REVIEW

Bone Health following Bariatric Surgery: Implications for Management Strategies to Attenuate Bone Loss

Tair Ben-Porat,[1,4] Ram Elazary,[2] Shiri Sherf-Dagan,[3] Ariela Goldenshluger,[1] Ronit Brodie,[2] Yoav Mintz,[2] and Ram Weiss[4]

Departments of [1] Nutrition and [2] Surgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [3] Department of Nutrition, Assuta Medical Center, Tel Aviv, Israel; and [4] Department of Human Metabolism and Nutrition, Hebrew University, Jerusalem, Israel

ABSTRACT

Bariatric surgery (BS) is an effective treatment for morbid obesity and its associated comorbidities. Following such a procedure, however, patients are at risk of developing metabolic bone disease owing to the combination of rapid weight loss, severely restricted dietary intake, and reduced intestinal nutrient absorption. Patients undergoing malabsorptive procedures are at a higher risk of postoperative bone health deterioration than those undergoing restrictive procedures; however, studies have demonstrated negative skeletal consequences of restrictive procedures as well. The clinical practice guidelines of some international associations have previously addressed preoperative evaluation and postoperative clinical care in order to maintain bone health in BS patients. Nevertheless, some issues regarding bone health in BS patients remain unclear owing to the lack of relevant randomized clinical trials, including doses of nutritional supplements pre- and post-BS. This review summarizes the current data regarding the skeletal consequences of BS and its mechanisms, with an emphasis on the preventive strategies and nutritional care that may be warranted in order to attenuate bone deterioration following BS. *Adv Nutr* 2018;9:114–127.

Keywords: obesity, weight loss, bariatric surgery, bone health, nutrition care

Introduction

High body mass has a positive effect on bone formation owing to the effect of mechanical loading, but it is questionable whether the mass derived from an excessive accumulation of fat is beneficial to bone (1). Diet-induced weight loss and short- as well as long-term weight reduction interventions have been found to be associated with decreased bone mineral density (BMD) and increased bone resorption (2), particularly in cases of very-low-calorie diets or relatively rapid weight loss (3, 4). Bariatric surgery (BS) is an effective treatment for morbid obesity and its related comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, and obstructive sleep apnea) (5). Surgical procedures include adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) with or without duodenal switch (DS) (6), and single anastomosis gastric bypass (7). Despite their advantages, one side effect of these procedures is the detrimental impact on bone metabolism (8). The combination of rapid weight loss, restricted dietary intake, and decreased micronutrient absorption places BS patients at relatively high risk of bone loss over the long term (9). The mechanisms for postoperative bone health deterioration include reduced mechanical loading, changes in gastrointestinal and adipocyte hormone levels, and malabsorption, mainly of calcium and vitamin D (10). These negative effects on bone health may be especially relevant for young women undergoing BS during their early 20s, prior to achieving peak bone mass (11).

Currently, the most prominent published literature regarding postoperative bone health is derived from studies of RYGB patients (12). The available data suggest that patients undergoing malabsorptive BS (e.g., RYGB and BPD) are at a higher risk of developing bone health deterioration postoperatively than those undergoing restrictive procedures

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Address correspondence to TB-P (e-mail: tairbp20@gmail.com).
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Abbreviations used: AGB, adjustable gastric banding; BMC, bone mineral content; BMD, bone mineral density; BPD, biliopancreatic diversion; BS, bariatric surgery; DS, duodenal switch; DXA, dual X-ray energy absorptiometry; EWL, excess weight loss; GIP, gastric inhibitory polypeptide; GLP, glucagon-like peptide; LBM, lean body mass; PTH, parathyroid hormone; PYY, peptide YY; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VBG, vertical banded gastroplasty; vitamin D2, ergocalciferol; vitamin D3, cholecalciferol; 25(OH)D, 25-hydroxyvitamin D.

(e.g., AGB and SG) (13), although studies have demonstrated negative skeletal consequences following restrictive procedures as well (14, 15). Management strategies to attenuate bone loss during weight reduction include physical exercise and dietary interventions with calcium, vitamin D, and protein intake (16). Furthermore, clinical practice guidelines published recently have addressed pre- and postoperative management aimed at the prevention of bone loss in BS patients (6, 17–22). Although these guidelines are comprehensive and are based on available data, the lack of randomized clinical trials (RCTs), particularly regarding recommendations for doses of micronutrient supplements pre- and postoperatively, leaves many of these issues unclear. Accordingly, we undertook a review to summarize the published literature on the skeletal consequences of BS and its mechanisms, with an emphasis on nutritional and lifestyle strategies for the management and prevention of metabolic bone disease following BS. This review presents the body of knowledge currently in existence and highlights the main issues that require further investigation, particularly regarding the nutritional aspects of the management for bone health maintenance in BS patients. It also addresses some issues that should be taken into consideration when recommending nutritional supplements to BS patients in terms of safety and efficacy.

Literature Search

A literature search was performed as appropriate for narrative reviews, including electronic databases of PubMed, Cochrane Library and Google Scholar. The main queries were: *1*) the impact of BS on skeletal status and its mechanisms; and *2*) the clinical strategies for prevention of metabolic bone disease following BS. Accordingly, a combination of the terms "obesity", "weight loss", "BS", "bone loss", "bone density", "BMD", "calcium metabolism", "nutritional deficiencies," and "dietary supplements" was used. The last of these searches was carried out on 26 July 2017. The exclusion criteria were case reports and editorials by key opinion leaders, and papers for which the full text was not available or which were not in English. All of the articles obtained were manually searched for additional references. Abstracts and full texts were screened for inclusion by all authors.

Current Status of Knowledge

Obesity and bone health

It is unclear whether excess fat accumulation is beneficial or detrimental to bone health, yet it is widely accepted that fat appears to be protective of bone in older populations (23). The higher BMD in obesity is attributed to the combination of higher mechanical loading and hormonal activity; however, other genetic and environmental factors, including smoking, eating habits, and physical activity, can also influence bone mass in obesity (16). Recent evidence suggests that excess weight owing to adiposity may in fact be detrimental to bone (16). A combination of several factors may be responsible for this, including increased marrow adipogenesis at the expense of osteoblastogenesis, proinflammatory cytokine activity, excessive leptin secretion, and reduced adiponectin (1).

Similar to other metabolic effects, it is probably lipid partitioning, rather than absolute amounts of body fat, that determines the metabolic impact of adipose tissue. Specifically, greater visceral (intra-abdominal) fat has been associated with secretion of proinflammatory cytokines, which may also adversely impact bone metabolism (24). In obesity, adipose tissue secretes a number of cytokines and adipokines that are involved in inflammation pathways and bone remodeling (25), including abnormal levels of TNFα, IL-6, C-reactive protein, adiponectin, and leptin (1).

Leptin is involved in energy homeostasis. It also plays a major role in neuroendocrine regulation and bone metabolism (26). Obesity is characterized by high levels of leptin. However, both negative and positive impacts of leptin have been reported on BMD (25), as it may regulate bone metabolism negatively through central pathways and positively through a direct local peripheral effect on bone cells (27). A recent meta-analysis of studies in a healthy population by Liu et al. (28) found that leptin was positively associated with BMD and bone mineral content (BMC) in postmenopausal women.

Adiponectin acts as an anti-inflammatory cytokine and its plasma concentrations are lower in obese individuals (1). The majority of in vitro studies found that adiponectin positively affects bone (29), but clinical studies have shown different results (30, 31).

The levels of inflammatory cytokines such as TNFα and IL-6, which acts as a trigger for osteoclast activation, are also higher in obese humans (1, 32). In addition, obese subjects often show lower vitamin D levels and higher levels of parathyroid hormone (PTH) (33), which are attributed to decreased bioavailability of the fat-soluble vitamin owing to its deposition in adipose tissue (34) and are related to higher bone turnover and resultant bone loss (35). On the other hand, as previously reviewed, obesity is associated with a higher secretion of hormones that have been demonstrated to be anabolic to bone, including amylin, preptin, and bone-active hormones such as estrogens (16, 36, 37). Furthermore, the incretin hormones, gastric inhibitory polypeptide (GIP), and glucagon-like peptide (GLP)-1 and -2, which are secreted by endocrine cells in the small bowel in response to feeding, may also have a beneficial effect on bone (37, 38).

Mechanical loading is a particularly potent stimulus for bone cells, improving bone strength (39), but dynamic loads imposed by muscle contraction are probably more anabolic to bone than static loads, owing to excess adipose tissue (16). Therefore, the relation between body mass and skeletal status is complex, and it is unclear whether obesity is indeed protective of bone.

The effect of weight reduction and bariatric surgery on bone metabolism

The degree of decline in BMD associated with conventional weight loss varies among different populations, but is

more pronounced among postmenopausal women and elderly men (40–42). Bone resorption may be promoted by both short- and long-term diet-induced weight loss (2), particularly when it comes to a very-low-energy diet or relatively rapid weight loss (3, 4).

As previously reviewed elsewhere (16, 36), several factors and their interactions are involved in the mechanisms of skeletal changes during weight loss, yet the effects of some of them are not entirely understood. The metabolic changes affecting bone that occur following conventional weight loss may be more extensive under conditions of extreme and rapid weight reduction as caused by BS, which is also associated with severely restricted food intake, micronutrient malabsorption, and other metabolic changes (9). The main mechanisms for postoperative bone loss include mechanical unloading and decreased absorption primarily of calcium and vitamin D, in addition to hormonal changes (10).

Mechanical unloading. Weight reduction decreases mechanical loading on bone (16), especially when not accompanied by physical exercise, which induces mechanical strain on the skeleton that is associated with the preservation of BMD (43).

Malabsorption. In contrast to conventional weight loss, which has been demonstrated to cause increased levels of 25 hydroxyvitamin D [25(OH)D] (44–46), vitamin D deficiency and secondary hyperparathyroidism do not necessarily improve in the long term postoperatively; in fact, they may even be accelerated, especially following malabsorptive procedures (47, 48). In the early postoperative period vitamin D status temporarily improves, but after long-term follow-up vitamin D deficiency remains persistent in BS patients following both malabsorptive procedures (46) and restrictive BS (49), potentially resulting in skeletal complications and bone loss (50). In our previously published paper (49) we found that the prevalence of vitamin D insufficiency 4 y after SG was 86%, with levels remaining clinically low throughout the whole postoperative period. This suggests that restrictive procedures may also result in a high rate of nutritional deficiencies related to skeletal status, thereby requiring long-term nutritional follow-up with supplementation maintenance.

Calcium intake and absorption have been shown to be decreased in subjects both during conventional weight reduction (16, 51) and after BS (52–55). Active, transcellular, 1,25-dihydroxyvitamin D–mediated calcium uptake occurs in the duodenum and proximal jejunum. Therefore, malabsorptive procedures which bypass these areas can result in an impaired calcium absorption (52). Although it has previously been demonstrated that calcium absorption decreased after RYGB (52, 56) and BPD procedures (53, 57–59), impaired calcium status may also appear after SG owing to the reduction of gastric acidity, which may decrease calcium uptake (54), and a low oral calcium intake owing to decreased gastric volume (55). Hyperparathyroidism and further elevation of PTH levels have also been reported following both malabsorptive (48, 60) and restrictive bariatric procedures (49). The most significant macronutrient deficiency following BS that could negatively impact bone health is protein depletion (27, 61). Other nutritional deficiencies following BS are common and depend on surgery type. They include deficiencies in thiamin, vitamin B-12, folate, and trace elements and minerals (17). Some of these deficiencies may also have an adverse effect on bone health (27).

Changes in gut hormones. The incretin hormone GIP is synthesized and released from the duodenum and proximal jejunum (62). Studies have shown a reduction in GIP after malabsorptive BS (63), and this might negatively affect bone (38). On the other hand, the incretin GLP-1 is increased following RYGB (64) and SG surgery (65), and this may positively affect bone metabolism; however, data correlating the increase in GLP-1 after BS with changes in bone metabolism are lacking, and thus further studies are needed (27). Peptide YY (PYY) is a gastrointestinal hormone secreted postprandially from the ileum and colon to limit meal size and caloric intake (66), secretion which decreases following weight loss (67). A negative correlation between PYY and BMD and BMC has been established in animal studies as well as among obese and anorexic subjects (68). Jacobsen et al. (64) and Yu et al. (69) found that PYY was increased following the RYGB procedure so, because human data support a negative relation between PYY and bone, a negative impact on bone mass may be expected (27).

Amylin is a pancreatic hormone that affects several different organ systems. Its plasma levels are increased in adiposity (70) and decreased during weight loss (71). Amylin has been shown to be anabolic to bone through stimulation of osteoblast activity as well as inhibition of bone resorption (37). Similar to conventional weight loss, BS surgery results in decreased levels of amylin (72), which is expected to negatively affect bone metabolism postoperatively (27).

The hormone insulin, which is secreted by the beta cells of the pancreas, is a potential regulator of bone growth, because osteoblasts have insulin receptors (73). In vitro insulin has been shown to promote osteoblast proliferation and differentiation (74), but insulin signaling in human osteoblasts led to bone resorption through a reduction in the level of osteoprotegerin (75). However, clinical studies have shown that circulating insulin levels are related to bone density (73). In addition, hyperinsulinemic patients show increased free concentrations of sex hormones, which are expected to have positive effects on bone (73). Thus, a reduction in circulating insulin levels following weight loss might also contribute to a reduction in BMD (76) by stimulating insulin sensitivity and reducing hyperinsulinemia, which has been indicated to have an anabolic effect on bone mass (77, 78). Decreased levels of insulin, which have been shown to occur after BS surgery in most studies (64, 72), are expected to negatively affect bone metabolism postoperatively. However, further studies are needed to determine the exact role of insulin in bone metabolism (27). Ghrelin, a peptide hormone primarily synthesized by cells in the stomach and released

in response to fasting (37), increases following weight loss (79, 80). In vitro, ghrelin suppresses osteoclastogenesis and enhances osteoblast proliferation and differentiation (81). However, evidence from human studies does not support an association between ghrelin and BMD (31). In contrast to conventional weight loss, ghrelin is decreased following all BS except AGB owing to the removal of the gastric fundus (79). However, the expectation of it having a negative impact on bone postoperatively is based primarily on animal studies, so further investigation is required. One study by Carrasco et al. (82) found that 12 mo after RYGB and SG, the percentage of reduction in ghrelin concentration was a main factor related to total BMD loss in the RYGB group and lumbar spine BMD loss in both groups.

Changes in adipose hormones. Leptin levels decrease during conventional weight loss (16) as well as after BS (83). However, the implication for bone is complex (16, 36), with both anabolic and catabolic effects of leptin on bone having been reported (25, 28, 84). One study by Fleischer et al. (85) found a correlation between the reduction in leptin levels post-RYGB and an increase in N-terminal telopeptide of type I collagen. A decrease in peripheral leptin levels is expected to result in bone loss, taking into account its peripheral effects on bone (27). However, the exact impact of leptin on bone metabolism both in general and specifically after BS remains unclear.

Adiponectin increases with moderate weight loss (86) as well as following BS (87), but, like leptin, its role in bone metabolism has yet to be clarified (29–31). One study showed that adiponectin at 12 mo post-RYGB was significant and positively correlated with the reduction of BMD, but was unrelated to the baseline or variations in body composition parameters (88). Other studies have not found any such correlation (82). Estrogen has been reported to be decreased after both conventional weight loss and BS, and the expected effect is decreased bone mass (16, 27, 36).

The changes following conventional weight loss and BS, and their anticipated effect on bone metabolism, are summarized in **Table 1**.

Surgical type and bone loss

Many studies have shown significant declines in BMD and BMC during the first year following BS (89), but accumulating evidence suggests that the negative effect on bone is dependent on the type of surgery (12). In their recent systematic review, Rodriguez-Carmona et al. (13) found that patients who had undergone malabsorptive BS (BPD-DS, RYGB and long-limb RYGB), but not restrictive procedures [vertical banded gastroplasty (VBG), AGB and SG], had significant BMD deterioration in several sites during the first postoperative year. However, the majority of the published literature comprises studies with relatively short-term follow-up among RYGB patients, with fewer studies of other types of BS (12), and other studies have demonstrated negative skeletal consequences following restrictive procedures as well (14, 15).

Adjustable gastric band. The AGB procedure leaves the patient with a 15–30 mL proximal gastric pouch, which acts simply by restricting oral intake (90, 91). The percentage of excess weight loss (EWL) in the first 1–3 postoperative years is 35–70% (92), and it is considered safe and effective in the short and medium term, but reports on the efficacy and safety in the long term (>5 y of follow-up) are controversial (91). Only a handful of studies have been performed regarding the impact of AGB on skeletal status. A negative effect was observed, but it appears to be less than that observed following RYGB (12). Giusti et al. (14) found that obese premenopausal women who underwent AGB

TABLE 1 Changes occurring following conventional weight loss vs. bariatric surgeries and their expected effect on bone metabolism[1]

	Conventional weight reduction	Expected effect on bone	Bariatric surgery	Expected effect on bone
Mechanical unloading	↓ Mechanical loading on bone	–	↓ Mechanical loading on bone	–
Nutrient intake and malabsorption	↓ Calcium, protein, and other nutrient intake	–	↓ Calcium, protein, and other nutrient intake	–
	↓Calcium absorption	–	↓ Calcium, protein, and vitamin D absorption[2]	–
Changes in adipose hormones	↓ Leptin (peripheral rout)	–	↓ Leptin (peripheral rout)	–
	↑ Adiponectin	?	↑ Adiponectin	?
	↓ Estrogen	–	↓ Estrogen	–
Changes in gastrointestinal hormones	↑ Ghrelin	+	↓ Ghrelin	–
	↓ GIP	–	↓ GIP	–
	↓ PYY	+	↑ PYY	–
	↓ GLP-1	–	↑ GLP-1	+
	↓ Amylin	–	↓ Amylin	–
	↓ Insulin	–	↓ Insulin	–

[1]BS, bariatric surgery; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY; 25(OH)D, 25-hydroxyvitamin D; ↓, decrease; ↑, increase; +, positive effect; –, negative effect; ?, unclear effect.

[2]Vitamin D deficiency has been shown to be accelerated after malabsorptive BS procedures and in the long term after restrictive procedures. After conventional weight loss 25(OH)D levels may increase owing to its release from the adipose tissue.

showed no evidence of secondary hyperparathyroidism 2 y postoperatively, although they did have decreased BMC and BMD at the femoral neck. Similar to these findings, another study of obese premenopausal women by Pugnale et al. (93) found that the femoral neck BMD had decreased significantly with no evidence of secondary hyperparathyroidism 12 mo after the procedure. In a different study, by von Mach et al. (94), BMC showed no significant change 12 mo post-AGB. In addition, a study by Guney et al. (95) compared bone outcomes in VBG to medical weight reduction–treated patients and noted that, 12 mo after the treatment, bone loss was pronounced in the surgical treatment group but occurred only at the hip, and that calcium excretion and PTH levels did not change after VBG or medical therapy. According to present data, it seems that the effect of this procedure on bone results primarily from weight reduction rather than impaired absorption of nutrients, and is less than in other bariatric procedures.

SG. SG involves a partial gastrectomy that creates a gastric pouch of 80–120 mL, accompanied by changes in the secretion of gut hormones, such as ghrelin (96, 97). Postoperative EWL ranges between 49% and 81% within 3–8 y (98). However, because it is a relatively new procedure, data are limited regarding the long-term efficacy of SG with respect to weight outcomes and metabolic changes (98). Accordingly, only a few studies have examined the effect of SG on bone (12). In their study, Pluskiewicz et al. (15) found that 6 mo post-SG there was a significant reduction in BMD in the spine (of 1.2%), femoral neck (7.0%), and total hip (5.2%) in 29 premenopausal women. On the other hand, Adamczyk et al. (99) found in their study of 36 premenopausal women that the total hip and femoral neck BMD decreased 12 mo postoperatively whereas changes in total body and spine BMD were not significant, and there was an actual increase in total body BMC. An additional study by Ruiz-Tovar et al. (100) found that spine BMD increased in 42 patients at 1 and 2 y post-SG. When comparing SG to RYGB, most studies showed less bone loss after SG (82, 101, 102), but some studies showed a comparable effect (103, 104). Thus, further studies are needed to determine the actual and long-term impact of SG on bone status.

RYGB. RYGB is a restrictive surgery with a malabsorptive component and is considered to be the "gold standard" of BS owing to its effectiveness in improving both short- and long-term weight and metabolic outcomes (105). This procedure creates a functional gastric pouch of about 20–30 mL that connects directly to the small intestine, leaving a gastric remnant and 2 anastomoses (gastro-enterostomy and entero-enterostomy) (106). The reported EWL during the first 2 y was 70–80% (92), and was 56.4% at 10-y follow-up (107). Studies on the effect of RYGB on bone indicated a significant reduction in BMD at several sites during the first postoperative year (87, 108–110), with an increase in bone turnover markers from 3 mo postoperatively (85, 108, 111, 112). In their recent meta-analysis, Liu et al. (89) included 344 subjects and showed significant decreases in serum calcium and BMD and increases in serum PTH, serum or urinary N-terminal telopeptide of type I collagen, and bone-specific alkaline phosphatase, but no significant difference in serum vitamin D postoperatively. Bypassing the duodenum and proximal jejunum, which are the dominant sites of calcium uptake, RYGB can result in decreased calcium absorption (52, 56), accompanied by secondary hyperparathyroidism and vitamin D deficiency (60, 85, 111).

BPD with or without DS. The BPD procedure reduces the stomach to a volume of ∼100 mL, with a common limb of ∼100 cm (113). By the combination of intake restriction, hormonal modifications, and significant intestinal malabsorption, the surgery causes an average EWL of 80–90% during the first 2 y and 70–80% over ≥10 y (114). The incidence and severity of long-term postoperative complications related to malabsorption are relatively high and include diarrhea, malnutrition, and nutritional deficiencies (114, 115). An increased incidence (nearly 75%) of metabolic bone disease was documented 1–5 y following BPD, accompanied by a high rate of hypocalcemia (37%) (116). Most studies reported a high prevalence of vitamin D hypovitaminosis and secondary hyperparathyroidism postoperatively despite nutritional supplementation (57, 59, 117, 118). Regarding BMD changes, one study by Tsiftsis et al. (119) found that 12 mo postoperatively lumbar spine BMD had significantly decreased in 52 women despite a 2-g supplement of calcium being given to 26 of them. In contrast, a study of 33 patients by Marceau et al. (120) showed that 10 y post-BPD surgery the overall BMD was unchanged at the hip but was decreased by 4% at the lumbar spine, and the overall fracture risk based on the *z* score was unchanged.

Fractures risk following BS

Osteoporosis occurs with a decrease in bone mass and quality, which can lead to increased risk of fracture, and is diagnosed according to the WHO by obtaining BMD measurements and *t* and *z* scores through dual X-ray energy absorptiometry (DXA), which is considered to be the current gold standard for diagnosis (121). Reductions in *t* and *z* scores are seen after BS. However, it is not clear whether bone loss has clinical relevance regarding the incidence of osteoporosis and fracture rates in these patients (122), and the data regarding fracture risk following BS are inconclusive, primarily owing to the lack of long-term prospective studies (18). One study by Lalmohamed et al. (123) concerning a population of mostly AGB patients, with a relatively large sample size ($n = 2{,}079$) and a mean follow-up time of 2.2 y, found no significant effect on the risk of fracture postoperatively. However, in their retrospective study of primarily RYGB patients, with a smaller sample size ($n = 258$) and a median follow-up of 7.7 y, Nakamura et al. (124) reported that the relative risk of any fracture was increased 2.3-fold. Rousseau et al. (125) demonstrated in their recent nested case-control study, which included 12,676 bariatric patients age and sex matched with 38,028 obese

and 126,760 nonobese controls, that, 4.4 y after undergoing BS, patients were more likely to have suffered a fracture than were obese and nonobese controls, but fracture risk reached significance only with BPD surgery. In addition, Lu et al. (126), in a 12-y longitudinal cohort study following 2064 patients who underwent different types of BS matched to 5027 obese controls, found that there was a significantly increased risk of fracture in the postoperative group and that malabsorptive procedures had a significantly higher risk of fractures.

It should be noted that the limitations of DXA technology may falsely inflate the observed outcomes of BS, owing to its limited accuracy in morbidly obese patients and under conditions of extreme weight loss, such as those following BS. This, together with the relative lack of long-term prospective studies with control populations, suggests that further studies are needed to conclusively determine fracture risk in BS patients (122).

Management of BS patients to attenuate bone loss: clinical implications

Strategies demonstrated by interventional studies to be protective of bone during weight loss include physical activity and higher calcium, vitamin D, and protein intake (16). Several international associations have published clinical practice guidelines in recent years regarding pre- and postoperative clinical care to prevent skeletal deterioration in BS patients. Although these guidelines are comprehensive and based on currently available data, some issues of bone health, particularly regarding recommendations for supplementation of micronutrients both pre- and postoperatively, remain partially unclear, mostly owing to the lack of RCTs. Monitoring vitamin D and calcium status by measurements of plasma vitamin D, PTH, and 24-h urinary calcium and an evaluation of BMD by DXA are recommended before and during BS follow-up, together with long-term follow-up and routine supplementation of calcium and vitamin D, based on the surgery type and the risk groups for postoperative bone loss. A summary of the current recommendations for clinical evaluation of skeletal status as well as the main issues of pre- and postoperative management is presented in **Table 2** (6, 17–22, 127, 128).

Calcium. Adequate calcium intake is an essential preventive strategy and is a substantial part of therapeutic supplementation for osteoporosis (129), with increased bone turnover during weight reduction shown to be suppressed by calcium supplementation (130, 131). In the BS patient population, RCTs are lacking regarding doses of calcium supplementation needed to prevent bone loss postoperatively, with most

TABLE 2 Clinical evaluation and management strategies for bone health pre- and post-BS[1]

	Prior to surgery	After the surgery	Treatment for depletion
Calcium	Measure: serum PTH, serum calcium, 25(OH)D, DXA at spine and hip prior to RYGB and BPD/BPD-DS and in patients at higher risk[2]	Daily intake of calcium from food and supplements should reach 1200–1500 mg/d after AGB, SG, and RYGB and 1800–2400 mg/d after BPD/BPD-DS Monitor: serum PTH, calcium and 25(OH)D every 6–12 mo (SG, RYGB, BPD/BPD-DS), 12 mo (AGB) and then annually for all patients DXA at spine and hip 2 y postoperatively for all patients, then every 2–5 y	When low bone mass is diagnosed preoperatively, evaluation should be undertaken for secondary causes Consider bisphosphonates when bone density T score is <2.5
Vitamin D	Measure: 25(OH)D, serum PTH Additional measurements: serum phosphorus, alkaline phosphatase, 24-h urinary	3000 IU D3/d, dose titrated to reach 25(OH)D >30 ng/mL Monitor: 25(OH)D and serum PTH every 6–12 mo (SG, RYGB, BPD/BPD-DS) or 12 mo (AGB), then annually for all patients, 24-h urinary calcium at 6 mo, then annually for all patients	≥3000 IU and ≤6000 IU D3/d or 50,000 IU D2 1–3 times/wk[3] Severe malabsorption may require higher doses (≤50,000 IU D2 or D3 1–3 times/wk to 1 time/d)[3]
Protein	Measure: serum albumin Additional measurements: serum protein, pre-albumin, DXA (fat-free mass)	60–80 g/d or 1.1–1.5 g/kg of ideal body weight and 90–120 g/d after BPD/BPD-DS Monitor: serum albumin 6–12 mo (SG, RYGB, BPD/BPD-DS) or 12 mo (AGB), then annually for all patients	Oral protein supplementation, artificial nutrition if necessary (enteral or parenteral nutrition)
Physical activity	—	Guide patients to incorporate moderate aerobic physical activity (a minimum of 150 min/wk with a goal of 300 min/wk) and to include strength training 2–3 times/wk (muscle force training and/or endurance training).	—

[1] AGB, adjustable gastric banding; BPD, biliopancreatic diversion; BS, bariatric surgery; DS, duodenal switch; DXA, dual X-ray absorptiometry; D2, ergocalciferol; D3, cholecalciferol; PTH, parathyroid hormone; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; 25(OH)D, 25-hydroxyvitamin D.
[2] Women aged ≥65 y, men aged ≥70 y, younger patients who have conditions associated with bone loss or low bone mass.
[3] Where rapid correction of vitamin D deficiency is required, a fixed loading regimen given either as separate weekly or daily doses followed by maintenance therapy is the preferred treatment. However, vitamin D loading should be given over a limited period, together with serum calcium and 25(OH)D monitoring and under medical supervision.

data deriving from observational studies alone. One study by Carrasco et al. (88) found significant reductions in total, spine, and hip BMD 12 mo following RYGB despite the intake of calcium supplements of 393 ± 230 and 468 ± 289 mg/d during the first 6 and 12 mo postoperatively, respectively, whereas Fleischer et al. (85) found that, 3 mo following RYGB, PTH and serum osteocalcin levels were increased and urinary calcium dropped despite calcium intake from food and supplements of nearly 2500 mg/d. However, the calcium intake in both studies was calculated from self-reported patient questionnaires, potentially reducing accuracy. The prospective interventional study by Schafer et al. (52), which included 33 obese adults who underwent RYGB, found that fractional calcium absorption decreased from 32.7% ± 14.0% pre-operatively to 6.9% ± 3.8% 6 mo postoperatively, 24-h urinary calcium and areal BMD at the spine and proximal femur decreased, and PTH and bone turnover markers increased despite a calcium intake of 1200 mg/d (nearly 600 mg/d by calcium citrate supplement), demonstrating that RYGB patients may need a higher calcium intake to prevent impairments in calcium homeostasis. Muschitz et al. (132), in their recent interventional 2-arm open-label study (the BABS study) of premenopausal women and similarly aged men with morbid obesity ($n = 220$) who underwent RYGB or SG, found that preoperative intervention of vitamin D loading together with postoperative supplementation of vitamin D (16,000 IU/wk), calcium (1000 mg/d), and protein in combination with physical exercise decelerated the loss of areal BMD and lean body mass (LBM) 2 y after the surgery. It is important to note that the benefit for bone was achieved through a combination of several therapeutic interventions, making it hard to determine the exact positive effect of calcium supplementation on bone metabolism in this study. The current recommendation guidelines for calcium consumption of patients following BS is between 1200 and 2400 mg/d, depending on the type of the procedure (20) (Table 2). Nevertheless, some issues should be taken into consideration when recommending calcium supplements to patients, including the supplemental sources of calcium (17, 20), the tolerable upper intake level (133), and some potential adverse effects of excess intake (134). These are summarized in **Table 3** (17, 20, 127, 128, 133–138).

Vitamin D. Vitamin D deficiency is defined as a serum 25(OH)D level of ≤20 ng/mL and it is widely accepted that concentrations >30 ng/mL are the optimal target level, yet there is a lack of consensus on the optimal supplementation doses for BS patients, and current postoperative vitamin D supplementation fails to raise 25(OH)D above that level for all BS patients (139). As recently reviewed elsewhere, studies investigating treatment with 200–800 IU/d for vitamin D deficiency following BS indicate that these doses are probably inadequate to re-establish vitamin D levels postoperatively (140). Flores et al. (141) used different doses of cholecalciferol (vitamin D3) post-RYGB based on the individual's 25(OH)D baseline levels and demonstrated that daily vitamin D3 supplementation (ranging between 1800 and 3600 IU/d) was effective and safe, resulting in an increase in the mean postoperative 25(OH)D level from 16.0 ng/mL to 30.8 ng/mL. Although the highest level observed in any individual in the study was 87.2 ng/mL, which is inside of the normal range, the author reported mild hypercalcemia in 5 patients, and so their supplementation was stopped and evaluations were initiated to unmask any primary hyperparathyroidism. A different RCT study, by Goldner et al. (142), compared 3 different daily doses of vitamin D (800, 2000, and 5000 IU) in 45 patients post-RYGB and showed that higher doses of vitamin D supplementation tended to produce higher levels of 25(OH)D, and that vitamin D loading ≤5000 IU/d was safe and necessary in many patients to treat the deficiency. However, vitamin D levels were still suboptimal in some patients at 12 mo post-RYGB. The current guidelines recently updated by the American Society for Metabolic and Bariatric Surgery recommend that all post-BS patients with vitamin D deficiency or insufficiency be treated with vitamin D3 at 3000–6000 IU/d or with 50,000 IU of ergocalciferol (vitamin D2) 1–3 times/wk (20).

Only a few RCTs studies have tested the effect of vitamin D supplementation prior to and following BS on bone mass outcomes in bariatric patients. One RCT study by Carlin et al. (143) ($n = 60$) found that supplementation with 50,000 IU vitamin D/wk following RYGB compared with a nonsupplemented group resulted in significantly improved vitamin D depletion and mean 25(OH)D level 12 mo postoperatively (14% and 37.8 ng/mL compared with 85% and 15.2 ng/mL, respectively) and with a significant (33%) retardation in the decline of hip BMD.

The impact of preoperative vitamin D loading among SG and RYGB patients was evaluated in 2 interventional studies, with one of them defining bone status as the main outcome. In the first study, Stein et al. (144) addressed the issue of the differences between vitamin D2 and D3 supplements. During this pilot clinical trial, 27 subjects with 25(OH)D levels <24.8 ng/mL were randomized to receive 50,000 IU vitamin D2 or 8000 IU vitamin D3/wk weekly for 8 wk before BS (equivalent to 7142 IU vitamin D2/d and 1142 IU vitamin D3/d for this period, respectively). Serum 25(OH)D significantly increased at 4 and 8 wk in both treatment groups, though the increase in 25(OH)D level was greater in the vitamin D2 group than in the vitamin D3 group (131% compared with 57%), yet PTH decreased significantly only in the vitamin D3 group, emphasizing the potential differences in the impact of those 2 vitamin D supplement regimens. No subject had evidence of hypercalcemia or any other laboratory abnormality during the study. It should be noted that earlier reports had shown that vitamin D3 may be more potent than vitamin D2, which should probably be considered when deciding on the doses of vitamin D supplements (145).

The second study, by Muschitz et al. (132) (the BABS study), included 2 mo of preoperative loading of of vitamin D3 at 28,000 IU/wk, followed by 16,000 IU/wk maintenance therapy postoperatively. At the 2-y postoperative study endpoint, when comparing the intervention group to the non-intervention group, the decline in lumbar spine, total hip,

TABLE 3 Calcium and vitamin D supplementation in BS patients: clinical practice[1]

	Calcium	Vitamin D
Threshold values	Serum calcium: normal limits in patients without renal disease 9–10.5 mg/dL. Serum PTH: hyperparathyroidism >65 pg/mL	25(OH)D: reference range 30–100 ng/mL; preferred range 30–50 ng/mL; insufficiency 20–30 ng/mL; deficiency <20 ng/mL
Routine preventive supplementation after BS	1200–1500 mg Ca/d from food and supplements after all BS (1800–2400 mg/d after BPD)	3000 IU D3/d to achieve blood levels of 25(OH)D >30 ng/mL
Supplemental type/source	Calcium citrate is preferable over calcium carbonate because it is independent of stomach acidity absorption	D3 is recommended as being more potent than D2, but both forms can be effective and dose dependent
Additional considerations	Calcium should be given in divided doses (single doses should not exceed 600 mg), separated by ≥2-h intervals from iron-containing supplements. Calcium carbonate should be taken with meals, whereas calcium citrate can be taken with or without meals	It is recommended that both D2 and D3 be taken with a meal containing fat to ensure maximum absorption
Tolerable daily upper intake level in the general population	19–50 y: 2500 mg/d; >51y: 2000 mg/d; pregnancy, lactation: 2500 mg/d	>9 y: 4000 IU/d (100 μg)
Safety and risk assessment	Potential adverse effects of excess intake include increased risk of kidney stones, constipation, hypercalciuria, hypercalcemia, vascular and soft tissue calcification, renal insufficiency, and interference with another mineral's absorption	Contraindications for vitamin D supplementation include patients with hypercalcemia or metastatic calcification Serum 25OHD chronically >50 ng/mL may be related to potential adverse effects. Levels of 25(OH)D >100 ng/mL reflect excess of vitamin D, levels of 25(OH)D >150 ng/mL indicating intoxication. Vitamin D doses <10,000 IU/d are unlikely to cause toxicity in adults Excessive vitamin D intake is associated with clinical adverse effects, including hypercalcemia, hypercalciuria, and renal stones (when taken together with excess calcium supplementation) In sensitive subpopulations (granuloma-forming disorders, chronic fungal infections, lymphoma, thiazide diuretics treatment) 25(OH)D and calcium levels should be monitored carefully Serum calcium levels should be monitored 1 mo after completing the loading regimen of high-dose vitamin D supplements to treat deficiency. If calcium levels are elevated, any calcium-containing vitamin D supplements should be stopped and further vitamin D loading should be delayed. Elevated calcium despite stopping calcium and vitamin D supplements requires PTH monitoring and referring to endocrinologist

[1] BPD, biliopancreatic diversion; BS, bariatric surgery; D2, ergocalciferol; D3, cholecalciferol; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

and total body BMD and the changes in BMI and LBM were significantly less in the intervention group, suggesting that the clinical intervention of vitamin D3 loading and ongoing vitamin D3, calcium, and protein supplementation and physical exercise decelerates the loss of BMD and LBM after surgery.

The guidelines of the US Endocrine Society published in 2011 recommend that obese patients consume at least 6000–10,000 IU/d of vitamin D2 or D3 in the case of vitamin D deficiency, followed by a maintenance therapy of at least 3000–6000 IU/d (128). Overall, it appears that vitamin D status requires continuous long-term monitoring and correction in BS patients. It is important to note that even if patients have demonstrated significant improvement in their vitamin D status, they may require continued supplementation; thus, doses need to be individualized and monitored (46). Further studies are needed to clarify the appropriate vitamin D dosing prior to and following BS, and to shed light on its effect on bone metabolism and skeletal health in BS patients. In relation to safety, an upper limit of 100 ng/mL serum 25(OH)D provides a safety margin for reducing the risk of hypercalcemia (128), and current evidence suggests that daily intakes of <10,000 IU of vitamin D are not linked to hypercalcemia or acute toxicity (128, 133). However, chronic serum 25(OH)D levels of >50 ng/mL may cause some adverse effects (135). Furthermore, certain populations may be more sensitive to vitamin D supplementation, so their 25(OH)D and calcium levels should be monitored carefully (128, 136). The relevant considerations when prescribing vitamin D supplements for patients before and after BS are summarized in Table 3.

Protein. Protein-rich diets were previously associated with favorable effects on bone density, but their implementation remains controversial (146), mainly owing to evidence of

increased renal calcium excretion and negative calcium balance with increased dietary protein (147). Increased protein intake can raise levels of insulin-like growth factor I [which is anabolic to bone (148)], increase gut absorption of calcium (149), and preserve LBM (150, 151). The source of consumed protein may also be a factor, as a high-protein, calcium-replete diet may protect against bone loss during weight reduction (146). Adequate dietary protein may be more important when bone mass is being acquired and increased bone loss occurs (149), whereas protein deficiency remains the most severe macronutrient complication associated with BS procedures (17).

Protein malnutrition, characterized by hypoalbuminemia, anemia, edema, and alopecia, is a serious potential late complication of BPD, related to excessive malabsorption from bypassing broad segments of small intestine (152), whereas protein depletion may appear after restrictive BS procedure, probably owing to decreased intake (61). Protein intake below the current guidelines for BS patients (60 g/d and $\leq$1.5 g · kg ideal body weight^{-1} · d^{-1}) (6) has been demonstrated by several observational studies (61, 153), along with an association between higher protein intake and lower percentage of LBM loss postoperatively (153–156). To date, no interventional studies to examine the effect of protein intake on bone loss outcomes have been published, except for the previously mentioned BABS study, which included protein supplementation ranging from 35 to 60 g/d postoperatively as a part of a multifactorial intervention that was shown to decelerate the loss of BMD and LBM 2 y following RYGB and SG (132).

Overall, it seems that an adequate protein intake is an essential part of the nutrition recommendations for BS patients to ensure a good nutritional status postoperatively (Table 2). However, future interventional studies specifically in the BS population are needed to clarify the appropriate amount of daily protein needed for the prevention of skeletal complications, especially for malabsorptive bariatric procedures.

Physical activity. Strength training during weight loss can minimize the negative effect on bone (157). Physical exercise in addition to weight reduction was found in several studies to be preventive for bone status deterioration in older obese subjects (158–160), but not necessarily in the younger obese population and premenopausal women (161, 162). The type of physical activity may be a significant factor in its effect on bone mass preservation, as training strategies that include heavy resistance training and high-impact loading such as occurs with jump training may be especially important in maintaining BMD with weight loss (157). However, some studies have documented a positive effect of aerobic exercise as well (163). Two longitudinal clinical interventional studies have been carried out to determine the influence of physical activity on bone outcomes in BS patients (132, 164). The BABS study described earlier included an aerobic and strength exercise program 2 wk after surgery (Nordic walking for 45 min $\geq$3 times/wk and strength perseverance and equipment training for 30 min $\geq$2 times/wk) (132). The second study, by Campanha-Versiani et al. (164), included as a postoperative intervention an exercise program of weight-bearing and aerobic exercises 2 times/wk for 36 wk (60 min of 8 types of muscle-building exercises) ($n = 18$), with a control group ($n = 19$). One year following RYGB, the training group showed a lower decrease in total BMD, and BMD in the lumbar spine and right hip, compared with the controls. Overall, physical activity following BS is extremely important, preventing muscle depletion during the drastic weight reduction period and probably helping maintain bone mass (17, 19), with most benefit being derived from weight-bearing and muscle-loading exercise (Table 2).

Additional micronutrients. The effect of dietary magnesium intake on the risk of fractures and osteoporosis has been investigated, but findings thus far have been contradictory. A recent meta-analysis that included cohort, case-control, and cross-sectional studies of a mostly generally healthy population (n = 118,664, 0.8 mo to 67.7 y old) found a positive, marginally significant correlation between magnesium intake and total and femoral neck BMD, but not BMD in the lumbar spine (165). In one study, hypomagnesemia was reported primarily following malabsorptive bariatric procedures, although in some patients magnesium deficiency existed preoperatively (21). Zinc may also be an important element from the point of view of bone health, as has been recognized by human studies (166). The skeleton contains a large proportion of the body's total zinc, and many zinc-related proteins are involved in the regulation of cellular functions in osteoblasts and osteoclasts (167). Zinc is absorbed in the duodenum and in the proximal jejunum, thus deficiency is described mainly following RYGB and BPD, with a wide range of deficiency prevalence of 12–91%. Zinc may also interfere with iron and copper absorption (21). The Framingham Study, a population-based cohort, suggested that vitamin B-12 may be an important determinant of bone health, but there is little evidence to support folate or vitamin B-12 supplementation as a means to prevent fracture (147). As previously reviewed, vitamin B-12 deficiency is one of the most common causes for anemia following BPD or RYGB surgery, and preoperative deficits of $\leq$18% have been reported (21). Although all of the above nutrients may play a role in bone health, no studies have yet been carried out regarding the impact of their intake or deficiency on bone outcomes in BS patients. Thus, presently they are not part of the main practical considerations for prevention of bone loss in BS patients.

Conclusions

BS is an effective treatment for morbid obesity and its related comorbidities, but it may have a detrimental effect on bone metabolism, depending on the amount of weight loss and malabsorption of several micro- and macronutrients, which are related to the type of procedure performed. In this review, we have presented a summary of the possible mechanisms for bone loss and have addressed strategies to reduce bone loss following BS. Early prevention via comprehensive

clinical evaluation accompanied by nutritional and medical counseling should begin in the preoperative period, with continued long-term monitoring postoperatively; these are key for successful outcomes. An individualized nutritional and health behavior program to minimize bone loss post-BS should include recommendations for sufficient intake of calcium, vitamin D, and protein, together with an appropriate physical activity that benefits the skeleton. This individualized program should be suggested for all post-BS patients, but especially for populations at higher risk of bone deterioration, such as postmenopausal women, older men, patients with pre-existing conditions associated with low bone mass, and those who are candidates for malabsorptive procedures. Some factors impacting bone health among BS patients remain unclear, and require future investigation to create uniform, evidence-based guidelines. Such factors include clarifying the impact of specific BS types on skeletal status and fracture risk, the optimal repletion and maintenance dosing regimens of several nutrients pre- and postoperatively to prevent bone loss, and postoperative deficiency-related complications.

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