Bariatric Surgery: Bad to the Bone, Part 1

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Abstract

Obesity is now a global epidemic affecting a significant and rapidly increasing number of adults, adolescents, and children. As the incidence of obesity has increased, so has the use of bariatric surgery as a medical solution. A growing number of studies now report that, despite calcium and vitamin D supplementation, the most frequently performed types of bariatric surgery, the Roux-en-Y gastric bypass and the sleeve gastrectomy, cause significant ongoing bone loss. In resources available to the general public and to physicians, this adverse outcome is rarely mentioned or is attributed solely to reduced calcium absorption. Recent studies investigating micronutrient malabsorption and changes in a wide range of hormones induced by bariatric surgery now indicate that calcium malabsorption is the tip of a formidable iceberg. The current article, part 1 of a 2-part series, reviews the latest research findings confirming that obesity prevalence is skyrocketing and that bariatric surgery causes ongoing, accelerated bone loss. Part 1 also discusses the mechanisms through which the bariatric surgery-induced malabsorption of key nutrients adversely affects bone homeostasis. Part 2 discusses the specific changes seen in bone metabolism after bariatric surgery and reviews current data on the underlying mechanisms, in addition to nutrient malabsorption, which are thought to contribute to bariatric surgery-induced ongoing accelerated bone loss. These processes include mechanical unloading and changes in a wide variety of hormones (eg, leptin, adiponectin, testosterone, estradiol, serotonin, ghrelin, glucagon-like peptide 1, and gastric inhibitory peptide). Also, part 2 covers interventions that may help lessen bariatric surgery-induced bone loss, which are now beginning to appear in the medical literature. Bariatric surgery's adverse effects on bone must be widely recognized and protocols developed to prevent early onset osteoporosis in the recipients of an increasingly utilized and otherwise potentially life-saving surgery.

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The prevalence of obesity has increased by 70% worldwide in the last decade. Obesity now affects 300 million individuals, including 35% of Americans as of 2012. As obesity incidence has skyrocketed, so has the popularity of bariatric surgery. The number of bariatric surgeries performed in the United States increased nearly 6-fold from 1998 to 2002.[1-5]

Bariatric surgery is a highly effective treatment for morbid obesity. Patients experience not only rapid, dramatic weight loss but also improvements in obesity-related comorbidities, including insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, and obstructive sleep apnea.[6] Unfortunately, metabolic bone disease, resulting in significant, ongoing bone loss, is also a key, although unintended, consequence of bariatric surgery.[7,8]

Although weight loss typically plateaus in the first 6 months after bariatric surgery, a growing number of studies have revealed persistent increases in bone-turnover markers and progressive, continuing declines in both bone density (ie, bone mass) and bone microarchitecture (ie, bone quality).[1,9-19]

Little prospective data exist to document the full duration and magnitude of bone loss following bariatric surgery, but the data that scientists currently have indicate continuous, accelerated bone loss for the length of time that has been studied to date, which is now more than 10 years.[17,19,20] One reason such continuous bone loss is of concern is that it may increase skeletal fragility and ultimately fracture risk in bariatric-surgery patients, the majority of whom are young adults in their 30s and 40s.

Further, obesity is increasing in incidence globally, not only among adults, but among young people. Estimates of the prevalence of obesity show its rapid and escalating growth as a serious health problem in adolescents, with the incidence now reaching 35.8% in Latin America, 18.3% in England, and 18.1% in the United States.[21] Across Europe and North America, increases of up to 100% in preadolescent obesity rates have been reported from the 1970s to the late 1990s. In urban areas in China, obesity in children aged 2 to 6 years rose from 1.5% to 12.6%, a more than 8-fold increase from 1989 to 1997, a period of only 8 years.[22]

The negative effect of continuous, accelerated bone loss induced by bariatric surgery on the long-term health of obese children may be substantial. A further reason for concern is that the most frequently performed bariatric procedures worldwide, the Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy (SG), are not reversible.[3]

Physicians' awareness of the ongoing bone loss induced by bariatric surgery, of the necessity for regular laboratory testing to identify macro- and micronutrient deficiencies induced by bariatric surgery, and of treatments to restore nutrient sufficiency may help prevent early onset osteoporosis in the rapidly increasing number of bariatric surgery recipients.[18] The fact that awareness is especially needed in caring for recipients of bariatric surgery is underscored by 2001–2008 data from the National Health and Nutrition Examination Survey (NHANES), which shows that micronutrient insufficiency in the United States is worse among the obese population. Intakes of calcium; magnesium; and vitamins A, C, D, and E are below the recommended daily intake (RDI) in more than 40% of US adults; in obese adults, intakes of these micronutrients are a further 5% to 12% lower.[23]

Awareness of Bariatric Surgery-induced Bone Loss Needed

Although a number of papers have now reported that the most frequently performed types of bariatric surgery, the RYGB and SG, result in significant ongoing bone loss, despite calcium and vitamin D supplementation, the issue is often not mentioned in discussions of the surgery.[9,10,12,15,24-28]

A Google search for *bariatric surgery United States* produced links to Web sites for numerous hospitals offering the RYGB and SG procedures, none of which included ongoing, accelerated bone loss in their lists of potential adverse effects. Nor was persistent, accelerated bone loss noted (1) in a recent discussion of bariatric surgery posted on Medscape[29]; (2) in an article in *US News*, "Information on Bariatric Surgery," for which Duke Medicine provided the content[30]; (3) in the Mayo Clinic's discussion of the risks of gastric bypass surgery[31]; (4) on the Web site of the American Society for Metabolic and Bariatric Surgery[32]; or (5) at the Weight-Control Information Network, a part of the National Institutes of Health's (NIH's) information services, whose mission is to "provide the general public, health professionals, the media, and Congress with up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues."[33]

Virtually none of these resources for physicians and/or patients mentioned that bariatric surgery causes significant, continuing bone loss. One of the few that does, the Cleveland Clinic's Bariatric and Metabolic Institute, states,

> Nearly 30 percent of patients who have weight-loss surgery develop nutritional deficiencies, such as anemia, osteoporosis, and metabolic bone disease. These deficiencies can be avoided if intakes of vitamins and minerals are maintained.

That claim is one, however, that the current medical literature, as discussed below and in part 2, renders questionable.[34] Wikipedia informs readers that metabolic bone disease, osteopenia, and increased risk of fracture are common side effects of bariatric surgery[35] but attributes these adverse outcomes simply to reduced calcium absorption, which recent studies investigating changes in a wide range of hormones that are induced by bariatric surgery now indicate is only the tip of a formidable iceberg.

Effects on Bone

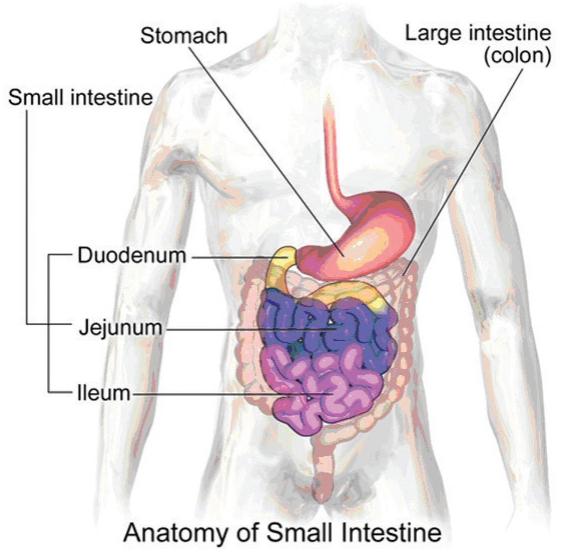
Research published in 2015, including 2 papers in the *Journal of Clinical Endocrinology & Metabolism*—one in the February 2015 issue[10] and another in the March 2015 issue,[9] continue to confirm that gastric bypass surgeries, including both the RYGB and the increasingly popular SG versions, cause significant ongoing bone loss. Yu et al[10] has reported that bone mineral density (BMD), at 2 years after a gastric bypass, was 5% to 7% lower in the spines and 6% to 10% lower in the hips of recipients of bariatric surgery compared with controls.

Objectives of a study by Muschitz et al[9] included comparisons of the effects of the RYGB and SG on bone. In patients receiving either bariatric surgery, bone loss was significant, and the 2 bone-loss outcomes were comparable (ie, an overall loss in total-body BMD of 18%). BMD at the lumbar spine and at the total hip persistently decreased, and the decline in BMD in specific regions of the skeleton (the arms, legs, trunk, and ribs) did not differ between the bariatric surgeries. In the research conducted by both Yu et al[10] and Muschitz et al,[9] bone turnover markers remained elevated for the full 2 years that patients were followed after bariatric surgery.

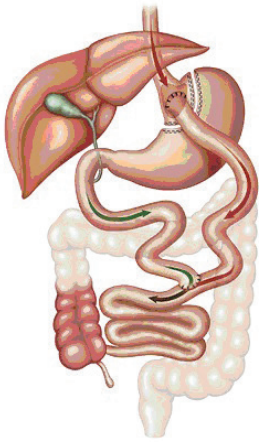
Similar bone-loss outcomes have been seen in a number of other studies. The majority of papers are still reporting data gathered during the first 1 to 2 years after bariatric surgery,[9,10,24-27] but a growing number are now providing data on patients followed for longer periods. Those data include results from an article published in 2004 in which participants were followed for at least 3 years after bariatric surgery[28] and one published, in 2009, in which participants were followed for up to 5 years.[15]

Figure 1. The digestive tract. Figure 1A shows the normal digestive tract. Figure 1B shows the tract with a Roux-en-Y gastric bypass, in which staples are used to create a small, egg-sized gastric pouch, which holds slightly less than 1 ounce (28.3 g), from approximately 5% of the stomach. Figure 1C shows a sleeve gastrectomy, which removes approximately 85% of the stomach, with the surgeon removing the fundus, creating a small, sleeve-shaped stomach approximately the size of a banana.

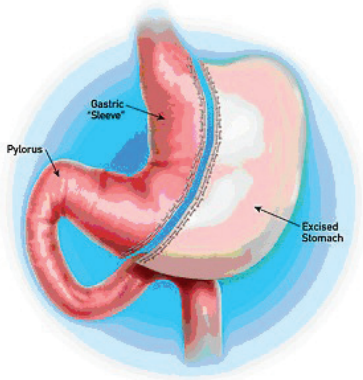
1A



1B



1C



In another study, patients (N = 258), with an average age of 44 years when they underwent bariatric surgery, were followed for a median of 7.7 years. In this study, the fracture risk increased 2.3-fold. Unfortunately, in this research, neither BMD nor markers of bone turnover were measured.[12] The key point, however, is that the research consistently indicates that bone loss, unlike weight loss, does not subside, regardless of the length of time it has been investigated.

Similar losses in bone have been seen in adolescents.[21] In a study of 61 obese adolescents who underwent bariatric surgery, a decrease in whole-body bone mineral content (WB BMC) of 5.2% was seen at 1 year and 7.4% at 2 years. Weight loss accounted for only 14% of the decrease in BMC in the first year after surgery. BMD values also declined significantly, from 1.5 to 0.1. Despite those results, the BMD *z* score did not fall below the expected value for gender and age (ie, a *z* score of 0, by 2 y after surgery). The researchers thought that the finding was likely to be a consequence of the high BMC and BMD before surgery in this extremely obese population. However, they noted, "if bone loss continues, even at a slow rate, these patients may have an increased risk of fractures later in life."

Nutrient Malabsorption

The above findings are not all that surprising given that the most popular forms of bariatric surgery, the RYGB and the SG, greatly reduce not only the size of the stomach (Figure 1) and, thus, the amount of food that can be consumed, but also the ability of the digestive tract (1) to secrete the hydrochloric acid (HCl) required to digest food and (2) to absorb macro- and micronutrients, including calcium, magnesium, and the fat-soluble vitamins A, D, and K, which are required for bone formation, as well as numerous other micronutrients with important roles in healthy bone remodeling (eg, vitamin E, the B vitamins, the essential fatty acids, vitamin C, boron, and a number of other trace minerals).

Roux-en-Y Gastric Bypass

The procedure reduces the stomach to a gastric pouch that is created from approximately 5% of the former stomach and is able to hold approximately 1 ounce (28.3 g), thus reducing by 95% the amount of food that can be consumed at one time. In doing so, it bypasses (1) the outside curvature of the stomach, the fundus; and (2) the first 2 sections of the small intestine, the duodenum and proximal jejunum, which are the sites where all active calcium absorption occurs and are the primary areas in the intestines where many micronutrients are preferentially absorbed.

Sleeve Gastrectomy

In the procedure, a large portion of the stomach along its greater curvature, including the fundus, is removed, leaving a sleeve- or tube-like, banana-shaped

structure that is approximately 15% of the stomach's original size. SG reduces by approximately 85% the amount of food that can fill the stomach, thus also reducing by *at least* 85% the amount of the nutrients that can be provided per meal of ingested food. ("At least," because by removing the fundus, both the RYGB and the SG greatly diminish digestive function in what remains of the stomach.)

Both the RYBG and SG bypass the outside curvature of the stomach, the fundus, which contains the rugae, or folds, that help the stomach expand and also contain several specialized cells involved in digestion including (1) parietal cells, which release hydrogen (H^+) and chloride (Cl^-), creating HCl; (2) chief cells, which produce pepsin, which breaks down proteins in foods by releasing the pepsinogen that reacts with HCl to make pepsin; and (3) mucus cells, which release mucus to coat the stomach, protecting it from the low-pH, high-acid environment.

By eliminating all HCl-secreting parietal cells and pepsin-secreting chief cells, which are found only in the fundus, both the RYGB and SG severely compromise digestion. In relation to bone, specifically, it is important to note that calcium requires the action of stomach acid to become solubilized, which renders it able to be absorbed.

Magnesium, another mineral essential for bone, also requires HCl to be solubilized but is primarily absorbed in the distal end of the small intestine and in the colon via the transient receptor potential cation channel, subfamily M, member 6 (TRPM6).[36,37] Magnesium shortage is clinically associated with osteoporosis and may occur in any bypass surgery, both because HCl-secreting parietal cells are bypassed and because magnesium binds with fatty acids, the absorption of which is also compromised. Compromised absorption is discussed in the next section of the current article.[38]

Pizzorno[39] discusses the importance of magnesium for bone in considering the clinical effects of hypomagnesemia, indicating that approximately 60% of the magnesium in the human body is found in bone, where it is a cofactor for key enzymes that regulate calcium metabolism. Zofková et al[40] found that the majority of magnesium in bone resides on cortical bone as an integral part of the structure of the apatite crystal. Apart from its structural role in apatite crystals, magnesium is required in osteoblasts and osteoclasts and in all living cells, within which magnesium is fundamental for adenosine triphosphate (ATP) production and serves as the cofactor of more than 300 of enzymes involved in lipid, protein, and nucleic-acid synthesis. Castiglioni et al[41] found that magnesium, because of its positive charge, stabilizes cell membranes, balances the actions of calcium, and functions as a signal transducer.

Further, although calcium is absorbed passively as well as actively in the small intestine, passive absorption, which takes place in the final portion of the small intestine, the ileum, accounts for only a small fraction of the amount of calcium normally absorbed.[42] Active absorption, the primary means of absorbing calcium, takes place in the duodenum, which is also where absorption of the majority of minerals and vitamins (including the fat-soluble vitamins A, D, E, and K) primarily occurs. Vitamin B_{12}, which is preferentially absorbed in the final portion of the small intestine, the ileum, would appear to be an exception; however, B_{12} absorption is also affected because it requires intrinsic factor, which is produced by parietal cells in the fundus of the stomach, an area bypassed in both the RYGB and SG surgeries.

Compromised Absorption

Bile

Normally, absorption of the fat-soluble vitamins, along with that of fats including the essential fatty acids, occurs in the small intestine, primarily in the parts of the duodenum that are bypassed in the RYGB.

Absorption of fat-soluble vitamins, essential fatty acids, and other fats occurs with the help of bile, which is produced in the liver from cholesterol. The bile is sent, in the form of water-soluble bile salts, to the gall bladder from which it exits via the common bile duct into the uppermost portion of the duodenum in response to food consumption. In the RYGB, nutrients bypass the duodenum, which as a result is exposed to undiluted bile. Bile and nutrients do not mix until they reach the distal jejunum and, thus, fats and fat-soluble nutrients have much less exposure to bile prior to transit through the ileum.[43]

Bile acids are used to produce micelles, which are amphiphilic organic compounds containing both hydrophobic groups, their tails, and hydrophilic groups, their heads. These combinations of fatty acid and water are required for the absorption of the fat-soluble vitamins and of all fats, including the essential fatty acids. In the absence of bile, fats become indigestible and are excreted in feces, a condition called steatorrhea, which has been associated with osteodystrophy,[44] and in both animal and human studies, with bariatric surgery.[45,46]

Bile acids have also recently been shown to exert hormonal actions systemically. Receptors activated by bile acids serve as braking signals on inflammation in the gastrointestinal tract and liver, which is yet another way in which bile protects bone against chronic inflammation that may excessively activate osteoclasts.[47]

Chronic inflammation from any cause can promote bone loss. A diverse range of papers noting this connection underscores this point.[48-62]

Vitamins D and K

The bone-essential roles played by vitamins D and K are well documented.[63] Vitamin D is required for the active absorption of calcium; without adequate vitamin D, only 10% to 15% of dietary or supplemental calcium that is consumed is absorbed, even when calcium has been solubilized by HCl.[64]

Vitamin K (as phylloquinone [K_1]) lessens inflammation and (in its menaquinone [K_2] forms) activates the vitamin K-dependent proteins that regulate calcium deposition into bone (osteocalcin) and prevent calcium from depositing in soft tissues, such as the heart, vasculature, kidneys, brain, and breasts (matrix Gla protein).[65-69]

Vitamin A

Although it is well established that hypervitaminosis A in rodents decreases cortical thickness by increasing the number of periosteal osteoclasts, clinical studies in humans have suggested that vitamin A can be beneficial as well as harmful to bone. The most recent papers indicate that high vitamin A intake combined with low intake of vitamin D is what favors a decrease in BMD and an increase in fracture risk. Current thinking is that it is the ratio between vitamin A and vitamin D that determines vitamin A's effects on bone, not vitamin A alone.[70-72] Further, vitamin A is required for immune tolerance, and vitamin A insufficiency promotes inflammation.

The recently recognized subset of helper T cells, the TH17 lineage, generate interleukin 17 (IL-17) cytokines, which initiate activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thus provoking inflammation. Retinoic acid inhibits the differentiation of TH17 cells and promotes the generation of regulatory T cells that produce anti-inflammatory IL-10.[72]

Vitamin E

Dietary vitamin E, which is high in gamma-tocopherol, may be beneficial for bone, but alpha-tocopherol alone is not, and alpha-tocopherol is the only form of vitamin E found in more than 80% of supplements. High serum levels of gamma-tocopherol, but not alpha-tocopherol, have been found to be associated in postmenopausal women with high levels of bone-specific alkaline phosphatase (BAP), a marker of bone formation.

In a study of postmenopausal women (N = 497), with a mean age of 65.5 years, 81.4% of those using dietary supplements consumed a supplement containing only alpha-tocopherol, and 39.4% of the women taking alpha-tocopherol supplements had intakes of alpha-tocopherol more than 400 IU (180 mg). High alpha-tocopherol status, defined by the ratio of serum alpha-tocopherol to gamma-tocopherol, was found to have a significant inverse relation with BAP levels in unadjusted and adjusted analyses. Conversely, high serum-gamma-tocopherol levels were associated with high BAP levels in both unadjusted and adjusted models.[73]

What might explain these outcomes? In vivo studies show that gamma-tocopherol neutralizes nitric dioxide (NO_2), which inhibits collagen synthesis and is also converted into nitric oxide (NO), which can uncouple bone resorption and formation. In the presence of proinflammatory cytokines, high NO may inhibit osteoblast differentiation and growth.

Gamma-tocopherol also neutralizes reactive nitrogen species (RNS) (eg, peroxynitrite), improving osteoblastic production and activity. In addition, gamma-tocopherol and its metabolite, gamma-2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman (gamma-CEHC), inhibit cyclooxygenase-2 (COX-2) activity and the resulting production of prostaglandin (PG)E2. Reducing PGE2 has been associated with increased bone formation in growing rats, minimized bone loss in ovariectomized adult rats, and improved osteoblast function in vitro.

Further, gamma-tocopherol and its metabolites inhibit proinflammatory cytokines that induce osteoclast differentiation.[73] In contrast, alpha-tocopherol has been shown to inhibit the differentiation of osteoblasts in vitro.[74]

Last, high intake of alpha-tocopherol suppresses serum levels of gamma-tocopherol for several reasons. First, increased intake of alpha-tocopherol causes an increase in the CYP450 enzyme, CYP3A, which metabolizes both alpha- and gamma-tocopherol. Second, alpha-tocopherol transfer protein (alphaTTP), which mediates the transfer of absorbed tocopherols in the liver into the circulation, preferentially transfers alpha-tocopherol and has lower affinity for gamma-tocopherol, so although all remaining alpha-tocopherol is taken into circulation by alphaTTP, almost all of the gamma-tocopherol is metabolized and excreted. Third, gamma-tocopherol is preferentially taken up by cells over alpha-tocopherol, which further helps explain why serum levels of alpha-tocopherol are typically higher.[75,76]

Because it is gamma-tocopherol that appears to uncouple bone turnover, promoting increased bone formation, and because high intake of alpha-tocopherol suppresses serum levels of gamma-tocopherol, vitamin E supplements containing only alpha-tocopherol may negatively affect bone formation. Given bariatric surgery's adverse effects on fat-soluble nutrient absorption, dietary vitamin E is not likely to be well absorbed; thus supplements providing mixed tocopherols with a higher ratio of gamma:alpha (5:1) are recommended. A 5:2:1 ratio among the gamma:delta:alpha tocopherols is the ratio found in vitamin E-rich foods.[77]

Essential Fatty Acids

Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have anti-inflammatory actions that help prevent excessive osteoclast activation.[78-81]

B Vitamins

B-vitamin insufficiency increases homocysteine levels. B_{12}, together with B_6 and folate, plays an important bone-protective role in the methylation cycle; insufficiency of these B vitamins promotes an increase in levels of homocysteine. Chronically elevated levels of homocysteine promote oxidative stress, increase osteoclast activity, and decrease osteoblast activity. Homocysteine binds directly

to the extracellular matrix and reduces bone strength and resilience by decreasing bone's blood flow and increasing the activity of matrix metalloproteinases that degrade the extracellular bone matrix.[82-87]

Why Consider Bariatric Surgery?

Given the adverse effects of the RYGB and SG on the ability to absorb nutrients required not only for healthy bones but also for health overall, why consider bariatric surgery?

Morbid obesity, in addition to its emotional challenges, adversely affects mobility, even basic physical functions such as walking and breathing, and typically brings with it numerous comorbidities that greatly increase the risk of death. Comorbidities of obesity include insulin resistance; type 2 diabetes; chronic, low-grade inflammation; high blood pressure; high cholesterol; increased risk of cardiovascular disease, heart attack, and stroke; gallbladder disease; liver disease; osteoarthritis; asthma; obstructive sleep apnea; gastroesophageal reflux disease; urinary stress incontinence; menstrual irregularities; infertility; depression; and more.[88,89]

Both the RYGB and SG procedures not only result in rapid, impressive weight loss, but also greatly lessen or even completely resolve, in more than 60% of patients, many of the potentially life-shortening conditions that accompany obesity, particularly diabetes, high cholesterol, high blood pressure, and obstructive sleep apnea.

Unfortunately, as researchers have begun to learn, bariatric surgery also changes the digestive tract in ways that immediately, significantly, and relentlessly adversely affect its ability to absorb not only calcium and vitamin D, but also many nutrients necessary for healthy bone remodeling and overall health.

Conclusion

Bariatric surgery causes significant ongoing bone loss. Nutritional assessment of patients undergoing bariatric procedures, ideally both prior to and after surgery at regular intervals life-long, is strongly recommended. Physicians can assess the nutritional status of bariatric surgery patients and, where indicated, help prevent nutritional deficiencies that promote bone loss. By increasing bariatric surgery patients' awareness of their increased needs for a healthy diet and, where indicated, for nutritional supplements, physicians can greatly help these patients avert potential long-term, adverse outcomes, in particular osteoporosis. The adverse effects of bariatric surgery on bone must be widely recognized, and protocols must be developed to prevent early onset osteoporosis in the recipients of this increasingly utilized and otherwise potentially life-saving surgery.

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The author has no conflicts to disclose.

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