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## PREVENTION AND TREATMENT OF NUTRITIONAL COMPLICATIONS AFTER BARIATRIC SURGERY

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## **SEARCH STRATEGY AND SELECTION CRITERIA**

We identified references through searches of PubMed, MEDLINE and Embase using the following terms (“nutritional OR malnutrition OR deficiency OR neuropathy OR anemia OR hypoglycemia OR bone OR oxalate OR liver OR complications”) AND (“bariatric surgery”) from the opening date of the databases to 1st March 2020. Articles were also identified through searches in the authors' files. Only papers published in English were included. We selected and reviewed the articles describing long-term nutritional and metabolic complications after bariatric surgery. The final reference list was generated based on the novelty and relevance to the broad scope of this review.

## **UNSTRUCTURED SUMMARY**

Obesity and the corresponding burden of related diseases is a major public health issue worldwide that is reaching pandemic proportions. Bariatric surgery is the only intervention that has been shown to result in significant and lasting weight loss and a decrease in overall mortality for patients with severe obesity. Consequently, the population of patients having undergone this procedure is growing. Multifactorial weight-dependent and independent mechanisms underlying the metabolic improvement may also drive preventable, but potentially life-threatening, long-term nutritional complications. However, the diagnosis of nutritional complications may be delayed, especially as these patients are prone to functional gastro-intestinal symptoms and as a dramatic weight loss is sought. This review focused on the prevention and treatment of nutritional complications after bariatric surgery in the clinical setting.

## MANUSCRIPT (4961 words)

### INTRODUCTION

Obesity is a major public health issue that is reaching pandemic proportions. The prevalence of obese adults, defined by a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, tripled from 1975 to 2016, accounting for 13% of the world adult population (>650 million subjects).<sup>1</sup> As a major risk factor for type 2 diabetes (T2D), cardiovascular diseases, nonalcoholic fatty liver disease (NAFLD), osteoarthritis, and many cancers, obesity has replaced smoking as the number one lifestyle-related risk factor for premature death, with the lifespan reduced by an estimated 5 to 20 years.<sup>2,3</sup> Lifestyle intervention, consisting of diet, behavioral modification, and exercise remains the first-line treatment,<sup>4</sup> but generally results in limited short-term weight loss in patients with severe obesity.<sup>5</sup> Data on the long-term efficacy, tolerability and safety of obesity medications and endoscopic treatments (intra-gastric balloons, gastric aspiration device, endoscopic sleeve gastropasty) are still limited.<sup>6-10</sup>

Bariatric surgery (BS) is the most consistently effective method for sustained weight reduction and has been shown to result in a significant improvement in T2D, metabolic syndrome, NAFLD, and quality of life.<sup>11</sup> Moreover, a related decrease in cardiovascular events, cancer occurrence, and mortality have also been suggested in observational studies.<sup>12-20</sup> According to guidelines, patients with a BMI  $\geq 40$  kg/m<sup>2</sup> or BMI  $\geq 35$  kg/m<sup>2</sup> and obesity-related comorbidities are eligible for BS.<sup>10</sup> The 2016 survey of the International Federation for Surgery of Obesity and Metabolic Disorders (IFSO) estimated that the number of BS procedures has increased to > 600,000 operations per year, of which > 80% were performed in USA, Europe, and Latin America.<sup>21,22</sup>

Given the major impact of obesity and bariatric procedures on digestive-system physiology and nutrition, multifactorial mechanisms underlying the metabolic benefits of BS can also

drive preventable but potentially life-threatening nutritional complications. However, the diagnosis of nutritional complications may be delayed, especially as these patients are prone to functional GI symptoms and as a dramatic weight loss is sought. Consequently, gastroenterologists should be familiar with the management of post-BS patients. They should be knowledgeable of the type of bariatric intervention performed, the typical post-surgical anatomy, and related-nutritional complications that may occur to prevent, diagnose, and treat them in a timely manner. This narrative review focuses on the prevention and treatment of nutritional complications after BS in the clinical setting.

## **COMMON BARIATRIC PROCEDURES AND PHYSIOLOGICAL CHANGES**

Conventional procedures in BS are adjustable gastric banding (AGB), sleeve gastrectomy (SG), gastric bypasses – including Roux-en-Y gastric bypass (RYGB) and mini (one-anastomosis) gastric bypass (MGB-OAGB) – and biliopancreatic diversion with duodenal switch (BPD/DS) (Figure 1 and Table 1). These procedures generally result in substantial total weight loss (TWL) within the first 6 to 12 months, achieving a maximum at 1 to 2 years of approximately 20% after AGB, 25% after SG, 30% after RYGB, and 35% after BPD-DS.<sup>10,11,23,24</sup> These correspond to excess weight losses (EWL) of: 50% after AGB, 50-60% after SG, 60% after RYGB, and 70-90% after BPD-DS.<sup>14,23-27</sup> This chapter presents the anatomical and physiological changes that drive not only the metabolic benefits but also potential nutritional complications (Table 1 and Figure 2).

### **Adjustable gastric banding**

AGB consists of the placement of a silicone band around the stomach, leaving a small gastric pouch (30-40 ml) above the band, thus restricting food intake (Figure 1). The gastric pouch

pressure and altered emptying might increase satiation through vagal signaling. The diameter of the band can be adjusted by filling it with water for injection from a subcutaneous port connected to the band. Since the era of laparoscopy (in the 1990s), this procedure has become widespread due to the low rate of complications, good midterm weight loss results, easy technical aspect, and absence of resection or significant modification of the digestive tract anatomy and physiology.<sup>23,28</sup> However, its use has gradually decreased from 42% to 3% of bariatric procedures by 2016, probably due to the high percentage of weight regain, major complications and reoperation rates reported in long-term follow-up studies.<sup>21,29</sup>

### **Sleeve gastrectomy**

SG consists of performing a calibrated longitudinal gastrectomy by removing 2/3 of the stomach and leaving a volume of 75 to 100 ml (Figure 1). SG has shown good results in long-term weight loss, a low complication rate, and significant improvement in comorbidities. Its metabolic efficiency on glucose homeostasis and lipid profiles is clearly established.<sup>14,26,27</sup> Conceptually, the physiology of weight loss after SG is based on the restriction of food intake.<sup>25-27</sup> However, the role of hormonal mechanisms is increasingly recognized.<sup>30</sup> The surgical removal of the fundus may decrease orexigenic ghrelin secretion by P/D1 cells.<sup>30</sup> Moreover, the acceleration of gastric emptying may increase anorexigenic peptide levels (GLP1, CCK, PYY), as observed after RYGB.<sup>31-33</sup> Combining technical straightforwardness and the possibility of subsequent endoscopic access to the upper digestive tract and a lower risk of malnutrition than bypass procedures, SG has become the most commonly performed bariatric procedure in the world within a few years (54% in 2016).<sup>21</sup> With an estimated rate of 2%, the most life-threatening perioperative complication is staple-line leak.<sup>34</sup> Mid-gastric stricture causing chronic vomiting may occur in the short term.<sup>35</sup> Gastroesophageal reflux disease (GERD) is the main long-term side-effect (20-30%), most often successfully treated with proton pump inhibitors.<sup>36</sup>

## **Gastric bypass**

Developed in the late 1970s, first by open then by laparoscopic surgery, RYGB is currently the second most frequently performed procedure and considered to be the reference standard in BS.<sup>21</sup> Anatomically, this procedure consists of creating a small gastric pouch (15-30ml), leading to food restriction and rapid satiety (Figure 1). After the jejunum division, at 50 cm from the duodenojejunal angle, a gastrojejunostomy is performed between the small gastric pouch and the distal part of the divided jejunum, creating the alimentary limb, and thus bypassing both the excluded stomach and duodenum. The last step is the creation of a jejunojejunostomy between the alimentary and biliopancreatic limbs 150 cm from the gastrojejunostomy, allowing the biliopancreatic secretions to mix with food in the common channel and to enable the digestion of proteins. Beyond the reduction in caloric intake and malabsorption induced by bypassing GI tract segments and secretions, multiple hormonal mechanisms are involved in the long-term weight loss and metabolic benefits of RYGB, and it is the surgical model that has been studied the most to investigate these mechanisms (Figure 2).<sup>14,26,27,37,38</sup> Indeed, anatomical alterations lead to major changes in secretive hormonal and neuronal pathways, modifying circulating levels of multiple gastrointestinal and pancreatic hormones (GLP-1, GLP-2, oxyntomodulin, glicentin, GIP, PYY, glucagon, and major proglucagon fragment).<sup>31-33</sup> Increased levels of oxyntomodulin and glicentin are associated with increased satiety and are independently predictive of greater weight loss at 12 months after RYGB.<sup>30</sup> Despite the malabsorptive component, long-term morbidity in patients complying with vitamin and trace element supplementation is mainly represented by functional disorders (dumping syndrome, marginal ulcer) and mechanical complications (bowel obstruction, internal hernia).<sup>39</sup>



Indeed, malabsorption after RYGB would only account for 11% of the total reduction in caloric absorption.<sup>40</sup> The main factors that contribute to macro- and micronutrient maldigestion and malabsorption after gastric bypass include: reduced gastric acid, bypass of bile salts and pancreatic secretions (impaired fat digestion and glucose absorption), bypass of major intestinal absorption sites (duodenum and proximal jejunum), and decreased absorption surface in the common limb. Small intestine bacterial overgrowth (SIBO) is present in 15% of obese patients before surgery (vs. 2.5% in non-obese subjects)<sup>41</sup> and increases to 40% after RYGB, probably as a result of intestinal dysmotility and the blind biliopancreatic limb.<sup>42</sup> Excessive and pathological flora increase the malabsorption of macronutrients (mainly fat) and micronutrients (fat-soluble vitamins, vitamin B12, thiamine, iron) by inducing villous atrophy, exudative enteropathy, and bacteria-derived deconjugation of bile acids.<sup>43</sup> Exocrine pancreatic insufficiency, occurring in 31% of a RYGB patients series, may be another cause of malabsorption following GI-tract remodeling.<sup>44,45,46</sup>

MGB-OAGB was introduced in the early 2000s as an alternative to RYGB. Anatomically, it consists of a long and narrow gastric pouch made at the small curvature and anastomosed to a jejunal loop (200 cm from the duodenojejunal angle in its original description).<sup>47</sup> (Figure 1) With the advantages of being technically easier and causing less short-term morbidity (single anastomosis), MGB-OAGB showed excellent weight loss and improved or resolved comorbidities and was thus rapidly adopted by several bariatric surgeons.<sup>48-50</sup> In the 2016 IFSO survey, MGB-OAGB was the 3rd most frequently performed procedure in the world.<sup>21</sup>

### **Biliopancreatic diversion with duodenal switch**

Developed in the late 1990s, BPD-DS is currently the most effective procedure in terms of weight loss and improvement of obesity-related comorbidities.<sup>37</sup> This procedure combines SG (wider than conventional SG) and Roux-en-Y post pyloric duodenoenterostomy, with a 150-

cm alimentary limb and a 100-cm common channel (Figure 1). Preserving the pylorus aims to avoid dumping syndrome and marginal ulcers, which can occur after RYGB. Due to its very prominent malabsorptive effect, its metabolic efficiency is superior to RYGB.<sup>37</sup> However, this procedure should be restricted to patients with very severe obesity (BMI > 50) and remains uncommon (0.5% in 2016) due to its surgical complexity, relatively high early surgical morbidity (compared to other procedures), and higher rates of long-term nutritional complications.<sup>21</sup>

## **EPIDEMIOLOGY**

The most common nutritional deficiencies described after BS are vitamin D, iron, folate and vitamin B12. Zinc deficiencies are also frequent but with uncertain clinical significance, whereas thiamine deficiencies are less frequent but with potential severe consequences (Table 2).<sup>51</sup> After malabsorptive procedures, copper, vitamin A and E deficiencies are also frequently described while other deficiencies such as those of selenium, niacin, pyridoxin (vitamin B6), vitamin C, and K may occur more rarely.<sup>51</sup> However, obesity is paradoxically a risk factor for malnutrition and pre-existing deficiencies are frequently reported before surgery (mainly vitamin D and iron)<sup>51,52</sup> as a result of multiple factors, including poor diet, eating disorders, and consumption of dietary supplements or herbal preparations, as well as intrinsic factors, including SIBO, increased oxidative stress, sequestration of fat-soluble vitamins in adipose tissue, and increased hepcidin production.<sup>51,53</sup> As a result, the incidence of nutritional deficiencies induced by surgery is difficult to evaluate and their reported prevalence varies considerably, depending on the pre-existing nutritional status, eating habits, measurement methods, quality and duration of follow-up, patient compliance with micronutrient

supplements, amount of weight loss, and type of bariatric procedure (the deficiencies being roughly proportional to the length of the intestinal loops that are excluded).

After surgery, deficiencies may appear or worsen in as many as 60% of patients at six months and 100% of patients at two years.<sup>54</sup> Factors involved in the development of macro- and micronutrient deficiencies after surgery include not only the physiological changes due to the malabsorptive bypass (bypass of absorption sites, digestive secretions, and SIBO in the biliopancreatic limb, shortened absorption surface in the common limb) but also an excessive reduction in caloric intake, food intolerance, prolonged vomiting, and no adherence to supplements and vitamins prescriptions (Figure 2). However, certain nutritional parameters can also improve after surgery,<sup>55</sup> not only because of taking multivitamins but also as a result of improved obesity-related factors.

Postoperative nutritional deterioration is generally avoidable in the patient population regularly followed after SG and RYGB, for which the number of deficiencies may not increase after BS.<sup>55,56</sup> Thereaux *et al.* reported a low incidence of severe nutritional complications requiring hospitalization after gastric bypass over a seven-year period (mainly iron deficiency anemia), occurring in 36 of 1000 person-years, whereas thiamine deficiency occurred in less than 1 in 1000 person-years).<sup>19</sup> However, several studies have reported poor-quality nutritional monitoring after surgery and a high level of long-term loss-to-follow-up.<sup>57</sup> In addition, although adherence to vitamins prescriptions tends to be acceptable within the first six months, longer-term adherence rates have been reported to be as low as 50% of adults and 27% of adolescents.<sup>58-60</sup>

## **CLINICAL PRESENTATION**

For most post-bariatric patients, nutritional deficiencies present with mild symptoms including fatigue, hair loss, cramps, or paresthesia.<sup>61</sup> However, severe cases, which may be life-threatening or lead to irreversible disability, have been reported after all types of BS. This chapter reviews the clinical presentation and management of the most common and most severe clinical nutritional complications. A list of potential nutritional causes of systemic symptoms is provided in Figure 3. Overall, any unexplained symptom (in particular neurological) or chronic GI symptoms, such as vomiting or post-bypass diarrhea, or persistent or recurrent weight loss after 1 to 2 years post-surgery should be considered as red flags for nutritional deficiencies.

### **1. Digestive red flags for nutritional complications**

Obese patients often suffer from functional GI tract symptoms before surgery, such as abdominal pain or bloating, which tend to improve after weight loss.<sup>62</sup> After surgery, occasional vomiting can occur in patients with inappropriate eating behavior.<sup>63</sup> Recurrent or persistent nausea/vomiting, however, is a major risk factor for acute thiamine deficiency and should prompt specific testing and supplementation before any intravenous glucose administration.<sup>64</sup> Specific causes of vomiting and upper GI tract symptoms include GERD or band slippage after AGB, and marginal ulcer, stomal stenosis (anastomosis diameter < 10 mm), internal hernias, and SIBO after bypass procedures.<sup>65</sup> These potential complications require specific GI investigations, such as upper GI series, abdominal CT, and upper GI endoscopy.

Chronic diarrhea is a particular concern when it occurs after bypass surgery, as it may correspond to a malabsorption syndrome with steatorrhea. Steatorrhea frequently pre-exists before surgery in obese patients, due to high dietary fat intake, and has been reported for as many as 90% of patients after RYGB, with a poor correlation with symptoms (only a quarter

of patients had diarrhea).<sup>66</sup> Although transit time may be unaffected,<sup>67</sup> diarrhea occurs in 8 to 46% of patients after bypass surgery, especially those resulting in a shorter common limb (< 150 cm) and is thus suggestive of malabsorption. The main factors that contribute to malabsorptive diarrhea are (see gastric bypass anatomy and physiological changes section and Figure 2) 1) the induced asynchronism between food intake and delayed delivery of biliopancreatic secretions and 2) the short length of the common limb available for absorption.<sup>40</sup>

SIBO in the biliopancreatic limb (or afferent loop) may also induce vomiting, bloating and diarrhea, the latter being potentially worsened by exocrine pancreatic insufficiency.<sup>42,65</sup> In most cases, malabsorptive diarrhea may be improved by the administration of oral uncoated exogenous pancreatic enzymes, and if necessary antidiarrheal agents. Antibiotics should be the first line treatment in case of SIBO.<sup>44</sup> Biliary excreted antibiotics may be more active on the biliopancreatic limb bacterial overgrowth, and infusing enteral nutrition in the bypassed remnant stomach by performing gastrostomy may be proposed in refractory cases associated with severe malnutrition and hepatopathy (see Liver disease chapter below). As SIBO may be difficult to prove due to anatomical changes after bypass surgery,<sup>68</sup> suspected SIBO may be treated empirically. The first line of antibiotic treatment that may be recommended is ciprofloxacin 250 mg orally twice a day for seven days.<sup>69</sup> Second-line therapeutic options are doxycycline, amoxicillin, metronidazole, rifaximin.<sup>70</sup>

For severe diarrhea with protein malnutrition, reversion or conversion to a more proximal bypass, with lengthening of the common channel, may be necessary.<sup>71-73</sup> Finally, other causes of diarrhea have been reported after BS and must be considered, such as *Clostridium difficile* infection, medication side-effects, choleric diarrhea, exacerbation of diabetic enteric neuropathy, or the onset of celiac/inflammatory bowel disease.<sup>74</sup>

## **2. Micronutrient deficiency syndromes**

### **Anemia**

Due to pre-existing deficiencies, anemia is reported in 10 to 20% of patients before surgery<sup>75</sup> and up to 17% after SG and 50% after RYGB or BPD-DS within the first two-years.<sup>35,76</sup> The most common cause is iron deficiency (Table 2), which may be pre-existing or develop as early as six months post-surgery as a result of hypochlorhydria (reducing non-heme and heme-iron absorption), bypass of duodenal iron absorption sites, interaction with other divalent ions (calcium and zinc supplements), and the influence of phytate-rich (tea) or phosphorus-rich (eggs) dietary components (Figure 2).<sup>3,76</sup> Iron supplementation may be optimized with vitamin C and taken at a different time than calcium or zinc supplements (Table 2).

As a result of decreased gastric-acid and intrinsic factor secretion and bypass of duodenal absorption sites, vitamin B12 deficiency is another frequent but later cause of post-operative anemia.<sup>35,76</sup> Indeed, clinically relevant cobalamin deficiency usually occurs several years after BS due to high and sustained body storage.<sup>35,76</sup> Additional risk factors include a history of vitamin B12 deficiency or neuropathy and medications that exacerbate the risk of vitamin B12 deficiency, such as proton-pump inhibitors, metformin, anti-epileptic drugs, nitrous oxide, neomycin, and colchicine.<sup>10</sup> As the measurement of serum vitamin B12 levels may not be adequate to identify a deficiency, the measurement of serum methylmalonic acid, with or without homocysteine, may be considered. As 1% of ingested vitamin B12 is passively absorbed throughout the small bowel, daily or weekly oral vitamin B12 may be sufficient to meet vitamin B12 requirements (Table 2).<sup>77</sup> Other forms of post-bariatric nutritional anemia may involve copper, selenium, zinc, or vitamins B9, A, or E deficiencies.<sup>35</sup>

### **Encephalopathy**

Thiamine deficiency may lead to acute (Wernicke) and chronic (Korsakoff) encephalopathy, which are life-threatening and disabling medical emergencies that have been reported after all types of bypass or restrictive procedures, including banding. It is fully preventable though. As body storage of thiamine is low, most cases present after few days/weeks of recurrent vomiting after BS.<sup>78</sup> In a review of 84 cases of post-bariatric Wernicke encephalopathy, 94% appeared within six months after BS.<sup>79</sup> Recurrent nausea/vomiting and intravenous glucose administration without thiamine were the main risk factors, reported in 90% and 18% of cases, respectively.<sup>64,80</sup> Additional risk factors that require specific routine screening and supplementation include: pre-existing malnutrition, alcohol consumption, cardiac failure/furosemide medication, and poor compliance.<sup>10</sup> Aggravating factors, such as SIBO-related malabsorption and magnesium deficiency, have also been suggested and treated in refractory cases.<sup>81,82</sup> As the classical triad of symptoms (confusion, eye movement abnormalities, and gait instability) is often incomplete and MRI findings inconsistent, suspected encephalopathy should prompt immediate treatment (Table 2).<sup>10,83</sup> Also, any BS patient should not receive intravenous glucose without thiamine supplementation.

### **Neuropathies**

A large spectrum of nutritionally-related neurological disorders has been reported for 1 to 16% of post-bariatric patients.<sup>84</sup> Peripheral neuropathies are the most common complications, whereas myelopathy, and optic neuropathy are the most severe, potentially disabling, complications. As they may develop many years after surgery, patients should be educated to recognize the early signs that require prompt consultation, such as memory troubles, weakness, gait problems, and mild confusion. Prevention or, in the worst case, urgent recognition and management is crucial, as most of neurological complications can reverse or improve with timely therapy. Thiamine, vitamin B12, folate, vitamin A, and copper are the most frequent deficiencies responsible for neuropathies (Table 2, Figure 3), but vitamins E,

niacin (vitamin PP), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), and biotin (vitamin B7) can also be involved.<sup>85</sup>

Polyradiculopathy may account for 2% of neurological complications after BS.<sup>84</sup> Its presentation closely resembles that of Guillain-Barré syndrome but respiratory function and cerebrospinal fluid are normal.<sup>86,87</sup> The diagnosis is confirmed by electromyography and parenteral thiamine improves symptoms. Rarer types of neuropathies include peroneal neuropathy (foot drop, related to multiple deficiencies, and fat-pad loss), optical neuropathy (a mean of 3 years after surgery, related to vitamin B12, A, or copper deficiencies), myelopathy (a mean of 10 years after surgery, related to vitamin B12 and copper deficiencies) and progressive peripheral neuropathy (> 10 years after surgery, related to multiple deficiencies).<sup>78,88</sup>

### **Bone consequences**

Bone loss following BS is multifactorial, and beyond skeletal unloading that can be considered as an adaptive mechanism to weight loss, several mechanisms can induce osteoporosis including decrease in vitamin D and calcium absorption (Figure 2), hyperparathyroidism (reported in up to 60% of patients after SG and RYGB),<sup>44,89-93</sup> as well as changes in body composition and bone-marrow fat,<sup>94</sup> protein malnutrition and maybe changes in gut hormones and adipose tissue derived factors.<sup>95</sup> In addition to bone loss, microarchitecture, an important factor of fracture risk, is also altered by BS.<sup>95</sup>

Despite early stigmata of bone remodeling and bone loss as early as the first postoperative year, fracture risk seems to increase later, starting 2-5 years after BS and increasing thereafter. Bone loss depends on the surgical procedure and appears to be greater after RYGB (and BPD) than after SG and seems to be low after AGB. Fracture risk has been shown to be increased essentially after RYGB.<sup>96-98</sup> Further studies are needed to clarify the risk of bone fractures in the long term after each procedure.



Current management includes correction of calcium and vitamin D deficiencies (according to guidelines) and regular assessment of calcium metabolism and bone mineral density is required to adapt the supplementation (Table 1, Table 2 and panel).<sup>10,51,99</sup> Physical exercise also appear to prevent bone loss after BS.<sup>95</sup> Bisphosphonates should be considered for high-risk patients after vitamin D/calcium restoration.

### **3. Post-bariatric intestinal insufficiency or intestinal failure**

Signs of severe protein malnutrition in post-bariatric patients include hair loss, edema, muscle wasting, anemia, hypoalbuminemia, and possible liver dysfunction.<sup>100</sup> Although severe protein malnutrition can occur after any bariatric procedure, it is more frequent after distal bypass procedures with a short common limb < 150 cm or long biliopancreatic limb > 150 cm.<sup>101,102</sup> The main risk factors include excessive weight loss (mean 50% TWL) and excessive loss of absorptive surface, similar to that of short bowel syndrome (“short common-limb syndrome”), worsened by biliopancreatic secretion bypass, and SIBO-related exudative enteropathy and hepatopathy (Figure 4).<sup>100,103</sup>

Nutritional support, best delivered in intestinal failure centers via enteral or parenteral nutrition with adequate prevention of refeeding syndrome, combined with treatment of malabsorptive diarrhea, usually resolves malnutrition and the related-hepatopathy (Figure 4).<sup>100,103</sup> Post-bariatric intestinal failure (IF) is considered to be an emerging indication for home parenteral nutrition (HPN). Indeed, 3 to 6% of HPN patients from IF centers have a history of BS, mostly RYGB (72-78%) and BPD-DS (9%), but also SG (2-9%) and AGB (2-8%).<sup>100,104</sup> High rates of HPN-related complications, corrective/reversal surgery (30-80%), and mortality (9-11%) provide an idea of the complexity of these patients.<sup>100,104</sup>

## **4. Liver disease**

### **Hepatic dysfunction**

Despite the remarkable efficiency of BS on nonalcoholic fatty liver disease,<sup>105</sup> cases of fatal post-operative hepatocellular failure have been reported, especially after bypass procedures leaving a long biliopancreatic limb.<sup>106-109</sup> Hypoalbuminemia and kwashiorkor syndrome, associated with exudative enteropathy and hepatic cytolysis, secondary to microbial overgrowth in the afferent loop, is a complication classically reported after the first bariatric surgical procedures such as the jejunoileal bypass in the 1960s, and could be medically treated before disassembly of the intervention. After this intervention, very serious cases of steato-hepatitis were reported with 2.3% of deaths. The histological lesions described were similar to those of alcoholic hepatitis,<sup>110-112</sup> with 7 to 9% developing cirrhosis within 15 years following surgery.<sup>110,113</sup> In the 1970s-1980s, the physiopathology of these complications was well described by several teams who showed the major role of microbial proliferation in excluded loop or blind loop syndrome. These authors showed the efficacy of metronidazole treatment in the prevention of this hepatopathy, the pro-inflammatory role (liver) of the endotoxins from this flora, the role of deconjugated bile acids (hepatotoxic lithocholic acid) and of the decrease in the bile acid pool, as well as the role of acetaldehyde secreted by the anaerobic flora (proinflammatory and profibrosing).<sup>113-116</sup> In this setting, the deficit in protein intake may play an aggravating role, although inflammation and insulin resistance are likely the primary reasons responsible for liver steatosis.

### **Alcohol misuse**

Alcohol addiction has been spotted as a long-term risk factor for patients requiring BS, with major potential downstream effects on nutritional status and liver disease. A previous study showed a faster and higher peak of blood alcohol concentration post-ingestion after both RYGB and SG than after AGB, suggestive of increased sensitivity after surgery.<sup>117</sup> This result

was confirmed at two years following surgery using questionnaires to evaluate alcohol addiction.<sup>118</sup> Only a few long-term studies are available on this topic. In a seven-year French nationwide population-based cohort based on 8,966 patients and matched controls, the risk of alcohol dependence of patients following RYGB was almost double than with SG.<sup>19</sup>

## **5. Metabolic complications**

### **Dumping syndrome and hyperinsulinemic hypoglycemia**

Dumping syndrome (DS) corresponds to the postprandial occurrence of symptoms related to the rapid delivery of unprocessed nutrients into the small bowel (see Figure 2 and Appendix table).<sup>119</sup> The presence of hyperosmolar contents in the small bowel induces a fluid shift, causing symptoms of hypovolemia, and the release of vasoactive gut peptides, causing GI and vasomotor symptoms within minutes to one hour after food intake.<sup>119</sup> GI symptoms include abdominal pain, nausea, bloating, and diarrhea. Vasomotor symptoms include acute fatigue, the need to lie down after meals, tachycardia, flushing, and perspiration.<sup>120</sup> Associated glycemia is normal or elevated. DS is a common functional complication of gastric bypass and SG, occurring early after surgery and generally improving over time.<sup>121</sup> The reported prevalence ranges from 10% to 75%, depending on the study and definition.<sup>122</sup> Dietary measures are generally sufficient to control the symptoms (Appendix table).<sup>10,123</sup>

Hyperinsulinemic postprandial hypoglycemia is a delayed and potentially severe metabolic complication of BS. It especially occurs after RYGB, after a minimum of one year (up to three years) after surgery, but some patients experience hypoglycemia after other procedures, including SG.<sup>124</sup> Continuous glucose monitoring has shown that asymptomatic hypoglycemic episodes are frequent after BS, but only 10% are symptomatic. Severe signs of

neuroglycopenia (confusion, loss of consciousness, seizures) are rare (0.2% to 1%) but may lead to life-threatening and disabling consequences.<sup>125-128</sup> The pathophysiology may involve accelerated gastric pouch emptying (Figure 2), leading to an increased peak of postprandial glucose, enhanced GLP-1 secretion (and/or beta-cell sensitivity to GLP-1), and increased insulin secretion (and/or insulin sensitivity), whereas beta-cell hyperplasia does not appear to be a dominant factor.<sup>125,126</sup> Most patients are effectively treated by dietary modification alone and education to recognize symptoms of hypoglycemia.<sup>126</sup> Pharmacotherapy produces varying results on hypoglycemia but may be attempted before surgical options, including reversal surgery (Table3).<sup>119,123,129</sup>

### **Kidney stones**

BS may expose patients to acute and chronic oxalate nephropathy.<sup>130</sup> Under physiological conditions, dietary oxalate forms insoluble salts with dietary calcium and is poorly absorbed. After gastric bypass, calcium is saponified within fats because of fat malabsorption. Hence solitary oxalate is absorbed (in the colon). Plasma oxalate is then eliminated by glomerular filtration and forms complexes with calcium in the tubular lumen. Longitudinal studies have shown a two-fold increase in oxalate excretion and an increased risk of stones approximately 1 to 3 years after BS.<sup>130,131</sup> In a large case-control study, a diagnosis of kidney stones was significantly higher for post-RYGB patients than matched obese controls (8% vs. 5%).<sup>132</sup> When rapid crystallization occurs, acute kidney injury with poor renal prognosis has been reported.<sup>133,134</sup> Management of oxalosis and calcium-oxalate stones include avoiding dehydration, a low oxalate meal plan, oral calcium, and potassium citrate therapy (citrate strongly competes with oxalate for binding to calcium).<sup>10</sup> Probiotics containing *Oxalobacter formigenes*, a normal microbiota component that metabolizes oxalate, have shown conflicting results.<sup>10,131,135,136</sup> Future treatment options include oxalate degrading enzymes delivered by bacteria or enzyme tablets.<sup>137</sup>

## **Gallstones**

BS and rapid weight loss are well-established risk factors for cholesterol cholelithiasis. In a prospective study of gastric bypass patients, gallstones and sludge developed within six months in 36% and 13% of patients, respectively.<sup>138</sup> However, the risk of needing a postoperative cholecystectomy is low, ranging from 7 to 10% after a mean of 3 years.<sup>139</sup> As a result, cholecystectomy may be reserved for symptomatic gallstone disease. However, as endoscopic retrograde cholangiopancreatography can no longer be performed in RYGB, MGB-OAGB and BPD-DS patients, asymptomatic patients with known gallstones may be considered for prophylactic cholecystectomy before BS.<sup>10,140</sup> In other cases, systematic prescription of oral ursodeoxycholic acid for six months prevents gallstone formation.<sup>10</sup>

## **FOLLOW-UP AND SUPPLEMENTATION**

Severe nutritional complications after BS are potentially disabling and life-threatening, yet they are often easily preventable. A strict lifelong follow-up plan with the administration of multi-vitamin supplements and routine assessment of nutrient serum levels are recommended for all patients by American and European societies (Table 1 & panel).<sup>10,51,83,99</sup> Additional screening for specific micronutrient deficiencies are required in situations of increased risk for malnutrition (eating disorders, alcohol misuse, adolescence and during pregnancy) or the presence of red flag deficiency symptoms (Figure 3). Dietary advice is also necessary to ensure sufficient protein intake ( $\geq 60\text{g/d}$ ) and protein supplements may be prescribed.

However, these recommendations are poorly followed in practice, possibly due to the persistence of many unresolved questions that arise for clinicians and patients. First, these recommendations are mainly based on expert opinion, since few randomized trials available to establish the choice of supplementation regimen for most vitamins and trace elements.

Concerning SG, American and European recommendations<sup>35,99</sup> advocate for the same nutritional substitution as for RYGB, due to the paucity of data from SG studies.<sup>141-143</sup> Second, deficiencies often occur in spite of systematic recommended supplementation. As a result, increased awareness is needed by both patients and their physicians concerning the situations at risk and early signs and symptoms that should prompt additional nutritional investigations during long-term follow-up (Figure 3). Finally, long-term adherence to post-BS nutritional supplement regimens by patients and follow-up is poor and is associated with higher micronutrient deficiency rates. Suggestions to improve patient adherence include reducing the number of tablets, reducing their cost, improving education of the patient and his general practitioner.<sup>144</sup>

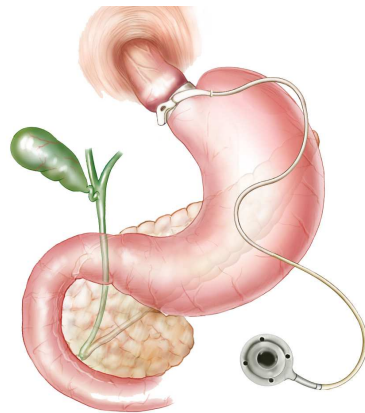
## **CONCLUSION**

BS is currently the most effective long-term treatment for the management of severe obesity. Surgeons and endoscopists innovate to simplify procedures, treat complications, and improve results, with two main goals: inducing weight loss and improving complications associated with obesity. However, it is essential to consider the global upheaval for the patient and to keep in mind that the choice of the technique will be based on the balance between the benefits and risks of each procedure. Given the growing epidemic of obesity and the extent of BS indications, the number of bariatric patients with potentially severe long-term nutritional complications is rising. Long-term follow-up and patient adherence are essential in this paradoxical clinical situation, in which the long-awaited weight loss can also be synonymous with malnutrition. It is our responsibility as physicians to be familiar with these increasingly common interventions and potential consequences and to develop strategies to improve patients' lifelong adherence to dietary measures, supplements prescriptions, and follow-up.

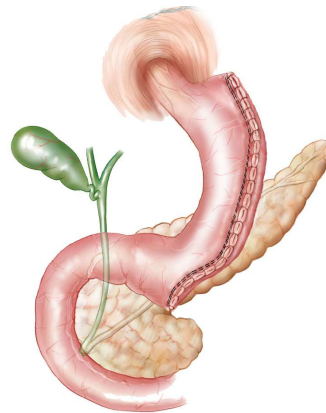
**FIGURES**

**Figure 1. Anatomy of common bariatric procedures**

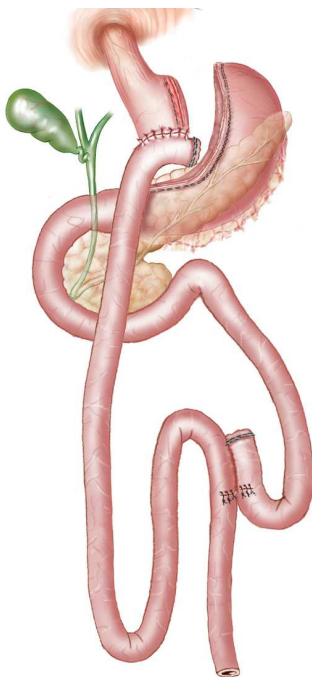
**Adjustable  
Gastric Banding**



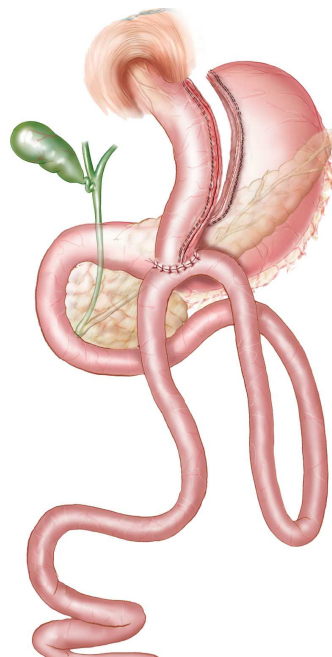
**Sleeve  
Gastrectomy**



**Roux-en-Y  
gastric bypass**



**Mini Gastric Bypass  
One-anastomosis  
Gastric Bypass**



**Bilio-Pancreatic Diversion  
with Duodenal Switch**

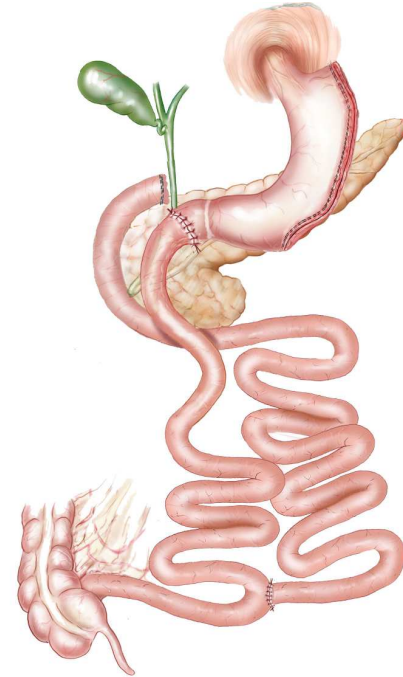
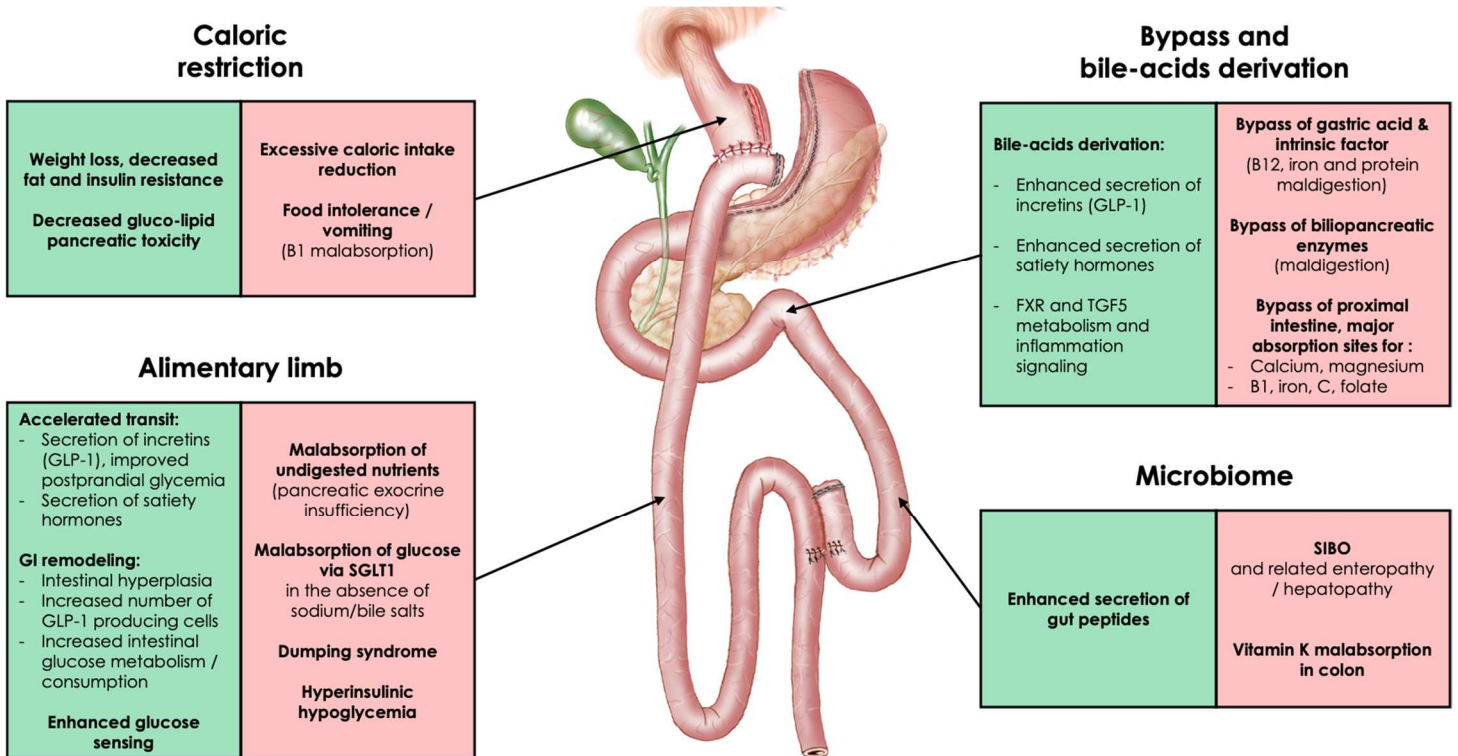


Figure legend: Roux-en-Y gastric bypass includes a food limb of 150cm and a biliopancreatic limb of 50cm. Mini gastric bypass - one-anastomosis gastric bypass includes a biliopancreatic limb of 200cm. Biliopancreatic diversion with duodenal switch includes a sleeved stomach and an alimentary limb of 150cm and a common channel of 100cm.

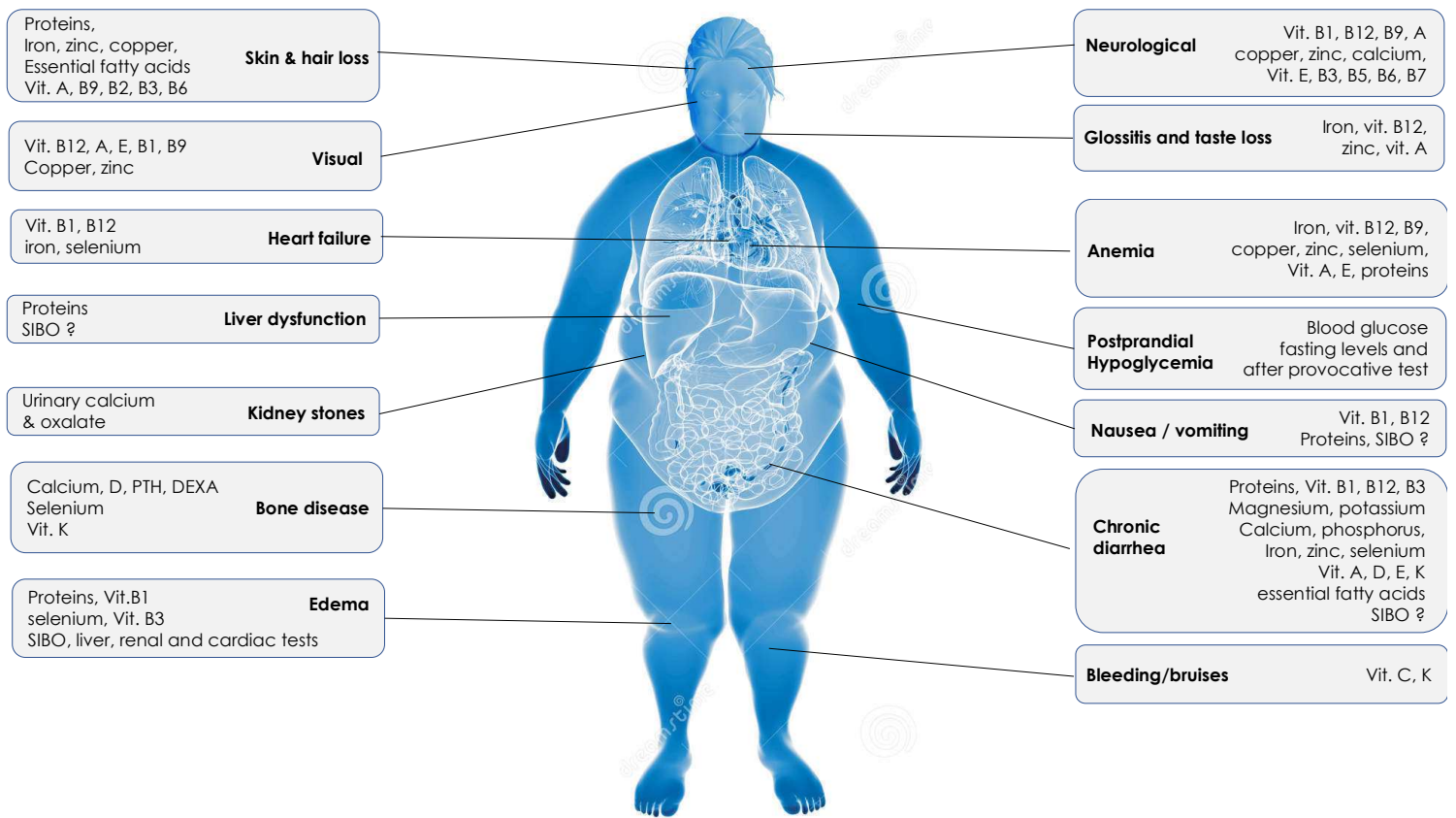
**Figure 2. Suggested physiopathology of metabolic benefits (green frames) and nutritional complications (red frames) after gastric bypass**





Legend: The green and red frames include the suggested mechanisms of metabolic benefits on glucose homeostasis and nutritional complications, respectively.

**Figure 3. Overview of the systemic clinical presentation of nutritional complications after bariatric surgery**



Legend: Long-term clinical follow-up is recommended annually (3-6 months in unstable patients or after bypass surgery). Potential deficiencies are classified according to the type of revealing symptoms that should prompt specific testing. Abbreviations: SIBO: small intestinal bacterial overgrowth, PTH: parathormone, DEXA: dual-energy x-ray absorptiometry (bone densitometry); Vit: vitamin, B1: thiamine, B2: riboflavin, B3: niacin (or PP vitamin), B5: pantothenic acid, B6: pyridoxine, B7: biotin.

**Figure 4. Management of bariatric intestinal failure**



Abbreviations: SIBO: small intestinal bacterial overgrowth

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