Review

Long-term complications of significant weight loss: lessons learned from bariatric surgery

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Abstract

The increasing prevalence of worldwide obesity calls for a comprehensive understanding of available treatment options. Bariatric surgery remains a very effective obesity treatment, showing substantial effects on obesity-related complications, including type 2 diabetes mellitus and cardiovascular disease, mainly related to significant long-term weight loss. Besides the benefits, weight loss can lead to some deleterious consequences, such as gallstones, constipation, muscle mass loss, bone fractures, vitamin deficiencies, peripheral neural palsy, suicide, eating disorders, alcohol dependency syndrome, and increased divorce. Those consequences may also be seen after long-term effective pharmacotherapy for obesity. Understanding these risks will lead to improved awareness and successful treatment with both surgical and nonsurgical treatments.

Keywords: Bariatric surgery, body composition, eating disorders, gallstones, GLP-1 receptor agonists, psychiatric disorders, vitamin deficiencies, and anti-obesity medications

INTRODUCTION

Obesity is a chronic disease with increasing prevalence worldwide[1]. According to the World Health Organization, there were over 650 million adults with obesity in 2016, representing almost 13% of the world's adult population[2]. The International Federation for the Surgery of Obesity and Metabolic Disorders reports that over 300,000 bariatric surgeries were performed globally in 2022[3]. Internationally, sleeve gastrectomy (SG) is the most common bariatric surgery performed, followed by Roux-en-Y gastric bypass (RYGB)[3]. The safety of bariatric surgery is outstanding, with a reported 90-day mortality of 0.11% following surgery[3]. Bariatric surgery also leads to substantial weight loss and has significant effects on obesity-related complications, including type 2 diabetes, liver fibrosis, cardiovascular events, and cancer[4]. In addition to the benefits of bariatric surgery, it is associated with some unwanted consequences of significant weight loss. This review article will highlight the diverse long-term weight-loss-dependent challenges after bariatric surgery, including increased risk for cholelithiasis[5], constipation[6], decreased bone density and muscle mass[7], vitamin deficiencies[8], peripheral neural palsy[9], suicide[10], disordered eating[11], alcohol dependency syndrome[12], and increased divorce rates[13]. Higher cognizance of these risks will lead to effective management of related issues. It may further aid the recognition and understanding of the long-term side effects of medical weight-loss interventions. New-generation anti-obesity medications have shown more than 10% of overall body weight loss, which is unprecedented compared to previously available pharmacologic agents[14]. Long-term data on the safety and efficacy of these medications, including high-dose Semaglutide, have not yet been established[14]. Understanding the physiology of the long-term risks of bariatric surgery can serve as an indicator of potential risks of newer anti-obesity medications. This study aims to provide a comprehensive review of the longer-term risks of bariatric surgery that are not surgery-related.

GALLSTONES

While obesity is an established risk factor for gallstone disease[15], rapid weight loss, as seen in the case of bariatric surgery, can lead to increased rates of gallstones[5]. Other risk factors for gallstone disease include the female sex, pregnancy, and genetic predisposition[16,17]. While rates vary, most studies report an incidence rate of cholelithiasis around 20%-30% after bariatric surgery[18-20]. Bariatric surgery patients with preoperative asymptomatic gallstones had a 15% chance of developing postoperative symptomatic gallstone disease, revealing a statistically significant increase compared to patients with no prior history[21]. Symptomatic cholelithiasis can lead to abdominal pain, jaundice, acute cholecystitis, biliary colic, and pancreatitis[22,23].

The mechanism of postoperative gallstone formation is not entirely understood but is believed to involve gallbladder hypomotility, cholesterol saturation of bile, decreased bile secretion, and hypersecretion of mucus[22-25]. However, recent studies explore other contributing factors[26]. Guman *et al.* compared the fasting metabolome, fecal microbiome, and liver and adipose transcriptome in preoperative and postoperative patients[26]. They discovered differences in the gut microbiome, revealing an increased abundance of Lactobacilli and Enterobacteriaceae in patients who did not develop gallstones. Transcriptome analysis revealed the suppression of four genes linked to cholesterol and bile acid metabolism in patients who developed postoperative gallstones[26]. These studies reveal a new potential pathological mechanism of post-bariatric surgery gallstones and can help predict which patients are more susceptible, leading to better treatment options.

Treatment for gallstone formation after bariatric surgery has been controversial, as multiple factors influence the incidence of development, including the patient's history of gallstones[21]. Prophylactic ursodeoxycholic acid (UDCA) in the first 6 postoperative months resulted in a significant decrease in post-

bariatric gallstone formation from 22% in the placebo group to 6.5% in the treated group[5]. The trial excluded patients with a previous history of cholelithiasis and/or cholecystectomy[5]. In this study, overall gallstone incidence after surgery was 9.7%, of which 3.8% were symptomatic. Other studies[16] have also revealed a decrease in symptomatic gallstones with prophylactic UDCA, decreasing the need for postoperative cholecystectomy. In a study by Haal *et al.*, the effect of UDCA prophylaxis in patients with preoperative gallstones was negligible[21]. While prophylactic cholecystectomy was previously recommended, the increased rate of complications, hospital stays, and mortality have led to a decline in this practice[22]. Given the risks, concomitant cholecystectomy should be reserved for preoperative symptomatic patients undergoing bariatric surgery[27]. The American Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of Bariatric Surgery patients recommend postoperatively treatment with UDCA during the first 3-6 months[28].

In the future, patients should be educated about their risk and consider suggested treatment options such as prophylactic UDCA and monitoring with ultrasound[17]. Given recent evidence, further studies should be conducted to determine the influence of statins on reducing risk[21]. Data should continue to be collected to guide physicians and patients on surgical and pharmaceutical prevention and treatment.

PANCREATITIS

Acute pancreatitis is a rare complication of bariatric surgery that most commonly presents with sharp abdominal pain in the epigastric region and back, jaundice, nausea, and vomiting. However, pancreatitis can be painless and only present with weight loss and steatorrhea[29]. Due to the concurrent weight loss component of bariatric surgery, pancreatitis can be challenging to detect. This complication is relatively rare compared to other nonsurgical consequences of bariatric surgery. Only 138 of 3,765 patients who underwent a SG developed postoperative pancreatic-biliary complications (3.6%). Of these 138 patients, only 10 (0.27%) developed acute pancreatitis after a 3-year follow-up[30].

Recognized risk factors of acute pancreatitis include gallstones and alcohol abuse, both of which are commonly observed nonsurgical complications of bariatric procedures. In individuals with gallstones or type 2 diabetes, the mortality rate can be as high as 20%[31]. About 20% of patients who undergo bariatric surgery develop gallstones, and 32% of patients can develop alcohol dependence[17,32]. These risk factors also contribute to higher rates of a second acute pancreatitis attack[33]. A related factor for acute pancreatitis is pancreatic exocrine insufficiency (PEI). PEI is a known complication after bariatric and gastric procedures. In a previously conducted study, 31% of observed bariatric patients were diagnosed with PEI over 52 months[34]. Another study revealed that 63.4% of observed bariatric patients had abnormal results from the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q)[35]. An additional risk factor is the use of medication.

LIVER FAILURE

The rapid weight loss after bariatric surgery may lead patients with decompensated nonalcoholic steatohepatitis and metabolic dysfunction-associated steatohepatitis to experience acute liver failure[36]. In both nonalcoholic steatohepatitis and metabolic dysfunction-associated steatohepatitis, fat deposits in the liver lead to inflammation and fibrosis of the liver tissue[37]. After bariatric surgery, a variety of metabolic changes in the body can increase the release of fat from the liver, which overwhelms the liver's capacity to efficiently process these fats[38]. As a result, liver tissue can become further inflamed, fibrosed, and injured, which may lead to acute liver failure[39].

Factors that may contribute to the process of acute liver failure in patients with nonalcoholic steatohepatitis and metabolic dysfunction associated with steatohepatitis after bariatric surgery include rapid weight loss[40], nutritional deficiencies[41-44], and metabolic changes[41]. In terms of rapid weight loss, there has been no observed consistent relationship between the speed or amount of fat loss and the development of acute liver injury after bariatric surgery[41]. However, one study showed that a weight loss greater than 1.6 kilograms per week was associated with an increase in inflammation and fibrosis of the liver portal system[40]. In addition to this study, one case study suggests that two patients who underwent bariatric surgery and reported a symptom-free postoperative period had no significant weight loss during that period. However, they experienced acute liver injury only directly after a period of significant, unexplained weight loss[45]. Furthermore, weight loss after bariatric surgery is associated with an increase in peripheral insulin sensitivity and a subsequent decrease in endogenously produced insulin from pancreatic islet cells[46]. This, therefore, leads to an increased breakdown of fat stores and the release of fatty acids, which reach the liver through the portal system, overwhelming hepatocytes' ability to metabolize them through mitochondrial beta-oxidization[38]. The substantial increase in beta-oxidization of fatty acids has been linked to the production of reactive oxygen species which has been linked to mitochondrial damage and subsequent release of cytokines, including tumor necrosis factor-alpha and interleukin-6, that may damage the liver[36,47,48]. However, more studies have suggested that in practice, interleukin-6 gene expression may decline in the post-bariatric surgery period. These inconsistencies have been addressed in another paper[49], which prompts further research into the reality of inflammatory cytokine release in post-bariatric patients.

In terms of nutritional deficiencies in post-bariatric patients, protein and amino acid deficiency may play a significant role in the pathogenesis of acute liver injury in patients with nonalcoholic steatohepatitis and metabolic dysfunction-associated steatohepatitis. The amino acids serine, histidine, phenylalanine, lysine, glycine, alanine, methionine, and threonine are among the most significant deficiencies after bariatric surgery. Deficiency of amino acids, especially arginine and threonine, is associated with an increase in hepatocyte triglyceride accumulation, which may make the liver vulnerable to injury[50]. In RYGB, the duodenum and proximal portion of the jejunum are bypassed, which are the locations where methionine and choline are absorbed[51,52]. Deficiencies in methionine may also be associated with a decrease in GI pH, which occurs because of decreased gastric volume. Methionine is absorbed by a pH-dependent carrier transport method, and therefore, a decrease in pH can cause a decrease in methionine uptake[53]. Deficiency of choline may occur because of a change in the gut microbiome after surgery[54], which may cause an accumulation of bacteria that convert choline to trimethylamine[55], therefore decreasing choline bioavailability[56]. In a society that already lacks sufficient choline intake, this leaves patients who undergo bariatric surgery especially at risk[57]. Deficiencies of both methionine and choline together have been linked to a decrease in beta-oxidation and very low-density lipoprotein production. Choline deficiency alone, however, has been linked to decreased liver function as a result of macrovesicular steatosis, oxidative stress, and hepatocyte apoptosis[58,59].

Although developing acute liver failure is rare in patients with nonalcoholic steatohepatitis and metabolic dysfunction-associated steatohepatitis who undergo bariatric surgery, it is important to understand these risks and create a pre- and postoperative plan of care. Providing proper nutrition and ensuring the surgery does not create a disproportionally long alimentary loop can help prevent acute liver failure in patients with existing liver disease[41]. Additional research is needed to find accurate biomarkers of sufficient nutrition.

CONSTIPATION
Changes in bowel habits, including constipation and diarrhea, often occur postoperatively in individuals who have undergone bariatric surgery[6]. Several factors contribute to postoperative bowel habits, including

changes in diet, patient predisposition, and the type of procedure performed[6]. A systematic review evaluating the impact of bariatric surgery on defecatory disorders revealed heterogeneous results in the literature[60]. In a study conducted by Afshar *et al.*, the proportion of patients suffering from constipation after either RYGB or SG increased from 8% to 27%, although this was not statistically significant[61].

Apart from the type of surgical procedure performed, several factors contribute to constipation in the post-bariatric surgery population. One cause could be decreased frequency of bowel movement and increased firmer stools after surgery[61]. Elevating gut hormones, specifically GLP-1 and PYY, may also contribute to slower bowel transit[62]. Another contributing factor in most patients is likely a significant decrease in dietary fiber after surgery[61,63,64]. Patients suffering from constipation postoperatively should consider appropriate dietary advice and fiber supplementation[61]. A study conducted by Shah *et al.* correlated post-bariatric surgery constipation with thiamine deficiency, and the frequency of defecation for these patients improved after properly treating the thiamine deficiency[65].

A thorough pre-surgical history should be taken to address constipation in postoperative patients to identify a predisposition to gastrointestinal issues. Given the considerable patient-to-patient variability, the choice of surgery type should be discussed, and the post-surgical team should involve dietitians and physicians. Patients experiencing long-term constipation after surgery should consider exercise, better hydration, and consuming at least five servings of fruits and vegetables daily[66]. Patients should also be educated about the importance of fiber intake, hydration, and other constipation treatments. If necessary, stool softeners and laxatives should be considered as pharmacologic treatments. Further, well-controlled studies are needed to assess the impact of bariatric surgery on constipation and other defecatory disorders appropriately[60].

BODY COMPOSITION
Muscle mass loss
Muscle mass loss can result in unfavorable health outcomes, including cardiovascular disease, metabolic syndrome, functional disability, decreased quality of life, and mortality[67,68]. Muscle tissue regulates metabolism, thermoregulation, bone health, and functional capacity[69,70]. Extensive and rapid weight loss, as observed in bariatric surgery, leads to both fat and muscle mass loss[7]. Studies have failed to reveal indicators for high-risk individuals, although insulin resistance and low baseline fat-free and skeletal muscle mass may impact post-surgical outcomes[71,72]. In a meta-analysis study conducted by Nuijten *et al.*, average lean body mass loss, defined by total body mass excluding fat mass and bone mineral content, was -8.1 kg[7]. Fat-free mass, consisting of bone tissue, organ tissue, and skeletal muscles, saw an average loss of -8.2 kg, and skeletal muscle mass loss average was 3.2 kg. Most of this loss occurs within the first 3 months postoperatively and continues during the first year[7,73]. Another study by Zhou et al. reported an average mean total body weight loss of 22%, 35% fat mass loss, 43% visceral adipose tissue loss, and 12% lean mass loss[74]. Voican *et al.* reported the prevalence of low skeletal muscle mass at 32% 1-year postoperatively, compared to 8% prior to surgery[75]. An additional report concluded that the loss of fat-free muscle was 21% ± 14% of total weight loss at 2 years follow-up[76].

The balance of muscle mass synthesis and breakdown can be externally influenced by diet and physical activity[68]. The mechanism of postoperative muscle mass loss involves a decrease in protein intake related to the restriction of overall food intake and a decrease in muscle protein synthesis[7]. Given the inability of the body to store protein, a prolonged state of deprivation leads to muscle wasting and proteolysis to provide amino acids necessary for metabolic function[7,74].

The multi-faceted mechanism of post-bariatric muscle wasting allows for multiple therapeutic approaches to minimize this effect. Regarding diet, studies have shown that an increased intake of whey protein aids in reducing muscle loss and preserving myofibrillar protein synthesis[68]. Dietary protein can influence satiety and energy expenditure, impacting lean body mass retention[77]. According to the American Association of Clinical Endocrinologists, along with other obesity-related associations, a protein intake of 1.5 g/kg is recommended for post-bariatric patients. In comparison, most patients report a protein intake of less than 60 g per day at three months post-surgery[78]. Along with a high-protein diet, moderately intensive resistance exercise can reduce muscle loss[68,69,73,78-80]. However, the influence of exercise is controversial, as some studies reveal only an increase in muscle strength[81,82], while others show an attenuation of the loss of fat-free muscle mass[69,83]. Suppression of the ubiquitin-proteosome system and an increase in angiogenesis following exercise could reduce muscle mass loss[69]. Further studies using magnetic resonance imaging to detect fat-free muscle mass should be conducted in the future to help determine the influence of exercise on post-bariatric muscle mass loss[69].

Interventions to limit muscle mass loss should start before or immediately after surgery[7,71]. Fat-free mass loss has been shown to play a role in weight regain due to its role in long-term appetite control[84]. Along with weight regain, sarcopenic obesity, a syndrome characterized by excessive body fat, low muscle mass, and reduced muscle strength, can increase morbidity and mortality[67,72]. Considering the timeline of postoperative muscle mass loss, patients should be informed on the subject and have a team of providers, including those specializing in nutrition and physiotherapy. Taken all this together, it does appear that in most cases, the fat-free mass loss is predominantly a physiological response related to the overall reduction in muscle work required due to total body weight loss. Fat-free-mass loss does not appear pathological as one would expect if purely calorie restriction was used to achieve 30% total body weight loss[67].

Bone fractures

Studies of bone loss in people who underwent significant weight loss are challenging. Dual-energy X-ray absorptiometry technology loses accuracy in persons with obesity, and changes in fat mass introduce artifacts that may compromise accuracy and precision[75]. Thus, it may be challenging to assess bone health and relate it to fractures in a long-term follow-up after surgery.

There is conflicting information regarding the relationship between bone fractures and bariatric surgery, with many results available. The risk of bone fractures increases by up to 2.3 times for individuals who have had bariatric surgery compared to the general population[85]. However, limited and sometimes conflicting information is available, making it challenging to understand the mechanism or direct link between bone fractures and bariatric surgery outcomes.

One randomized controlled trial did not observe increased risk after bariatric surgery[86]. The Swedish Obesity Subjects study compared three techniques with a medical control group with up to 26 years of follow-up[87]. It showed an increased risk of fracture after *RYGB* compared with the control. The gastric banding group and the vertical banded gastroplasty group had less risk of fractures compared to RYGB, but still greater than the control group. RYGB produced more weight loss than the other procedures (not performed anymore), and RYGB patients were mainly postmenopausal women prone to bone mass loss. An increased risk for fractures after surgery may be attributed to osteoporosis, reduction in mechanical unloading, nutritional deficiencies, hormonal changes, and endocrine factors[88].

The mechanical loading of bones directly determines their size, mass, and other biochemical properties. Any change in this load can lead to localized bone remodeling, either increasing or decreasing cortical bone

mass concerning the microstrain range[89]. This process can be observed in populations unrelated to weight loss, such as individuals on extended bedrests[90], demonstrating the fast-acting nature of mechanical loading changes and localized bone remodeling.

Loss in hip bone density has been shown in individuals who lose significantly less weight than individuals after bariatric surgery. In individuals who participated in a 1-year lifestyle intervention to lose weight, there was an 8.6% decrease in bone mineral density[91]. In a short-term study following individuals who underwent a sleeve gastrectomy, bone mineral density decreased for the spine by 1.2%, femoral neck by 7.0%, and total hip by 5.2% after 6 months, affecting a majority of participants[92]. After another six months, the number of participants impacted by bone density loss increased further. In a group of individuals who received RYGB, there was a 10.2% decrease in femoral neck bone mineral density, increasing to 12.9% three years post-operation[93]. Areas of the body that show the highest loss of bone mineral density are high-loading points, such as the hip[94]. A rapid reduction in the amount of weight loss can lead to decreased mechanical loading of the bones, causing localized bone remodeling and increased fracture risk[95].

Another potential mechanism for bone fractures is nutritional deficiencies after bariatric surgery[96]. Many individuals who undergo bariatric surgery experience micronutrient deficiencies due to decreased nutritional intake and, to a lesser degree, malabsorption of nutrients, which can vary based on the type of procedure performed. Common postoperative deficiencies in calcium and vitamin D have been observed in those who undergo any type of bariatric surgery[8], thought to be related to their impaired absorption due to alterations in the jejunum and ileum[97]. These changes are especially notable in RYGB and biliopancreatic diversion procedures[97]. These two deficiencies have explicitly been linked to an increased frequency of bone fractures and the development of osteoporosis[98]. This side effect may be directly related to the anatomical changes after surgery, which medications will not be subject to, but other mechanisms may also be involved. However, long-term use of the new anti-obesity medications may lead to a decreased food intake. This can be a possible cause of micronutrient deficiencies after long-term use of medications.

Different bariatric procedures are associated with varying levels of risk for bone fractures. While multiple studies have shown no increase in bone fracture risk in laparoscopic adjustable gastric banding (LAGB)[99,100], this procedure has been primarily replaced by RYGB, sleeve gastrectomy. To some extent, each of these procedures has been associated with higher risks of bone fractures. Roux-en-Y gastric bypass has been associated with a 43%-70% increased risk of nonvertebral fracture compared to LAGB and nonsurgical control groups[101,102]. It is important to highlight that LAGB was less effective than RYGB of SG and, in many cases, had a complication of being overly restrictive where the physiological mechanisms were overshadowed by non-physiological restriction of calories. Despite the rise in sleeve gastrectomy procedures, a limited number of studies evaluate each surgery method individually. The available information points to sleeve gastrectomies do not correlate with an increased risk of bone fractures[102]. In another study comparing sleeve gastrectomy patients with unoperated patients, those with surgery had a much lower risk of sustaining a humeral fracture when evaluated for 3 years post-operation[103].

More research is needed on bone mineral density changes following different bariatric surgeries, such as prevention methods and bone strengthening. The most widely supported recommendation to combat the possible risk of bone fractures is regular postoperative visits, exercise, and prescribed lifelong calcium and vitamin D supplements[88,97]. The recommended dose of supplements to prevent adverse bone effects after surgery is 1,200-1,500 mg/day of calcium and 3,000 IU/day of vitamin D[88]. The impact that anti-obesity medications may have on bone fracture rates will not be known for several years. Thus, mechanistic studies are needed earlier to pre-empt a potential problem.

VITAMIN DEFICIENCIES

There is a high prevalence of nutritional deficiencies in people with severe and complex obesity. The most common consequences and deficiencies include anemia, ferritin, folate, vitamin B12, and vitamin D. All candidates should have a comprehensive nutritional assessment before bariatric surgery. Nutritional deficiencies should be investigated and corrected as clinically indicated before surgery[104].

Vitamin deficiencies following bariatric surgery can often be attributed to reduced food intake, alteration in digestion and absorption, and patient non-adherence to postoperative nutritional regiments. This commonly occurs and affects several nutrients, including, but not limited to, thiamine (vitamin B1), vitamin B12, vitamin D, and iron levels, and can lead to further health issues[8]. Available information regarding each deficiency is limited, but the rapid loss of adipose tissue affects fat-soluble vitamins like vitamins A and E and changes in nutrient absorption can impact all deficiencies. These deficiencies may be more severe in patients undergoing biliopancreatic diversion than in Roux-en-Y gastric bypass[105]. Table 1 describes various vitamin deficiencies and their symptoms. While there is a high possibility of additional nutrient deficiencies beyond those described, insufficient information is available to make a significant connection between those deficiencies and bariatric surgery. Again, it should be noted that the rearrangement of the intestines may contribute to these deficiencies. However, the significant reduction in calorie intake and the nutrient composition of what is consumed may also become important with the new anti-obesity medications.

Thiamine deficiency can occur in up to 5% of bariatric surgery patients[114] and can cause a multitude of severe health complications if not adequately addressed. These complications include oxidative stress leading to cell death, peripheral neuropathy, cardiomyopathy, and the neuropsychiatric Wernicke-Korsakoff syndrome[106]. Due to thiamine's water-soluble nature, the body cannot produce and store its supply, making individuals dependent on dietary thiamine intake[115]. This property causes individuals who have undergone bariatric surgery to be susceptible to deficiencies due to reduced food intake and nutrient absorption. Additionally, individuals affected by alcoholism are much more likely to have a thiamine deficiency and develop Wernicke-Korsakoff syndrome, given the impact of ethanol metabolism on the gastrointestinal absorption of thiamine[116]. This puts bariatric surgery patients at further risk of deficiencies, given the higher likelihood of developing alcohol dependency syndrome after the procedure. A known side effect of the anti-obesity medications is vomiting, which may also contribute to thiamine deficiency.

Vitamin A deficiency is one of the most common deficiencies after surgery and can lead to further complications such as vision loss, impaired immune system function, and dermatological issues[108]. Vitamin A is a fat-soluble vitamin primarily stored in adipose tissue. Bariatric surgery causes rapid loss of this adipose tissue, depleting previously stored vitamin A. In a retrospective chart review of patients with RYGB, 35% and 18% were found to be vitamin A deficient after 6 weeks and 1 year, respectively[117]. An alternative study reported that 69% of patients who underwent a biliopancreatic diversion (duodenal switch) experienced vitamin A deficiency four years post-operation[118]. These findings highlight the importance of monitoring and addressing vitamin A levels in bariatric surgery patients to prevent potential complications associated with its deficiency. The fat mass loss with the new anti-obesity medications may not be dissimilar to what we currently see after surgery.

Patients must adhere to postoperative dietary changes and take prescribed supplements to ensure that nutrient levels remain stable and that future complications are avoided[96]. After bariatric surgery, lifelong supplementation is recommended as part of postoperative care[119]. Individuals with Roux-en-Y gastric

Table 1. Vitamins and symptoms of their deficiencies. These symptoms can become apparent post-bariatric surgery if not treated

Vitamin	Signs of deficiency
Thiamine (B1)	Cell death, peripheral neuropathy, cardiomyopathy, and Wernicke-Korsakoff syndrome[106]
Vitamin B12	Fatigue, shortness of breath, jaundice, vision problems, dementia, peripheral neuropathy, ataxia, and a loss of proprioception[107]
Vitamin A	Vision loss, loss of immune system function, and dermatological issues[108]
Iron	Anemia, fatigue, hair loss, and restless legs[109]
Vitamin D	Symmetric low back pain, proximal muscle weakness, muscle aches, and osteoporosis[110]
Vitamin K	Excessive bleeding, poor bone development, osteoporosis, and increased risk of cardiovascular disease[111]
Calcium	Muscle cramps, confusion, tingling in the lips and fingers, and osteoporosis[112]
Vitamin E	Neuronal disorders, impaired immune response, hemolytic anemia, and oxidative-based disorders[113]

bypass or a sleeve gastrectomy were followed to measure their adherence to their prescribed calcium-vitamin D, vitamin B12, and iron supplements. 60% of participants had a high adherence rate, and 15% had discontinued their use of prescribed supplements two years post-operation[120]. 30% of individuals who stopped supplements contributed to this being forgetful[119]. Regular post-operation appointments with the prescribing clinician appear necessary for monitoring supplement adherence. Making patients aware of the lifetime commitment to supplements is an important preoperative step and can reduce discontinuation rates[119]. Patients treated with anti-obesity medications are not asked to take nutritional supplements, but this may become necessary in subgroups of patients. In cases of long-term Orlistat treatment, supplementation of fat-soluble vitamins was deemed necessary[121].

PERIPHERAL NEURAL PALSY
Foot drop is an inability to lift the forefoot due to dorsiflexor weakness and can cause an antalgic gait, potentially resulting in a higher likelihood of falls[122]. Foot drops can be directly caused by peripheral neuropathy affecting the peroneal nerve[122]. Individuals with obesity are already at a higher risk of experiencing neuropathy prior to surgery because of concomitant metabolic diseases such as type 2 diabetes[123]. Peripheral neuropathy is a prevalent condition affecting 23% of individuals with diabetes[124] and 33.3% of individuals with obesity[125]. Studies consistently point to obesity and diabetes as the main metabolic factors associated with neuropathy[126-128]. For these individuals, there is a higher risk of developing peripheral neuropathy regardless of undergoing bariatric surgery[129].

Peripheral neuropathy is one of the most common neurological experiences for bariatric patients, with significant weight loss affecting between 16%-60% of patients[130,131]. The large variability in reported numbers is due to the broad criteria used to identify peripheral neuropathy and different postoperative parameters across studies[132]. Most studies focus on general peripheral neuropathy, rather than specific nerves, making it difficult to accurately evaluate the causal link between bariatric surgery and foot drop caused by peripheral neuropathy in the peroneal nerve[133]. Studies that specifically focus on foot drop have a much smaller subject group. In a retrospective study, 7% of patients who had undergone bariatric surgery developed peripheral neuropathy. However, < 1% developed foot drop[133].

In most cases of peripheral neuropathy after bariatric surgery, symptoms do not develop until about 4 years after the operation[9]. Some precipitating factors for foot drop may also include the reduction of protective fat pads where the nerve crosses long bones. Thus, the bone may cause mechanical pressure on the nerve when the fat pad disappears.

Peripheral neuropathy is strongly connected to thiamine levels. Thiamine deficiency has been observed in 5% of bariatric surgery patients and is one of the most common nutritional deficiencies[114]. In a previously studied case report, a patient who developed severe neuropathy after bariatric surgery was then diagnosed with an extreme thiamine deficiency. Once treated for this deficiency, the neuropathy condition improved but was not fully reversed[134]. Monitoring nutritional levels and avoiding deficiencies can effectively prevent severe postoperative neuropathy[135]. Thiamine deficiency numbers reported here mainly include patients with AGB or other operations where patients had an increased number of episodes of vomiting.

The recommendation to combat foot drop after surgery is controlled weight loss. A study compared bariatric patients who developed foot drop and those who did not. Among patients who developed foot drop, there was a mean weight loss of 45 kg over 9 months compared to the control group's mean weight loss of 44 kg over 22 months[136]. Not only is the amount of weight loss significant, but the time also impacts neuropathy outcomes[136,137]. Given the rapid weight loss period following bariatric surgery[138], controlled weight loss is difficult. Weight loss after medication can theoretically be controlled by slowing the dose titration, albeit many patients and clinicians want to achieve maximal weight loss in the shortest period of time. Thus, adjusting expectations and clinical practice may be required when medications become more commonly used in primary care.

MENTAL HEALTH
Suicide
The psychosocial impacts of bariatric surgery must be acknowledged and appropriately addressed. Overall, patients have a substantial improvement in quality of life as measured by SF36, but this is mainly attributed to the functional domain of SF36[139,140]. The mental domain of SF36 improves during the weight loss phase but returns to baseline after a few years. In subpopulations of patients, there may be an increased risk of depression, self-harm, and suicide following bariatric surgery[10,140-145]. Depression after surgery may lead to weight regain, comorbid psychopathology, and reduced quality of life[10]. The initial decline in depressive symptoms in the short term after surgery is also known as the "honeymoon phase," followed by a long-term increase in symptoms comparable to pre-surgical levels of depressive symptoms[10,140,143,144,146,147]. In a meta-analysis conducted by Castaneda *et al.*, the rate of mortality from suicide, thus the number of people who died after a suicide attempt, was 2.7 deaths per 1,000 people in post-bariatric patients, compared to 0.11 deaths per 1,000 people in the general population[143]. Other studies reported post-bariatric suicidal mortality rates ranging from 0.041%-0.3%[142,148,149]. Higher rates of suicidality occur 12 years postoperatively compared to control groups, and health-related quality of life (HRQOL) appears to be an accurate indicator of the risk of suicidal thoughts and behaviors in bariatric patients[140]. The SOS study reported that during long-term follow-up, suicide and self-harm are rare, but more common in the surgical arm, regardless of the technique employed[150].

The increased prevalence of suicide and self-harm in the post-bariatric population has not been linked to a singular, specific mechanism[140,143]. There is a greater level of preoperative depression and psychiatric disease in people with obesity prior to bariatric surgery compared to the general population[140,143,145]. Rates of alcohol and substance use are also increased in subpopulations of patients after bariatric surgery[143]. The potential impact of emotional eating, constituting binge eating in response to emotion despite a lack of physiologic hunger, and neurotic defense mechanisms may also impact suicide risk in post-bariatric patients[151]. Changes in peripheral released peptides after surgery can impact mood, and further studies are needed to understand this impact better[148,152,153]. Psychosocial factors involving disappointment with results, relationship changes, and weight gain can impact patients[140,143,153]. Medical complications of obesity may not always resolve following surgery, which can negatively impact a patient's mindset[148]. Males have an

increased risk of suicide post-surgery compared to females[154]. Van den Eynde *et al.* reported that the most significant predictor for postoperative self-harm was a history of a psychiatric health disorder within 5 years preoperative and, thus, should be an indication for appropriate monitoring[147]. Underlying mental health issues, an increase in substance use, feelings of disappointment, and low self-esteem could potentially contribute to the increased prevalence of suicide in this population, calling for supervision of at-risk patients[140,143,148].

To correctly address the risk of suicide in bariatric patients, action should be taken prior to surgery. The American Society for Metabolic and Bariatric Surgery (ASMBS) released guidelines for psychological consultation before bariatric surgery involving a face-to-face evaluator and follow-up visits after surgery to determine the need for psychotherapy or pharmaceutical intervention[143]. In The Bariatric Surgery and Education study[155], patients with clinically significant depression symptoms at baseline who underwent a 1-year postoperative videoconferencing-based psychoeducational group intervention had lower depressive scores and a significantly better health-related quality of life one year after surgery compared to the control group. HRQOL assessments should be used in the short-term following surgery to help predict the risk of suicidality in the long term[140]. Given the impact of gastric bypass procedures on pharmacokinetics, physicians should be aware of the physiologic changes being made. The altered metabolism of psychiatric medications and substances should be considered, and physicians should make appropriate dosing changes in these patients and provide counseling on the effects of surgery[143]. Additional clinical monitoring before and after bariatric surgery is necessary to address psychiatric concerns appropriately[150,151,156,157]. Mental health professionals should be involved in bariatric teams pre- and postoperatively to assess patients who may fall vulnerable to depression and suicide[10,148]. As early reports emerge regarding patients who have had suicidal ideation after treatment with anti-obesity medications, some thought must be given to how to identify and manage patients who may be more vulnerable to suicide before starting medications to treat the disease of obesity.

Eating disorders

A subpopulation of people seeking bariatric surgery are at high risk for eating disorders, but recent studies suggest that in some rare cases, patients may also be at risk of developing eating disorders in the postoperative period[11]. Eating disorders are associated with high rates of morbidity, mortality[158], and psychological issues[159], and are subsequently a severe potential consequence of bariatric surgery. Therefore, physicians need to consider the possible risks and complications of the procedure, including the development of eating disorders, to provide the appropriate treatment and support for patients in the long-term postoperative period. This section will focus on the prevalence, risk factors, potential mechanisms, and clinical implications of eating disorders among patients after bariatric surgery.

There are limited and conflicting data regarding the prevalence of eating disorders in bariatric patients. Concerning preoperative patients, one recent study shows that up to 42% of such patients have symptoms of binge eating disorder[160,161]. In terms of the postoperative population, another review claims that eating disorders were prevalent in 7.8% of patients. Of these eating disorders, binge eating disorder was the most common, with a rate of 3.8%[162].

Binge eating disorder or loss of control eating disorder (LOC) are eating disorders characterized by objective binge episodes (OBEs). Objective binge episodes occur when a person eats large portions of food and feels out of control. In the short-term postoperative period, this type of eating disorder is not usually possible due to a variety of metabolic changes, but over time can develop[11,163,164]. Additionally, patients in the postoperative period can experience loss of control while eating, even if the portion is not objectively

large. This is a subjective binge-eating episode[165]. Patients who have experienced objective binge episodes or qualified for a binge eating disorder prior to undergoing bariatric procedure are most at risk of developing LOC or binge eating disorder postoperatively[11,166]. By 2 years post-surgery, 10%-39% develop LOC eating regardless of their preoperative history of eating disorders[11,163].

The degree to which we can learn from this information is limited by the variation in data collected on eating disorders. This variation arises from the use of several different guidelines used to diagnose eating disorders, including the DSM (Diagnostic and Statistical Manual of Mental Disorders[162,167] and ICD (International Statistical Classification of Diseases and Related Health Problems)[162,168]. Additionally, the lack of standardization of survey materials contributes to the variability in data. For instance, only one survey was specific to bariatric patients[169]. Furthermore, the timing of the survey administration, whether pre- or post-surgery, is not standardized[162]. Consequently, several factors prevent the retrieval of reliable data on eating disorders in the postoperative period.

Aside from a pre-existing eating disorder, other psychological factors may also influence post-bariatric eating disorders. While more research is needed to confirm the impact of different psychiatric disorders and psychopathological traits on post-surgical outcomes, studies suggest that "greater affective instability" is associated with worse results after bariatric surgery. Emotional dysregulation and psychological issues are significant in weight control and eating behaviors[170]. The postoperative period can be challenging for some individuals as they may struggle to cope with stress and other emotions[171]. After surgery, hormonal changes in the gastrointestinal tract make weight loss a passive process driven by less food intake, which may prevent patients from coping with stress the same way as before the surgery[172]. Therefore, patients with a previous LOC eating pattern may develop a new, restrictive eating disorder, such as bulimia nervosa or anorexia nervosa, in the postoperative period[153,171]. Studies also suggest that patients with disordered eating behaviors display decreased executive function[173]. Additionally, after bariatric surgery, patients may experience a more active reward system and, therefore, be at a higher risk of developing an eating disorder[162,174,175].

Unrealistic expectations regarding bariatric surgery results may lead to body dissatisfaction after surgery. A longitudinal study involving 64 bariatric patients measured their desired post-surgery weight, comparing it against three different surveys, including an Eating Disorder Examination Questionnaire, Beck Depression Inventory, and Body Shape Questionnaire. Results revealed that 81.1% of patients did not achieve their desired weight. Notably, the study found a significant association between higher differences in desired and actual post-surgery weight and increased levels of body image dissatisfaction and eating psychopathology scores[176].

The development of eating disorders in patients after bariatric surgery is a rare but significant complication that requires standardization of assessment measures to intervene and support at-risk patients. Patients need to follow up with providers after surgery to prevent the development of eating disorders in the long term. A multidisciplinary approach to treatment can include mental health and dietary counseling and management of post-surgical expectations[11].

It is possible that the development of new eating disorders after anti-obesity medication can be attenuated by reducing or stopping the medications, but it is another significant effect that is not being considered at the moment.

Alcohol dependency

While substance abuse, particularly alcohol dependency syndrome, is a rare complication of bariatric surgery, it can significantly impact patients' health and quality of life in the long term[12]. One study suggests that substance abuse alone is prevalent in 32% of postoperative bariatric surgery patients[32,177]. Furthermore, alcohol dependence may increase over time following the surgery, with the Roux-en-Y gastric bypass being especially linked to alcohol misuse in the postoperative period[12,177,178]. Moreover, women may be more susceptible to developing alcohol dependence than men in the postoperative period. Further investigation is warranted for potential gender-specific approaches to alcohol recommendations[177].

One risk factor for developing alcohol dependence after bariatric surgery is the alteration of alcohol metabolism that occurs due to changes in gastrointestinal physiology. Although most alcohol metabolism in the body occurs in the liver through hepatic alcohol dehydrogenase, some alcohol is metabolized in the gastric mucosa. After a Roux-en-Y gastric bypass, less alcohol passes through the patient's stomach, and therefore, less alcohol is metabolized, ultimately leading to higher blood alcohol concentration[177,179]. This may cause an increased sensitivity to the effects of alcohol, given its longer-lasting effects[12,179-181]. This would not apply to the new anti-obesity medications.

A change in the brain's reward system after surgery can also play a role in developing alcohol dependence. Similar responses in the brain are triggered by alcohol, drugs, and food[12]. This aligns with the theory of 'addiction transfer' that suggests patients cannot fulfill the behavior of eating and experience its reward as they did before surgery, so it is replaced with a new behavior that achieves a similar reward, like drinking alcohol[12,182]. Patients can also have an increase in sensitivity to the hormone ghrelin after surgery, which may increase the rewarding properties of alcohol quicker and more frequently[12]. Furthermore, alterations in neurotransmitter balance are also associated with an increased risk of alcohol abuse. Patients with RYGB are seen to have a decrease in dopamine D2 receptor availability, specifically in the ventral striatum and caudate nucleus, which are areas of the brain that play an important role in regulating the body's alcohol reward system[12]. Some individuals may be genetically predisposed to reduced dopamine signaling in the alcohol reward system[12,182]. Additionally, psychosocial factors such as depression, anxiety, smoking, and other substance abuse disorders may increase the likelihood of developing alcohol dependence in postoperative bariatric patients[12]. These mechanisms may also apply to the new anti-obesity medications.

Given the significance of alcohol dependence as a potential complication after bariatric surgery, it is crucial to closely monitor patients and provide appropriate preventative measures to improve quality of life and patient outcomes. While alcohol misuse is common after bariatric surgery in the short term, emerging evidence suggests that patients may also be at risk in the long term. As research continues to assess the complex relationship between alcohol dependence and bariatric surgery, the field also needs to consider what may happen with the new anti-obesity medications.

Divorce rates

Increased divorce rates are another rare outcome after bariatric surgery, prompting a need for a better understanding of this relationship. Although research on bariatric surgery's impact on marital relations is limited, several observational, longitudinal, and retrospective studies have tried to explore this. The Swedish Obese Subject study shows that bariatric surgery is associated with an increased incidence of divorce rates and separation in comparison to a control. The surgery group reported a 9.4% divorce/separation rate, whereas the control group reported a 5.5% divorce/separation rate after 4 years[13]. After 10 years, the surgery group reported a 17.1% divorce/separation rate, while the control group reported an 11.6% separation rate[13]. In an additional cohort study using data from the Scandinavian Obesity Surgery Registry (SOReg) of the general population, 14.4% of the surgery group reported divorce, whereas 8.2% of the control

group reported divorce after 4 years[13]. A Danish study also reported divorce rates among bariatric surgery (15%) to be higher than nonsurgical groups (8%)[183,184]. An American study measured the cumulative incidence of divorce after bariatric surgery over five years and presented evidence of an increased separation and divorce rate (8%) among married people who had bariatric surgery in comparison to the general US adult population (3.5%)[183]. These findings are consistent with the Swedish studies' conclusion that an increased divorce rate is associated with bariatric surgery. However, the incidence of divorce after surgery in the US (8%) is about half the incidence of divorce after surgery in the Scandinavian countries (15%).

Multiple studies suggest that poorly functioning relationships in the preoperative period are more likely to result in divorce in the postoperative period[13,185]. Bariatric surgery can add strain to a relationship, and any additional tension added to a poorly functioning relationship is more likely to lead to divorce[13,186]. The SOReg and SOS cohort studies reported that younger age, previous divorce, and shorter time in relationships were associated with an increased divorce rate after bariatric surgery[13,186]. It will also be necessary to understand whether this will be the case after anti-obesity medications.

Although many studies show that psychological factors such as depression and anxiety in patients undergoing bariatric surgery may improve in the short- and medium-term postoperative period[187], it is important to recognize that adjusting to life after surgery can be difficult and have negative psychological consequences[171]. A subset of patients who have undergone bariatric surgery are more likely to attempt suicide and experience alcohol and substance abuse disorders[188]. Additionally, there is an increased risk of divorce among couples in which one or both partners experience mental illness[189]. Moreover, starting psychiatric medication after surgery is associated with an increased divorce rate in the postoperative period[183]. Therefore, as some patients may be more likely to experience mental health issues after surgery, this could increase the risk of divorce in the postoperative period.

On the other hand, patients who experience a positive change in psychosocial factors, such as an increase in self-esteem, autonomy, and self-value, may be more likely to leave an unhealthy relationship[184]. Again, this needs to be understood in the context of anti-obesity medications.

The reason for the association between bariatric surgery and divorce is still unclear. The strength and duration of the relationship prior to surgery, age, mental health status, and medication may all contribute to increased divorce rates in the postoperative period. Additional studies are therefore needed to appropriately address the issues patients may face in their relationships prior to and after bariatric surgery, as well as prior to and after anti-obesity medications.

The design of this narrative review has several limitations. One notable limitation involves restricted access to detailed data, as only summary-level statistics were provided for some studies. Furthermore, specific topics discussed had limited available information, limiting the ability to generalize some research findings. This was often the case when non-randomized cohort studies or real-world data were used to understand the rare complications of surgery. In future studies, improved access to research and new findings will allow a more comprehensive review.

CONCLUSION

Understanding the long-term consequences of significant weight loss after bariatric surgery may help prepare clinicians and patients as the treatment with anti-obesity medications expands. Undoubtedly, the benefits of bariatric surgery include significant control of the disease of obesity and associated complications, including diabetes mellitus, cardiovascular disease, and various cancers[10,147,190].

Due to the varying prevalence of those consequences, different risk factors for each problem, and patient individuality, a thorough assessment of each patient is necessary. Patient phenotyping, which helps to characterize the diverse types of obesity, has not yet been utilized to guide diagnosis and implement treatment strategies[191]. Vitamin supplementation, psychiatric follow-up visits, and awareness of possible risks are integral to preventing developing nonsurgical complications. However, as data on some of the discussed topics remain conflicting and the underlying mechanisms are not fully understood, conducting further long-term studies is crucial to accurately inform patients of their risks and develop appropriate treatment plans should those issues arise.

Considering the increased use of anti-obesity medications and their increasing potency[192], studying the long-term effects of weight loss following bariatric surgery may provide insight into potential future situations with the medications. Ultimately, the goal is to reduce these issues through prevention and awareness and provide a framework for assessing and managing the potential consequences.

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Authors' contributions
Performed data acquisition, as well as providing administrative, technical, and material support: Harrington S, Kang S, Telesca L

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Ethical approval and consent to participate
Not applicable.

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