13 patients who had undergone one of several types of gastrectomy for gastric cancer, one being RYGB with the others being Billroth I and II and partial as well as total gastrectomy [82]. No reports exist for treatment with intravenous zoledronic acid, but one article does describe two cases of pamidronate used effectively for treating immobilization hypercalcemia in the postoperative period following RYGB [83]. The two subjects described by Alborzi and Leibowitz required direct ICU admission from home following RYGB for dangerously elevated serum calcium levels which were attributed to a combination of inactivity postoperatively, specifically reduced weight-bearing on a skeleton which had been used to carrying significant amounts of weight, and disruption of the calcium homeostatic axis which indirectly elevates osteoclastic activity. In the above cases, pamidronate was found to be safe and effective for hypercalcemia. Although its benefit for osteoporosis prevention has not been investigated, the initial safety data from the above case reports are encouraging.

In addition to considering medications to reduce fracture risk and optimizing nutritional stores, physicians should carefully investigate the long-term consequences of certain common medications given in the postoperative period, many of which can be continued long term. Cholestyramine is often used for diarrhea in patients who have developed a partial short gut syndrome, particularly common after RYGB in patients with a longer Roux limb and relatively shorter common channel. Cholestyramine reduces adverse effects of diarrhea by sequestering bile acids; however, it also reduces calcium absorption resulting in impaired vitamin D absorption and osteomalacia [78]. Because cholestyramine can cause bowel obstruction over time, many clinicians do not prescribe it for long-term use; however, evidence suggests that bone complications are avoided in persons using the medication simply for temporary relief of diarrhea.

Nonpharmacologic Treatment

As the findings of Alborzi and Leibowitz [83] illustrate, early mobilization following bariatric procedures is essential not only from the standpoint of conditioning but to prevent adverse postoperative complications of hypercalcemia, urinary calcium wasting, potential kidney stones, and ultimately osteoporosis. Even if some of the postoperative activity involves movement with reduced lower extremity weight-bearing such as pedaling a stationary bike, calcium exodus from the bones may be partially curtailed. The most important goal is to get patients up and moving through their daily routine, while incorporating exercise into that routine. Nakamura's long-term follow-up study [76] further demonstrates that exercise in the perioperative period is protective against fractures long term, particularly if weight-bearing exercise is maintained in the years following surgery. Activities such as walking, light aerobics, and treadmill may be a safe place to begin. A physical therapist or athletic trainer well educated in the precautions needed following bariatric surgery should be an essential participant in the rehabilitation plan.

Thiamine deficiency results in neuropsychiatric challenges including hallucinations if severe, confusion, and ataxia, ultimately making gait unsafe [47]. Speech therapists focus on attention and concentration, especially in busy or loud environments when patients become easily distracted or their attention is divided. Unplanned awakening in the middle of the night may increase confusion and can predispose patients to falls. Such events have resulted in a variety of injuries, including fracture to hips, spine, and forearms. Therapists focus on family education for those at home, while low beds, seizure pads on the floor, additional side rails to prevent climbing out without assistance, and bed alarms are used in the inpatient setting. In cardiac abnormalities including bradycardia and tachycardia, endurance can be altered through progressive muscle strengthening and activities that increase oxygen demand, especially stair climbing. Progressive strengthening and close attention to cardiac parameters are needed in initial therapy sessions. Numbness and weakness are other physical manifestations of both thiamine and pyridoxine deficiency. Vestibular training can help with both conditions.

Mononeuropathy, polyneuropathy, and radiculopathy have all been reported after various forms of bariatric surgery [84]. For patients who have experienced bariatric osteomalacia with adverse consequences of neuropathy or myopathy, case reports highlight the need for a comprehensive physical and occupational therapy program to correct functional deficits in the months immediately following surgery. Outcomes for these patients vary, with some improving fully and others partially. All reports indicate that recovery involves learning compensatory techniques and improving endurance and strength to address profound proximal muscle weakness, altered sensation, and proprioception. Georgoulas et al. [81] describes a patient with profound myopathy and waddling gait, needing to push off the chair with her hands due to quadriceps and gluteal weakness. In this case, profound vitamin D deficiency was treated with an extended period of intramuscular ergocalciferol and oral cholecalciferol. Moderate recovery in muscle strength was observed but not until months later, and laboratory studies indicated that alkaline phosphatase and serum phosphate did remain mildly elevated through vitamin supplementation.

In the case with osteomalacia illustrated by Panda [79], functional improvement was significant, but it remained unclear when initial electrodiagnostic findings might resolve. In his patient, evidence of acute denervation in the form of positive sharp waves and fibrillations was seen in the vastus lateralis, while high-amplitude, long-duration motor unit action potentials with decreased recruitment in proximal and distal muscles were found in bilateral lower extremities. From the initial EMG report, diagnosis was clear but prognosis was not straightforward and limited similar case reports are available to guide clinicians. Patients with neuropathy due to severe malnutrition and vitamin deficiencies progress in a manner different from those with traumatic or metabolic causes of denervation. In this instance, every patient is unique due to the amount of weight loss, the particular details of the surgery even among those with the same procedure, the physical condition of the

patient preoperatively, and their nutritional reserve. It remains unclear if a comprehensive physical therapy program, combined with aggressive nutritional repletion, will translate to full functional recovery and, if so, how long that process will take. This remains a major challenge for the rehabilitation physician attempting to provide guidance to patients and caregivers of those experiencing functional deficits after surgery.

Final Thoughts

For patients with inflammatory conditions of malabsorption including Crohn's disease and ulcerative colitis, management of the primary condition seems to be the key to success. The less the inflammation, the lower the upregulation of cytokines and other secondary compounds that leach calcium from bone. When such efforts fail, medications to treat osteoporosis can be utilized along with a comprehensive nutritional plan that addresses current deficiencies and emphasizes long-term prevention.

For those who have undergone bariatric surgery, careful presurgical screening should be carried out, including examination of levels of serum calcium, vitamin D 25OH, and PTH. Unfortunately, DXA scans often cannot be done preoperatively due to the usual 300 lb weight capacity of DXA scanners but, if possible, should be obtained before and within six months of surgery. Pre- and postoperative laboratory values should also be followed in the pre- and postoperative period including markers of bone formation, bone loss, PTH, and serum vitamin D25OH along with calcium. Deficits seen prior to surgery including low vitamin D should be addressed at that time.

Secondly, nutritional support with macro- and micronutrients is needed from the very start of the postoperative period and cannot end at a 1-year surgical follow-up. These patients need a lifetime plan. The same bone markers and electrolytes evaluated prior to surgery should be followed postoperatively, with the addition of alkaline phosphatase and serum phosphate to ensure that osteomalacia is not developing. The importance of initiating a comprehensive physical activity program preoperatively and a more intensive program after surgery cannot be underestimated. Prevention of immobilization hypercalcemia and functional mobility deficits is essential. Finally, an entire team of medical providers is needed from the planning stage of bariatric surgery, through the peri- and postoperative time, and for selected providers, throughout the life of the patient. Essential members of this team include the bariatric surgeons, physiatrists, endocrinologists, nutritionists, physical therapists, occupational therapists, and in many cases psychologists. All of these individuals play a critical role in ensuring the long-term health and success of individuals following bariatric surgery.

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