Bariatric Surgery: Bad to the Bone, Part 2

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Abstract

As discussed in Part 1, 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 to treat it. A growing number of recently published studies have reported that, despite calcium and vitamin D supplementation, the most frequently performed types of bariatric surgery, the Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy (SG), cause significant, ongoing bone loss. Recent studies investigating nutrient malabsorption and changes in a wide range of hormones that are induced by bariatric surgery have indicated that calcium malabsorption is just the tip of a formidable iceberg. Part 1 reviewed the latest research findings confirming that the prevalence of obesity is, in fact, skyrocketing and that bariatric surgery causes ongoing accelerated bone loss. Part 1 also discussed the mechanisms through which the malabsorption of key nutrients induced by bariatric surgery adversely affects bone. The current article, Part 2, reviews the specific changes seen in bone metabolism after bariatric surgery and the current data on the underlying mechanisms, in addition to nutrient malabsorption, that may contribute to bariatric surgery-induced bone loss. These mechanisms include mechanical unloading, calcium malabsorption despite maintenance of vitamin D levels of ≥30 ng/mL, and changes in a number of hormones, including leptin, adiponectin, testosterone, estradiol, serotonin, ghrelin, glucagon-like peptide 1 (GLP-1), and gastric inhibitory peptide (GIP). Research discussing the use of nutritional supplements to help ameliorate bariatric surgery-induced bone loss is summarized. The adverse effects of bariatric surgery on bone must be widely recognized, and protocols must be developed to prevent early onset osteoporosis in recipients of this increasingly utilized and otherwise potentially life-saving surgery.

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What happens to bone after bariatric surgery?

In all of the studies looking into the effects of bariatric surgery on bone, accelerated bone loss has been found to begin almost immediately and to be continuous, regardless of the duration of the study. In some studies, patients were followed for more than 9 years. These facts are alarming because both the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) surgeries—the most frequently performed forms of bariatric surgery in the United States and worldwide—are becoming increasingly common, and the majority of people receiving them are middle-aged or younger. As the prevalence of severe obesity has increased by 70% in the past decade,[1] so have the number of gastric-bypass (GB) procedures, which rose 761% from 1998 to 2008.[2]

It is well known that continuous, excessive bone loss over multiple years increases skeletal fragility and ultimately fracture risk. What is now being recognized is that upregulated bone loss over multiple years occurs not only in menopausal women, but also in premenopausal women, in men, and in adolescents and children who have had bariatric surgery, which is increasingly being used to treat morbid obesity in adolescents and in children as young as 5 years.[3-5]

Along with the immense increase in the frequency with which bariatric surgeries are being performed, research studying their outcomes—both their benefits and their immediate and potential long-term adverse consequences—is also increasing. Researchers now know that weight loss typically plateaus within 6 months after

surgery, but accelerated bone loss does not. The 2 papers mentioned in Part 1 that were published in February and March of 2015 in the *Journal of Clinical Endocrinology and Metabolism*[6,7] have again confirmed those facts.

In the study by Yu et al,[6] 50 obese adults were recruited from the Massachusetts General Hospital Weight Center and the surrounding community; 30 were undergoing RYGB surgery; and 20, who were not having surgery, served as a control group. Controls were of similar age, sex, and weight as those in the surgical group.

The average age of participants in that study was 47 ± 14 years. In the group of 30 patients receiving GB, 53% were premenopausal women, 33% were postmenopausal women, and 13% were men. In the control group of 20 patients, 60% were premenopausal women, 25% were postmenopausal women, and 15% were men. So, the majority of the individuals undergoing GB (66%) were either premenopausal women or men in their 30s and, therefore, should not have been at increased risk for bone loss. In fact, young and middle-aged obese individuals are often found to have higher-than-average bone density, which has been thought to result from the additional mechanical load placed on bone by their extra weight. When carrying an extra 50 to 75 pounds (22.7 to 34 kg) or more, even daily activities have been thought to send stress signals to osteocytes triggering an anabolic response within bone to withstand the trauma.[7]

Participants in the study by Yu et al[6] who were undergoing GB were counseled to get 1200 to 1500 mg of calcium and 3000 IU of vitamin D each day through a combination of diet and supplements. Their bone density was checked at baseline and at 6, 12, and 24 months after GB surgery.

What happened? Markers of bone turnover had (1) already become elevated at 6 months when the study's participants were first checked postsurgery; (2) remained elevated throughout the 24-month study period; and (3) could be used to predict how much bone was being lost, particularly in the spine and hip. The markers evaluated were carboxy-terminal collagen crosslinks (CTx), a marker of bone resorption, and procollagen 1 intact N-terminal peptide (P1NP), a marker of bone formation. CTx is a specific, crosslink peptide sequence of type 1 collagen that is found in bone, in the portion cleaved by osteoclasts during bone resorption. Serum levels of the peptide sequence are proportional to osteoclastic activity at the time that the blood sample is drawn.

Despite weight stabilization by 6 months postsurgery, the decline in bone mineral density (BMD) did not plateau but persisted at all skeletal sites evaluated (the spine, hips, lower arm and lower leg) at 2 years post-RYGB, the duration of the study. BMD decreased in both cortical and trabecular bone. Bone structure (ie, its microarchitecture) at the wrist and shin bone had deteriorated so greatly in the RYGB group that by the end of the study, these changes had resulted in a 9% to 10% decrease in estimated bone strength at both peripheral sites. Bone density in the control group did not decline but remained stable, as would be expected due to the participants' mostly young or premenopausal age.

An earlier study, published in 2009, had found continuing increased bone resorption in individuals who underwent GB, on average, 3 years earlier.[8] Another study, published in 2011, investigated changes in hip and spine BMD after GB surgery and reported that BMD dropped an additional 3% between the second and third years after GB.[9] In the study by Yu et al,[6] further cause for concern was raised by the fact that the deleterious changes in bone in RYGB patients had occurred even though the average blood levels of calcium, 1,25-dihydroxyvitamin D (1,25[OH]D) and parathyroid hormone (PTH) had been maintained within the normal range in those patients as well as in the controls during the 2 years.[i]

Why is this additional cause for concern? Because insufficient calcium and/or insufficient vitamin D, and a resultant elevation in PTH, are the key mechanisms through which bone loss is *typically* regulated. So, this outcome suggests that RYGB disrupts other regulatory functions that affect bone, which is what researchers are now beginning to investigate. They are finding that a number of other hormones in addition to PTH and the hormonally active form of vitamin D affect bone remodeling, as discussed later, and they do not yet know all of the functions that are affected by bariatric surgery, much less what to do to re-establish normal functioning or to counteract the adverse effects of these hormonal disruptions.

It should be noted that the preoperative bone density was high in most of the severely obese patients in the study by Yu et al[6] and, as already mentioned, young and middle-aged obese individuals are often found to have a high BMD. Most of the participants in the study by Yu et al[6] were young adults, so despite their significant bone loss during the 2-year study, they remained in the normal BMD range (ie, for the moment). But if bone loss continues to occur at an accelerated rate, it is concerning to consider where they may be in their 50s and 60s.

It is not surprising that relatively short-term follow-up (2 years) postsurgery showed no increase in fracture rates, but research that provides data on longer term follow-up (7 years postsurgery), a study published in the January 2014 issue of *Osteoporosis International*,[10] found

i. PTH levels rise when blood levels of calcium drop too low. PTH increases production of the active, hormonal form of vitamin D, 1,25(OH)D, which increases calcium's resorption from the kidneys and its active absorption from the intestines. However, consistently elevated PTH levels promote bone loss because PTH also increases osteoclast activity to liberate calcium from bone for its many immediate uses in the body. These include enabling muscles, including the heart muscle, to contract. Calcium is triaged to meet immediate needs, compared to which its loss from bone is a much lower survival priority.

a 3-fold increase in spinal fracture and a 5-fold increase in hip fracture after bariatric surgery. Another study[11] published in 2014 that evaluated patients more than 10 years after RYGB revealed that 65% had a vitamin-D deficiency, and 69% had elevated PTH levels.

The 2-year study conducted by Muschitz et al[7] looked at whether bone loss differed after RYGB compared with SG. Participants were 52 premenopausal women, with an average age of 40 years, who underwent RYGB, and 38 premenopausal women, with an average age of 41 years, who had SG. In both groups, BMD at the lumbar spine and at the total hip persistently decreased, resulting in a 2-year loss in total-body BMD of 18%. Despite the relatively young average age of the participants, 2 fragility fractures occurred in the RYGB group: 1 radius fracture after 14 months and 1 humerus fracture after 17 months.

How significant is the bone loss that *typically* occurs after GB? The best data that researchers currently have to estimate the loss are provided by a review published in 2012 in *Obesity Surgery*[12] that included 15 prospective studies. It found significant bone loss, preferentially in the hip, following GB procedures. During the first year post-GB, BMD in the hip dropped an average of 9.2% to 10.9% in the femoral neck and 8% to 10.5 % in the total hip (ie, in the femoral neck, trochanter, and Ward's triangle regions). Declines, however, in the BMD of hip sites that were as large as 15% were seen in some individuals in the first year.[12] Drops in BMD occurred in other studies (both in this review and in the 2 recently published, 2-year studies in the *Journal of Clinical Endocrinology and Metabolism*[6,7]) in which GB patients were counseled to take supplemental calcium and vitamin D.

It is undeniably clear that GB surgery triggers ongoing, excessive bone loss. To quote the authors of a study in which the follow-up averaged 7.7 years: "Bariatric surgery, which is accompanied by substantial biochemical, hormonal, and mechanical changes, is associated with an increased risk of fracture."[13]

This finding does not bode well for the long-term bone health of those undergoing GB procedures. But given the continuing increases in morbid obesity seen worldwide, bariatric surgery is not going away, and its benefits in treating obesity and its comorbidities are unquestionable.

The question is: Can bariatric surgery's highly negative effects on nutrient absorption and bone be ameliorated? To answer this question, we need to understand why patients taking supplemental calcium and vitamin D still experience massive drops in BMD. What is causing the loss? The mechanism(s) responsible for bone loss after GB, in addition to the issues regarding nutrient malabsorption that were discussed in Part 1, are not yet fully known, but the following section provides an overview of current theories.

Potential Causes of Bone Loss—Beyond Nutrient Malabsorption—After Bariatric Surgery

Mechanical Unloading

One commonly postulated theory is that bone loss results from mechanical unloading of the skeleton due to substantial weight loss. Mechanical unloading of the skeleton affects osteocytes, which act as mechanostats and respond to the reduction in bone deformation with weight loss by secreting sclerostin, which in turn negatively regulates Wnt canonical signaling, a key factor in osteoblast differentiation. However, both animal and human studies indicate that mechanical unloading resulting from weight loss plays only a partial, minor role in the loss of bone seen after bariatric surgery.[14]

Rats that undergo GB have greater bone loss than do sham-operated rats that have been calorically restricted to achieve the same amount of weight loss.[15] Also, increased body fat, particularly visceral adipose tissue (VAT), has been shown to lower BMD and shrink muscle mass in humans as well as animals. VAT releases proinflammatory adipokines and cytokines, which provoke inflammation that increases osteoclast production and activity.[16] Excessive belly fat (VAT) promotes *ectopic adiposity*, an accumulation of fat in tissues where fat is not supposed to localize, including the liver as well as skeletal muscle. Ectopic adiposity is strongly associated with metabolic dysfunctions such as insulin resistance, type 2 diabetes, and nonalcoholic fatty liver disease. When fat infiltrates skeletal muscle, bone is harmfully impacted as well. Ectopic adipose tissue can be depositing long before a person meets the body mass index (BMI) criterion for obesity or is considered at clinical risk for fatty liver, type 2 diabetes, or bone loss.

Results of an 18-year-long study published in the February 2015 issue of the *American Journal of Clinical Nutrition*[16] confirm this. Conducted at the University of Michigan Health System, this study involved 7230 patients, of whom 46% were women and 53% were men, and who ranged in age from 18 to 64.9 years. Computed tomography (CT) scans were taken each year between 1995 and 2013, and the results were used to evaluate fat infiltration into muscle, specifically into the psoas muscle, and to determine the relationship between ectopic fat and BMD in cortical and trabecular bone. The primary finding was that VAT was strongly inversely associated with BMD in the spine in both vertebral trabecular and cortical BMDs, and also with muscle shrinkage in adults, even after adjustment was made for BMI and age.

These findings question the theory that being overweight is a protective factor for bone health and muscle strength. Having a high BMI means carrying more VAT, regardless of sex or ethnicity, and VAT is increasingly considered an underlying driver linking overweight/obesity to chronic cardiometabolic diseases, including nonalcoholic fatty liver disease, high blood pressure, insulin resistance, and type 2 diabetes. Now we may want to add osteopenia and osteoporosis to the list.

Obesity greatly increases risk of sarcopenia-related bone loss. Surprisingly, men may be at greater risk for VAT-related sarcopenia than women. Young and middle-aged men tend to have a larger proportion of VAT to total fat than women have, who tend to carry fat on their hips and thighs (ie, women show the proverbial pear shape in contrast to the apple shape seen more frequently in men). Their propensity to accumulate VAT may put men at earlier risk of diminished spinal musculoskeletal quality or, in other words, at earlier risk of fatty muscles and bone loss.

A study published in the March 2014 issue of *Obesity*[12] supports this hypothesis. BMI and body fat were tracked in more than 2000 people for a 5-year period. Increases in BMI and body fat coincided with decreases in both muscle and bone mass: (1) average BMI increased from 26.9 kg/m^2 to 27.2 kg/m^2; (2) average fat mass increased by 9.0%; (3) average lean-muscle mass decreased by 0.9%; and (4) average bone mass decreased by 1.6%. These undesirable effects occurred when the average percentage of fat in the men increased only slightly, from 23.4% to 25.2%. Lean body mass decreased more than 2%, from 72.6% to 70.9%, and mean percentage of bone decreased from 4.0% to 3.9%. Further, these effects were not seen primarily in older men. Many of the men in this study were younger. Age stratification at baseline ensured that approximately 100 men were included for each 5-year age group, starting at ages 20 to 24 years, and that approximately 200 men were included for each of the age groups 70 to 79 years and 80 years and older.[17]

In sum, both rat and VAT study findings indicate that, even if mechanical unloading plays a role in bone loss after bariatric surgery, other factors are likely to be the important drivers.

Calcium Malabsorption Despite "Adequate" Vitamin D Status

Another proposed cause of bone loss is the marked decline in intestinal calcium absorption that has repeatedly been documented after GB, a drop that has been recently shown to occur despite optimization (ie, ≥30 ng/mL) of vitamin-D status.[18] Schafer et al's[18] findings were presented at the American Society for Bone and Mineral Research conference in 2014 and were then published in the *Journal of Bone and Mineral Research* in 2015.

The study's participants were 33 severely obese adults, mostly middle-aged, premenopausal women. Before GB, fractional calcium absorption (FCA) was 32.7%, which is within the range of normal. In healthy adult women, FCA is expected to be approximately 37.8% after consuming 200 mg of supplemental calcium (in the form of calcium citrate) and approximately 33.9% when given 300 mg of calcium. Post-GB, when the study's participants were given 200 mg of supplemental calcium, their calcium absorption dropped from an average of 37.8% to an average of 6.9%. This dramatic decline in FCA occurred despite careful attention to maintaining a $25(OH)D_3$ status of ≥30 ng/mL and a stable calcium intake of 1200 mg/day. Nonetheless, after GB, the participants' average, daily, absorbed calcium fell from 392 mg to 82 mg.

Part of the drop in bariatric surgery patients' calcium-absorbing ability surely has to do with the fact that calcium is actively absorbed in the part of the digestive tract that is bypassed in RYGB surgery. In both the RYGB and SG, the 85% to 95% of the stomach that is removed includes the fundus, which contains the parietal cells responsible for secreting the hydrochloric acid required to solubilize calcium, rendering it ready for absorption. Further, GB greatly compromises absorption of the fat-soluble nutrients, which include vitamin D. The results seen in this study suggest that in individuals who have had GB, it may be necessary to maintain the $25(OH)D_3$ status of 40 to 80 ng/mL recommended by the Vitamin D Council,[19] together with a calcium intake of 1300 mg/day, which is the upper recommended daily intake (RDI) suggested for postmenopausal women.[20] Calcium intake of 1500 mg/day as calcium citrate is now recommended in the 2014 position statement of the American Society for Metabolic and Bariatric Surgery.[21]

As one would expect, with so little calcium being absorbed after bariatric surgery in these patients, PTH levels in the study by Schafer et al[18] rose significantly, as did levels of the hormonal form of vitamin D, $1,25(OH)_2D_3$ (calcitriol). PTH levels increased from a median of 41.3 pg/mL (IQR: 32.0 to 53.1) to 48.4 pg/mL (IQR: 39.3 to 59.1), and $1,25(OH)_2D_3$ increased from 37.1 pg/mL (IQR: 33.6 to 45.6) to 51.4 pg/mL (IQR: 41.0 to 63.3). Levels of CTx increased an average of 276% (IQR: +167 to +381%).

In the 2-year study conducted by Yu et al,[6] PTH levels were only minimally affected after GB, but levels of both CTx and P1NP immediately rose and remained elevated. In the GB patients, both CTx and P1NP were more than double the levels seen at baseline and in controls at 6, 12, and 24 months.

Despite the rise in P1NP, bone formation cannot not keep pace with bone loss after GB, because it takes significantly longer to build than to remove bone. Resorption by osteoclasts is normally completed in 2 weeks, after which the body begins to switch gears. Just preparing osteoblasts to take over requires approximately 2 more weeks, following which new bone formation, which takes at least 13 weeks, begins. When all systems are functioning in proper balance, a full cycle of both aspects of the remodeling process is completed in 3 to 6 months.[22]

It should be underscored that the 2 aspects of the bone-remodeling process, bone resorption and formation, are not separate, independently regulated processes.[23] Osteoclasts and osteoblasts work together inside a unique temporary structure, the basic multicellular unit (BMU). Each BMU contains a team of osteoclasts in the front, a team of osteoblasts in the rear, a central capillary/blood vessel, a nerve supply, and associated connective tissue. In healthy human adults, 3 to 4 million BMUs are produced each year with approximately 1 million operating at any moment.

The lifespan of each BMU is 6 to 9 months, which is much longer than the lifespan of either its osteoclasts or osteoblasts. So, a continuous supply of new osteoclasts and osteoblasts from their respective progenitors in the bone marrow is essential for the origination of BMUs and their progression on the bone surface. The balance between the supply of new cells and their lifespans are key determinants of the number of both cell types in the BMU and of the work performed by each type. This balance between osteoclast and osteoblast production, which is critical for the maintenance of bone homeostasis, is disrupted by bariatric surgery.

In the second year after they underwent GB in Yu et al's[6] study, participants were evaluated both by dual-energy X-ray absorptiometry (DXA), an indicator of bone quantity, and by a newer type of scan called quantitative computed tomography (QCT), which provides better insight into bone quality. Both the DXA and the QCT showed significant bone deterioration. DXA showed an average additional loss of 2.2% BMD at the spine and 2.6% at the hip. The QCT scores were worse, showing a loss of 4.2% in the hip and a 1.7% loss in the spine. The participants were younger people, primarily premenopausal women and men with an average age of 47 years (ie, an age-group that is not supposed to be rapidly losing bone).

Further, GB patients in this study were consistently more physically active than controls: (1) at baseline, the GB patients' physical activity averaged 19 hours per week compared with 15 hours per week for controls; (2) at 6 months post-GB, GB patients' physical activity averaged 27 hours per week compared with 14 hours per week for controls; (3) at 12 months postsurgery, GB patients' physical activity averaged 23 hours per week compared with 21 hours per week for controls; and (4) at 24 months postsurgery, GB patients' physical activity averaged 19 hours per week compared with 9 hours per week for controls. Yet despite keeping vitamin D, PTH, and blood levels of calcium largely in the normal range, which participants in other studies have not been found to do, and despite being much more physically active than controls, who were not losing bone, these GB patients were experiencing significant, continuous bone loss at 2 years after GB.

Muschitz et al[7] studied the effects of GB on levels of several markers of bone metabolism in 52 premenopausal women, ranging in age from 32 to 48 years (40 ± 8, BMI: 43.4 kg/m^2) after RYGB, and in 38 premenopausal women, ranging in age from 34 to 48 years (41 ± 7, BMI: 45.7 kg/m^2) after SG. Muschitz et al's[7] primary focus was sclerostin, an antagonist of bone morphogenetic protein (BMP). BMP is produced by osteocytes, which are the type of cell that osteoblasts become after they begin laying down new bone, and it triggers bone-building activities. Sclerostin, by inhibiting BMP, inhibits bone formation.

Muschitz et al[7] also checked other markers of bone turnover: CTx (resorption) and P1NP (formation). Sclerostin and CTx, both of which promote resorption, and also but to a far lesser extent P1NP, which is involved in bone formation, rapidly increased after surgery and remained elevated during the entire study period. The result was an imbalance in bone homeostasis, resulting in an increase in resorption that produced significant loss of BMD at all skeletal sites. BMD dropped regardless of which type of GB was performed, RYGB or SG.

Altogether, the findings from these studies suggest that what we have understood to be the usual bone regulating mechanisms—vitamin D, PTH, and calcium, and the beneficial effects we expect to see from weight bearing exercise—are not the principal pathways determining bone loss after GB.

Bariatric Surgery-induced Hormonal Changes

Researchers are just beginning to look into the finding that GB is accompanied by large changes in hormones, many of which are now being found to have direct or indirect effects on bone, including (1) leptin, gastrin, ghrelin, and serotonin, which are produced by cells lining the gastrointestinal tract; (2) hormones like adiponectin, which are produced by fat cells; and (3) endocrine hormones, including estrogen, progesterone, testosterone, cortisol, thyroid hormones, and others.[24-27]

Normally, the processes of bone resorption and formation are tightly coupled through a complex network of endocrine and paracrine signals that maintain balance between osteoblast (formation) function and osteoclast (resorption) function. An increasingly large body of research indicates that this network is dysregulated by bariatric surgery. The rapid reduction in adipose tissue results in changes in adipokine secretion (ie, leptin is decreased, and adiponectin is increased) and a decrease in estradiol levels due to a decrease in aromatization of testosterone. In addition, removal of the duodenum changes the secretion of gut-derived hormones; in particular, it causes an increase in secretion of serotonin and GLP-1, and a decrease in secretion of ghrelin and GIP.[24]

Leptin. Leptin is released systemically by adipocytes in amounts proportional to total body fat and is thought to inform the brain about systemic fat (ie, energy stores). Leptin levels decrease significantly after bariatric surgery in proportion to the loss of total body fat. This decrease affects bone metabolism via at least 2 separate central nervous system mechanisms, one that promotes bone formation and another that promotes resorption.[24]

Leptin binds to its receptors in the hypothalamus, triggering secretion of brain-derived serotonin (BDS), which, by modulating sympathetic nervous system tone, activates cell surface β-adrenergic receptors in osteoblasts, thereby upregulating osteoblast function and bone formation. Leptin-binding also downregulates production of cocaine-amphetamine regulated transcript (CART), which regulates RANKL expression in osteoblasts via as yet undetermined mechanism(s). RANKL increases osteoclast production and activity, promoting increased bone resorption.

The decrease in leptin seen after bariatric surgery has been found to inversely correlate with increased levels of markers of both bone formation and resorption; however, the increase in bone resorption markers significantly exceeds that of markers of formation, tipping the balance toward bone loss.

Adiponectin. Adiponectin is also produced by adipose tissue. Circulating levels are reduced in obesity and diabetes, and increase following bariatric surgery. Osteoblasts express both adiponectin and its receptors and increase differentiation in response to the peptide. Studies in mice also suggest that adiponectin suppresses osteoclastogenesis and osteoclast activity.[24]

On the other hand, circulating adiponectin has been shown to induce osteoclast formation via stimulation of RANKL and to inhibit osteoprotegerin production by osteoblasts. Adiponectin also reduces circulating insulin concentrations, which would tend to mitigate against its potentially anabolic effects on bone and other tissues.

A large cohort study (N = 1735 nondiabetic women, average age 50 years) found that each doubling of serum adiponectin was associated with a mean 2.7% decrease in BMD (total hip, -3.2%; femoral neck -3.1%; forearm, -2.0%; spine, -2.6%), a negative relationship that persisted after adjustment for potential confounding factors, including BMI, serum leptin, central fat mass, hormone replacement therapy, smoking, and exercise. The relationship was stronger in postmenopausal women but disappeared in premenopausal women.[28]

Further support that the increase seen in adiponectin after GB promotes bone loss comes from a prospective study of 42 women evaluated 12 months post-GB surgery.[29] The participants' weight decreased by 34.4% ± 6.5%; excess weight loss was 68.2% ± 12.8%. The adiponectin concentration increased from 11.4 ± 0.7 mg/L before surgery to 15.7 ± 0.7 and 19.8 ± 1.0 at months 6 and 12 after GB, respectively. Total BMD dropped by 3.0% ± 2.1%, spinal BMD decreased by 7.4% ± 6.8%, and hip BMD showed a loss of 10.5% ± 5.6%.

Estrogen. Estrogen is the major hormonal regulator of bone metabolism in women and men, and has pleiotropic effects on maintaining bone formation at the cellular level.[24,30] Estrogen's direct effects on osteocytes, osteoclasts, and osteoblasts lead to inhibition of bone remodeling, decreased bone resorption, and maintenance of bone formation. Estrogen also modulates osteoblast/osteocyte and T-cell regulation of osteoclasts. In men and postmenopausal women, adipose tissue, in which testosterone is converted to estradiol via the actions of the enzyme aromatase, is the primary source of estrogen. Rapid depletion of adipose tissue after bariatric surgery results in decreased aromatization of testosterone, decreased levels of estradiol, and a decrease in estrogen's beneficial effects on bone.

Serotonin. Both gut-derived serotonin (GDS) and brain-derived serotonin (BDS) affect bone. Most serotonin (95%) is produced in the periphery, primarily in the gut and only approximately 5% in the brain. GDS inhibits bone formation by binding to and activating the osteoblastic HTR1B receptor on osteoblasts. This action initiates a signaling cascade (ie, inhibition of cyclic adenosine monophosphate [cAMP] production and protein kinase A [PKA]-mediated cAMP response element binding [CREB] phosphorylation), which results in decreased expression of cyclin genes and decreased osteoblast proliferation.[31]

The effects of serotonin that originates in the brain (BDS) differ in relation to leptin levels and binding in the hypothalamus. In response to increases in leptin, BDS levels drop with a consequent increase in sympathetic tone, inhibition of bone formation via activation of the osteoblastic ADR2B receptor, and stimulation of bone resorption through the RANKL system. When leptin levels decrease, as they do after bariatric surgery, BDS levels increase, producing effects on both bone formation and bone resorption, but more of the latter, as covered above in the discussion of leptin.[24]

Ghrelin. Ghrelin is a potent appetite-stimulating hormone, synthesized in the gastric antrum and fundus. Circulating concentrations increase under preprandial and fasting conditions. Ghrelin is thought to play a role in long-term maintenance of energy stores because, in addition to stimulating appetite, it decreases energy expenditure.[32] Circulating ghrelin levels after various bariatric procedures have been inconsistent, ranging from reduced through unchanged to increased. In RYGB patients, most studies have shown a decrease in fasting and/or postprandial levels of circulating ghrelin compared with control patients and compared to RYGB recipients' baseline readings, a change that may be contributing to the greater weight loss associated with RYGB compared with less invasive procedures, such as gastric banding.

Ghrelin may play a role in the regulation of bone metabolism through its effects on growth hormone and, as a consequence, insulin-like growth factor-1 secretion. Ghrelin binds to the secretagogue receptor for growth hormone, which is also expressed by osteoblastic cells, which secrete ghrelin. Ghrelin stimulates osteoblast proliferation and differentiation in vitro, but also promotes osteoclastogenesis and mature osteoclasts' bone-resorbing activity. Ghrelin's anabolic effects predominate, at least in ghrelin-infused rats, in which BMD has increased.[33]

Although animal studies suggest a predominantly anabolic effect of ghrelin on bone, human clinical findings are unclear. Ghrelin secretion overnight was found to be positively and significantly related to BMD in adolescent women,[34] but no consistent relationship has been seen between fasting ghrelin levels and BMD in older men and women.[35]

In sum, ghrelin is emerging as a potentially positive regulator of bone,[36,37] but whether ghrelin contributes to changes in bone metabolism or mass after bariatric surgery is yet to be determined.

GLP-1 and GIP. GLP-1 and GIP[24,32] (called glucose-dependent insulinotropic polypeptide as well as gastric inhibitory peptide) are released from the lower intestinal endocrine L cells (GLP-1) and K cells (GIP) in response to ingested nutrients, and they are key among the incretins, a group of metabolic hormones that help lower blood-glucose levels by stimulating postprandial insulin secretion and slowing gastric emptying, promoting satiety before blood-glucose levels become elevated.

GLP-1-receptor knockout mice exhibit cortical osteopenia and bone fragility as assessed by bone densitometry as well as increased numbers of osteoclasts and heightened bone resorption. In contrast, in rats treated with GLP-1 for 3 days via a subcutaneously implanted osmotic pump, expression of osteoblastic genes in bone tissue increased. This effect of GLP-1 on bone was seen in normal and glucose-intolerant rats and occurred without any change in plasma glucose or insulin after treatment, thus showing an insulin-independent anabolic effect of GLP-1 on bone and suggesting that GLP-1 may be a useful therapeutic agent for improving the deficient bone formation and bone structure associated with glucose intolerance. However, information about the role of GLP-1 in the regulation of bone is scanty and, moreover, is yet to be investigated in human studies.

GIP's primary stimuli are fat and carbohydrates reaching the duodenum after meal ingestion. Although secreted throughout the small intestine, GIP is primarily secreted by the K cells present in maximum concentration in the duodenum and jejunum. The duodenum and the first section of the jejunum are bypassed in RYGB, resulting in a lack of exposure of the K cells to nutrients and less secretion of GIP. Further, to trigger GIP secretion, the presence of nutrients in the duodenum must be coupled with nutrient absorption, for which reason GIP secretion is reduced in patients with intestinal malabsorption.

Recently, membrane receptors for GIP were identified in osteoblasts, osteocytes, and osteoclasts, and GIP was shown to increase the activity of bone-specific alkaline phosphatase, a marker of bone formation, and to promote bone turnover both in vitro and in vivo. In addition, GIP inhibits osteoclast differentiation, decreasing resorption. Most human studies have shown a decrease in GIP after bariatric surgery; in one study, GIP levels were found to be reduced after RYGB but only in diabetic patients.[38]

In sum, it is too early to draw any firm, or even firmly hypothetical conclusions, about what effect GB has on the interactive network among these hormones and what long-term effect these GB-induced changes will have on bone. Unfortunately, clinicians do not have the luxury of waiting, while their GB patients continue to lose bone, until the bone-destructive ramifications of GB are fully determined. Practitioners need to look at what the current research suggests can safely be done now to try to promote healthy bone remodeling in patients who have had GB surgery.

Promoting Healthy Bone Remodeling After Bariatric Surgery

Although a number of papers have now been published discussing the nutrient deficiencies that occur after bariatric surgery,[39-47] none provide definitive clinical practice guidelines. As Bordalo et al[48] stated:

> There are no absolutely appropriate recommendations to prevent or treat most nutritional deficiencies after bariatric surgery yet; however, it is clear that preventive supplementation has been increasingly important in this setting. … The preventive use of multivitamins/minerals should compound the care protocol in all patients undergoing bariatric surgery. … [In] the treatment of these patients' nutritional deficiencies [practitioners] should consider micronutrient megadoses due to lower bioavailability resulting from physiological changes provided by the surgical techniques. Further studies are required to establish an effective dose to treat nutritional deficiencies following bariatric surgery.

Nutrient deficiencies commonly seen after bariatric surgery and repletion dosages used are summarized in the table.

To date, only 1 study[49] has formally evaluated the effectiveness of a multivitamin supplement specifically developed for RYGB patients compared to a standard multivitamin supplement. This trial was a triple-blind, randomized, 12-month study of 148 patients, 74 in each group, who underwent a RYGB procedure. One-half received the enhanced supplement, which contained vitamin B_{12} 14 000% c (RDA), iron 500% RDA, and folic acid 300% RDA; one-half were given a standard multivitamin supplement containing approximately 100% of the RDA for iron, vitamin B_{12}, and folic acid. Baseline characteristics were similar for both groups.

Receiving the standard multivitamin was associated with a decline in ferritin (-24.4 ± 70.1 μg/L) and vitamin B_{12} (-45.9 ± 150.3 pmol/L) for 12 months, whereas in those given the enhanced supplement, ferritin remained stable (+3.2 ± 93.2 μg/L), vitamin B_{12} increased significantly (+55.1 ± 144.2 pmol/L), and no adverse events occurred related to enhanced supplement use. The researchers concluded that "An optimized multivitamin supplement is safe and reduces the development of iron and vitamin B_{12} deficiencies after LRYGB."[49]

This study may help establish proof of concept but falls short of providing repletion for the full spectrum of nutrients discussed in Part 1 whose absorption is negatively affected by bariatric surgery.

Bone-specific Recommendations

In relation to bone, specifically, the current author offers the following recommendations to practitioners for consideration as potential interventions.

Counsel Patients to Make Every Bite Count

In individuals who have had GB, the amount of food that can be consumed at a meal has been reduced by 85% to

Table 1. Nutrient Deficiencies Associated With Bariatric Surgery

Deficiency	Symptoms	Assessment	Treatment
Water-soluble vitamins			
Thiamine (B_1)	• Bilateral lower limb edema, labored respiration (resting or with exertion), parasthesias of hands or feet, motor deficiency or loss of balance • Symptoms of Wernicke encephalopathy or acute psychosis—the neuropsychiatric forms of beriberi—to be considered a medical emergency • Possibility that Wernicke disease can present with bilateral blindness	• ↓ serum thiamine • B_1 body stores depleted within 18 d • Deficiency seen in 49% of RYGB patients and associated with small intestinal bacterial overgrowth • Measurement of catalytic activity of transketolase in erythrocytes, with transketolase activity depending on its binding to thiamine pyrophosphate, the active form of thiamine	• Prophylactic dose post-GB: RDA + 25–50 mg • In patients with symptoms, 100 mg BID • In patients with Wernicke encephalopathy or acute psychosis, 250 mg IM or IV for 3–5 d • Requirement for hospitalization of patients with Wernicke encephalopathy or acute psychosis, 250 mg thiamine/d IM or IV for ≥3–5 d
Riboflavin (B_2)	Sore throat, scaly dermatitis, stomatitis, normochromic, normocytic anemia	↓ serum riboflavin	5–10 mg/d
Pantothenic acid (B_5)	Depression, infections, orthostatic hypotension, paraesthesias, foot drop, gait disorder	↓ serum pantothenic acid	2–4 g/d
B_9 (folate)	Macrocytosis, anemia, fetal neural-tube defects in pregnant women	• ↓ serum folate, ↓ RBC folate, ↑ homocysteine • ↑ serum folic acid levels, validated as a marker of small intestinal bacterial overgrowth, common after bariatric surgery • Possibility of celiac disease if folate deficient	• 1–5 mg/d • 1 mg/d for women trying to become pregnant after bariatric surgery
B_{12}	Depression, pernicious anemia, development of potentially irreversible peripheral neuropathy, as well as neuropsychiatric symptoms or ataxia	• ↓ serum B_{12}, ↑ homocysteine • ↑ MMA levels; B_{12} required to metabolize MMA • Possibility that hepatic and kidney stores sufficient for 3 y	Possible forms: • Oral B_{12} (500–2000 mg/d) active form (eg, methylcobalamin preferred) • IM B_{12} (1000 mg/mo to 3000 mg every 6 mo) • Intranasal B_{12} (500 mg once weekly) • Sublingual B_{12} (500 mg/d)
Vitamin C	Poor wound healing, gingivitis, malaise, myalgias, increased susceptibility to infection, petechiae (red spots on the skin)	• ↓ serum vitamin C • Deficiency in approximately 35% of patients at 12 mo after RYGB	500 mg BID
Fat-soluble vitamins			
Vitamin D	Calcium malabsorption, secondary hyper-parathyroidism in 58% of patients after GB	1,25(OH)D ≥30 ng/mL (optimal levels 50–80 ng/mL)	• 5000 IU/d for 8–12 wk, then measurement of 1,25(OH)D levels to confirm repletion; possible that individual patients may require large regular doses (10 000 IU/d) • Possibility of 50 000 IU/wk to correct deficiency in many GB patients • Initial dose for Tx of osteomalacia = 600 000 IU, given as 50 000 IU/wk doses
Vitamin A	• Night blindness, itching, dry skin, hair, nails, increased susceptibility to infection • Deficiency common, in approximately 53% of GB patients already prescribed 5000 IU/d	↓ serum retinoic acid (≤50 mg/dL)	10 000 IU/d
Vitamin E	• ↑ oxidative stress, • Ataxia, muscle weakness, visual symptoms or findings of anemia or dysarthria • Deficiency in 4%–10% of patients 1–4 y post-GB	MMA, 8-OH-dG	Mixed tocopherols, 800–1200 IU/d
Vitamin K_1	• Bleeding disorder • ↑ inflammation • Low levels in 50% of patients 3 y post-GB	INR	• If no clotting abnormalities, 25 mg/d • If bleeding disorder, 2.5–25.0 mg/d or 5-15 mg IM

Table 1. (continued)

Deficiency	Symptoms	Assessment	Treatment
Vitamin K_2	Bone loss, soft tissue calcification (cardiovascular, kidney, breast)	unOC, unMGP	• If MK-7, 360 mg/d • If MK-4, 15 mg TID
Major minerals			
Calcium	• Osteomalacia, osteopenia, osteoporosis, fractures • Significant incidence (28%) of secondary hyperparathyroidism found after RYGB, even in those with 1,25(OH)D levels ≥75 nmol/L, suggesting selective calcium malabsorption post-GB	• ↓ $1,25(OH)_2D$ • ↓ PTH • ↑ alkaline phosphatase • ↑ DXA • ↓ QCT • Isolated serum measurements of calcium providing a poor marker of calcium metabolism; ionized calcium level providing a better indicator of hypocalcaemia • Serum alkaline phosphatase levels and 24-h urinary calcium commonly evaluated every 6–12 mo after RYGB	1200–2000 mg/d together with correction of vitamin-D deficiency
Iron	Iron-deficiency anemia in 36% of patients 1 y after RYGB, fatigue, shortness of breath, chest pain, brittle nails	↓ % transferrin saturation, CBC (hemoglobin), ferritin <20 mg/L	150–200 mg/d of oral elemental iron (ferrous gluconate, sulfate or fumarate) or a ferrous salt–vitamin C combination
Trace elements			
Zinc	Increased susceptibility to infection; loss of sense of taste; pale, rough, dry skin; eczema, acne, acrodermititis enteropathica; nail dystrophy; alopecia; glossitis; depression; hypoalbuminaemia in patients with severe deficiency	↓ RBC zinc level	Zinc sulfate 220 mg (or zinc gluconate 30–50 mg) on alternate days
Selenium	Cardiomyopathy, Keshan disease	• ↓ serum selenium levels • Dyspnea, fatigue, leg swelling	100 mg/d sodium selenite
Copper	• Anemia, neutropenia, pancytopenia • Sudden bilateral blindness and a new myeloneuropathy-like disorder with spastic gait and sensory ataxia in RYGB patients	↓ serum copper levels	Copper gluconate (2–4 mg/d on alternate days

Note: Adapted from Bal et al,[39] Ziegler et al,[40] Toh et al,[43] and Shankar et al.[44]

Abbreviations: GB, gastric bypass; RDA, recommended daily allowance; BID, twice per day; RYGB, Roux-en-Y gastric bypass; IM, intramuscularly; IV, intravenously; RBC, red blood cell; MMA, methylmalonic acid; 1,25(OH)D, 1,25-dihydroxyvitamin D; INR, international normalized ratio; unOC, uncarboxylated osteocalcin; unMGP, uncarboxylated matrix Gla protein; TID, 3 times per day; PTH, parathyroid hormone; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography.

95%. Stress the importance of choosing the most nutrient-dense foods and focusing on those richest in bone-building nutrients (eg, calcium, magnesium, boron, and other trace minerals) vitamin D_3, vitamin K_2, vitamin C, the B vitamins, and the omega-3 essential fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

Tell Patients to Maximize the Nutrient Density of the Foods Consumed by Choosing Organically Grown Foods When Possible

Numerous studies have now confirmed that organically grown vegetables and fruits, animal-products derived from pastured animals eating primarily grass rather than corn or grains, wild-caught rather than farm-raised fish, and free-range eggs rather than those from caged chickens deliver significantly more of the minerals and the omega-3 essential fatty acids required for bone health compared with conventionally produced foods.[50-55]

Consider Monitoring

Knowing the status of nutrients, cofactors, and hormone levels required for bone health is important. Pay attention to ionized calcium, magnesium, iron, zinc, vitamins A, E, D_3, B_1, B_2, B_6, B_9, B_{12}, holotranscobalamin, folic acid, and parathyroid hormone.[56]

Consider Genetic Testing

Identify single nucleotide polymorphisms (SNPs) indicating impaired methylation, detoxification, absorption, or utilization of key nutrients for bone,

particularly vitamin D_3 and vitamin K_2, or a tendency to chronic inflammation (eg, APOE4).

Consider High Potency Vitamin-and-Mineral Supplements

Supplements do not require removal from the food matrix; the nutrients they contain are immediately released in the stomach, enhancing GB patients' chances of absorbing more of them as they pass through what remains of the digestive tract. When 85% to 95% of the stomach has been removed, the greatly reduced amount of food that can be consumed cannot be relied upon to provide sufficient amounts of the nutrients necessary to sustain health and prevent bone loss.[39,42,45,48]

Consider Hydrochloric Acid Supplementation

Not only are post-GB patients able to consume much less food, but they lack the parietal cells to produce stomach acid, which is required to digest food and solubilize calcium, rendering it able to be absorbed. Consider supplemental hydrochloric acid with meals. In GB patients, the duodenum and the uppermost section of the jejunum have also been bypassed. These sections of the small intestine are where the majority of nutrients are absorbed and where intrinsic factor, a compound needed for absorption of vitamin B_{12}, is produced. Also, consider a sublingual or intranasal vitamin B_{12} supplement or B_{12} given intramuscularly.

Consider Not Only Supplemental Calcium and Vitamin D but Also Vitamin K_2 (MK-7)

In individuals who are vitamin-D deficient, only 10% to 15% of dietary or supplemental calcium is absorbed. Absorption of vitamin D may be significantly compromised after bariatric surgery because it is a fat-soluble vitamin. To determine how much supplemental vitamin D a patient requires, test blood levels of 25(OH)D. Optimal levels are 50 to 80 ng/mL. The Vitamin D Council now offers a finger-prick test that can be requested online and sent back in the mail, avoiding the patient's need to go to a lab for a blood draw.[19]

Consider recommending 1300 to 1500 mg of calcium citrate daily in approximately 300-mg doses spaced throughout the day. Studies have shown that more calcium is absorbed when smaller doses are consumed several times throughout the day.

Given that the digestive tract after GB is able to absorb less vitamin K_2, consider supplementing with the amount of vitamin K_2, as MK-7, that is now being recommended for individuals with kidney and cardiovascular disease, ≥360 µg/day. Vitamin K_2 activates osteocalcin, the vitamin K-dependent protein (VKDP) responsible for depositing calcium in bone, and matrix Gla-protein, the VKDP involved in preventing calcium deposition in soft tissues, including arteries, kidneys, brain, and breasts.[57-59]

No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals. In human studies, vitamin K_2 (MK-7) has been consumed in amounts of ≥800 µg/day with no adverse effects.[60] Doses as high as 25 µg per kilogram of body weight per day, the equivalent of 1750 µg for an adult human weighing 154 pounds (70 kg), have produced no noticeable toxicity. Thus, the Institute of Medicines recommendations for vitamin K do not include an upper tolerable limit.[61]

A notable exception is patients on warfarin therapy. Research published by the Rotterdam group in 2013 found that intake of MK-7 in doses as low as 10 and 20 µg/day significantly decreased mean values of both the INR and uncarboxylated prothrombin by 40% in all of the study's participants; the study had only 18 participants and so was small, but the results provided an indication that the use of MK-7 in patients on warfarin is contraindicated.[62]

Daily intakes of 10 and 20 mg of MK-7 were independently judged by 2 hematologists to cause a clinically relevant lowering of the INR in ≥40% and ≥60% of the participants, respectively, and to increase endogenous blood-clot formation significantly by 20% and 30%, respectively. Even worse, these miniscule doses of MK-7 had no beneficial effect on increasing carboxylation of circulating uncarboxylated osteocalcin (ucOC) or uncarboxylated matrix-Gla protein (dp-ucMGP). Virtually all the MK-7 was triaged to carboxylate prothrombin. Therefore, the result was an increased risk for blood-clot formation with no benefits. Practitioners should consider switching patients on warfarin to an Xa inhibitor, recently approved anticoagulants that act directly upon Factor X in the coagulation cascade without using prothrombin as a mediator. Therefore, vitamin K does not lessen their anticlotting effects, and their use does not require avoidance of supplemental vitamin K_2.[63]

Identify Potential Sources of Inflammation and Eliminate or Ameliorate Them

Anything that promotes chronic low-grade inflammation activates osteoclasts and promotes bone loss[64-79] (eg, homocysteine). If homocysteine is elevated, consider suggesting supplementation with activated forms of the B vitamins: methyltetrahydrofolate (folate), pyridoxal-5-folate (B_6), methylcobalamin and adenosylcobalamin (B_{12}; a combination may be most effective), and flavin adenine dinucleotide (B_2).[80] Also, make sure your patient is getting adequate rest. Insufficient sleep promotes inflammation.[81]

Minimize Exposure to Proinflammatory Chemicals

All of the following contribute to chronic inflammation and therefore bone loss[82,83]: pesticides, endocrine disruptors (eg, plasticizers such as BPA, BPS), cigarette smoke (eg, cadmium, nicotine), and heavy metals (eg, mercury, lead, cadmium).

Check Medications Your Patient Is Taking Regularly

A number of medications promote bone loss. If medications that your patient is taking regularly are among them, suggest another medication less likely to do so if possible.[64]

Evaluate Patients' Hormone Levels

Estrogen, progesterone, testosterone, and thyroid hormones all affect bone. Consider bioidentical hormone replacement (BHRT) if necessary. The rapid loss of fat tissue caused by GB surgery will trigger a precipitous drop in estrogen (estradiol) levels. Check not only estradiol, but its metabolites, some of which are proinflammatory and promote bone loss (and cancer), whereas others are anti-inflammatory, support healthy bone remodeling and are protective against cancer development. Progesterone activates osteoblasts.

Testosterone is the precursor, in both men and women, of the estrogen needed for healthy bones. Men convert far less testosterone to estrogen than women do, but men require this estrogen to maintain healthy bones. This is why treatment with aromatase inhibitors for prostate cancer causes bone loss in men. The end result of GB surgery in both men and women is a drop in estrogen production.

Thyroid hormones regulate metabolic rate, including in bone. If chronically elevated, the resulting increase in bone resorption outpaces bone formation, promoting bone loss. If chronically depressed, bone remodeling slows, again promoting bone loss. However, results of studies looking at subclinical thyroid dysfunction and risk of fracture have been mixed; some studies indicate a connection, whereas others do not.[84,85]

Recommend Regular Weight-bearing Exercise

Weight-bearing exercise puts stress on bone; specifically, it signals osteocytes within the bone matrix that act as a mechanostat, sensing the effects on bone of mechanical loading. The details of the transmission of that loading signal are slowly being elucidated and have been shown to be dependent on the protein sclerostin, a product of the SOST gene.[14] Mechanical loading that is sensed by osteocytes inhibits the production of mRNA for the SOST gene, which in turn results in decreased production of sclerostin. Lack of weight-bearing exercise results in insufficient stress by mechanical loading, increased sclerostin production, and inhibition of canonical-Wnt signaling, an important pathway for osteoblast differentiation and function. The end result, as demonstrated by astronauts, is that mechanical unloading causes a net loss in bone mass by reducing osteoblast function and, in turn, bone formation.

Conclusion

The benefits of bariatric surgery in treating obesity and its comorbidities are unquestionable; however, bariatric surgery also initiates significant ongoing bone loss. Nutritional assessment of patients undergoing bariatric procedures is strongly recommended, ideally both prior to and after surgery, at regular intervals lifelong. Further research is needed to understand and possibly ameliorate the effect on bone of changes induced by bariatric surgery in a wide range of hormones. Today, however, physicians can assess bariatric-surgery patients' nutritional status and, where indicated, recommend supplements to help prevent nutritional deficiencies. By increasing bariatric-surgery patients' awareness of their increased needs for a healthy diet and regular physical activity, along with regular testing to determine nutritional deficiencies and nutritional supplementation where indicated, physicians can help patients receive bariatric surgery's potentially life-saving benefits while avoiding a potential long-term adverse outcome, osteoporosis.

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