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Gut microbiome: Linking together obesity, bariatric surgery and associated clinical outcomes under a single focus

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Abstract

Obesity is increasingly prevalent in the post-industrial era, with increased mortality rates. The gut microbiota has a central role in immunological, nutritional and metabolism mediated functions, and due to its multiplexity, it is considered an independent organ. Modern high-throughput sequencing techniques allowed phylogenetic exploration and quantitive analyses of gut microbiome and ameliorated our current understanding of the gut microbiota in health and disease. Its role in obesity and its changes following bariatric surgery has been highlighted in several studies.

According to current literature, obesity is linked with a particular microbiota profile that grants the host an augmented potential for calory release while limited diversity of gut microbiome has also been observed.

Moreover, bariatric surgery procedures represent effective interventions for sustained weight loss and restore a healthier microbiota, contributing to the observed fat mass reduction and lean mass increase. However, newer evidence has shown that gut microbiota is only partially recovered following bariatric surgery. Moreover, several targets including FGF15/19 (a gut-derived peptide), could be responsible for the favorable metabolic changes of bariatric surgery. More randomized controlled trials and larger prospective studies that include well-defined cohorts are required to better identify associations between gut microbiota, obesity, and bariatric surgery.

INTRODUCTION

Obesity represents a huge health burden in society, linked with an increase in mortality rates[1]. Newer data suggest a crosstalk between gut microbiota (GM) and obesity, while obesity itself seems to be both a cause and a result of gut microbiota alterations[2]. In health, the gut microbiota is involved in energy intake, adjustment of glucose and lipid homeostasis, and micronutrient and vitamin composition[3]. This GM balance is disturbed in obesity presenting a series of pathological manifestations, including chronic inflammation, insulin resistance, and metabolic disturbance[2, 3]. Moreover, obesity is linked with vitamin and mineral deficiencies, that aggravate gut microbiota synthesis and function[4, 5].

Bariatric surgery (BS) is currently the sole long-term effective therapeutic option for morbid obesity [6]. A number of studies identify important qualitive and quantitive changes of GM after BS. Such treated patients have micronutrient deficiencies that may lead to deficiency-related syndromes[7, 8], that include anemia (10–74%) and neurological disorders (5–9%) [7, 9].

Given the presence of other coexisting factors that impair the postoperative nutritional status of these patients [energy-restricted higher protein intake and adequate nutritional supplementation diet, anatomical and physiological impairment of the gastrointestinal tract (GIT)] [7, 10], a consistent follow-up is essential.

The complicated interaction between obesity and GM phylae that includes gut microbiome modulations (and of their byproducts) in obese subjects who undergo bariatric surgery as treatment, are the aim of the review.

OBESITY

Obesity represents the discrepancy between caloric intake and energy outake and is affected by genetic and environmental factors [11]. Obesity has been associated with type

2 diabetes mellitus (T2DM), increased arterial pressure, hypercholesterolemia, cardiovascular disease, apnea, musculoskeletal disorders, cancer, impaired fertility, anxiety, and psychiatric disorders [12]. Currently, obesity results in more deaths than undernourishment and starvation together [13].

Worldwide, the term Body Mass Index (BMI) is a tool for estimating obesity's severity and is calculated by dividing the body weight (kg) by the square of height (m^2) of the individual. In adult subjects, a BMI between 18.5 to 25 kg m^{-2} is considered normal; overweight is BMI 25 to 30, while obesity is defined as BMI over 30 kg m^{-2}. Obesity is divided by WHO into three categories; class I corresponds to a BMI 30.00 to 34.99; class II between 35.00 and 39.99 and BMI that exceeds 40 is class III [14]. Additionally, BMI >50 kg m^{-2} is termed superobesity. Regarding its treatment, it has been shown that in a time period of 2 years, most subjects reclaim or even exceed their initial weight[15].

GUT MICROBIOTA IN HEALTHY SUBJECTS

Glossary of microbiota-related terms

Microorganisms are present in the skin, respiratory system, the GIT, and the male and female genitourinary tracts[16].

The ecological community of symbiotic and pathogenic microbes composes the microbiota [17]. The term microbiota includes all species which form microbial communities, such as eubacteria, archeobacteria, fungi, and protists[18].

The term 'microbiome' refers to the microorganisms themselves. The study of all microbial DNA of a sample directly recovered from a sample such as the gut is called metagenomics. The metagenome, refers to the complete genome of the microbiota [17], while the term 'shotgun metagenomics' describes the process of a sample's next-generation sequencing. This process produces primer-independent data that can then be analyzed with various reference-based and/or reference-free methods[16].

Gut microbiota under normal conditions.

In health, the microbial composition remains constant[19]. The largest microbe concentrations are found in the intestine, the skin, and the oral cavity[20]. Among these sites, GI is the most intensively colonized organ. In the past, it was widely shown that a healthy gut contains 1–1.5 kg of microbes a number that exceeds by about 10 times the number of the host's (human's) cells[21]. However, more recent estimates suggest that the number of gut bacteria is on the same order as the number of human cells, weighing a total of 0.2 kg[22]. Approximately 1000 species colonize the gut, with microbial density increasing along the GI tract from 10^1 to 10^4 microbes in the stomach to 10^{10} to 10^{12} cells per gram in the colon[17].

Due to the antimicrobial effects of hydrochloric acid and nitric oxide, microbes in the stomach and the small intestine are little[23, 24]. However, the large intestine presents a better milieu for microbes, with better conditions to extract energy as well as essential nutrients [25, 26]. The bigger number of living microbes is located in the colon but due to the impermeable adherent mucus layer, there is no direct contact with the epithelium[27]. It is believed these bacterial species yield collectively 2 million genes (100 times the number of the human gene)s. The number above agrees with the actual extent of microbial gene catalogs found in MetaHIT and the Human Microbiota Project[28].

GUT MICROBIOTA IN OBESE SUBJECTS

The gut microbiota along with the host's genotype and lifestyle, affect the pathophysiology of the disease and thus the research interest of these associations is increased. [2, 29].

An important increase in adipose tissue of germ-free (GF) mice implanted with microbiota harvested from the cecum of ob/ob mice has been found, when compared to mice transplanted with a GM from lean rodents[30]. Transferring GM from genetically

obese mice resulted in a 47% increase of fat mass, while the inoculation from lean mice increased adipose tissue mass by 26%[31].

Several factors contribute to how GM affects obesity, such as nutrient metabolism. For instance, hippurate, a microbial metabolite of dietary polyphenols, is reported to be associated with *Eubacterium dolichum* and visceral fat mass[32]. Additionally, it has been postulated that the circadian clock, which regulates diurnal oscillations of different biological processes such as feeding, can be influenced by the GM and therefore act as a contributor to diet-induced obesity[33].

Obesity also triggers low-grade chronic inflammation. A diet in high-fat for 28 days, increased more than twice the systemic lipopolysaccharide (LPS) levels and the LPS-containing GM, thus presenting what is known as "metabolic endotoxemia". The increased LPS levels could trigger inflammation and thus contributing to obesity and T2DM[34] [35].

BARIATRIC SURGERY

Bariatric Surgery modalities

When the lifestyle and/or medication-based approaches are ineffective, bariatric surgery is an option, as a highly effective therapeutic procedure for the treatment of obesity[36]. Bariatric surgery (BS) can be either restrictive or malabsorptive, by reducing food intake and promoting weight loss[37]. The available metabolic surgery procedures includes laparoscopic adjustable gastric band (LAGB), vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), and BPD with duodenal switch (BPD/DS)[7, 37] .

Vertical banded gastroplasty (VBG)

A restrictive procedure. An incision is made on the lesser curve of the stomach 6 cm from the esophagogastric junction. The lesser omentum is dissected followed by a 2 cm opening of the lesser sac. Dissection continues downward to 1 cm above the uppermost

portion of the short gastric vessels. A calibrated transgastric window is created using a circular stapler creating a 20 mL gastric pouch volume. A polypropylene band is placed around the distal part of the gastric pouch [36, 38, 39].

Laparoscopic adjustable gastric band (LAGB).

A restrictive procedure, more widely performed in the past, but its use has declined in popularity in the last 5 years[38]. A synthetic band is placed around the upper portion of the stomach, immediately after the gastroesophageal junction, thus creating a small gastric pouch of 20–30 mL. The band is inflated or deflated with saline to alter the level of constriction and to maintain a feeling of fullness with a smaller volume of food. At first, the early and prolonged satiety was attributed to the physically restricted meal volume and the delayed emptying of food from the pouch[40]. Today, it has been proved that most of the procedure's efficiency is due to the pressure applied on the Intraganglionic Laminar Endings (IGLES) which convey afferent signals resulting in hunger reduction[41]. The average weight loss is about 45%–47% of the excess weight by 4–5 years postoperatively[42].

Roux-en-Y gastric bypass (RYGB).

RYGB represents both a restrictive and malabsorptive procedure. Of note, apart from the mechanical restriction of caloric intake, RYGB impairs the absorption of nutrients. Of note, 15–30% of the weight loss is maintained for at least 20 years after RYGB[43]. Moreover, after RYGB the glycemic control improves in 90% of recipients[44].

Vertical Sleeve Gastrectomy (VSG).

A restrictive procedure. VSG has increased in popularity due to its relative ease to perform as well as the good clinical outcome achieved[45]. In VSG, a vertical excision of approximately 75% of the stomach lengthwise with preservation of the pylorus is performed. It aims to make a small gastric pouch ("sleeve"), having a volume of approximately 100 mL, and to create a high-pressure chamber that easily produces

sufficient pressure to overcome the tone of the pyloric sphincter, thus resulting in rapid gastric emptying[46]. This decreased gastric reservoir does not permit any distention and therefore provokes premature satiety, resulting in to substantially reduce portion sizes.

Sleeve creation has an impact on hormone regulation, decreasing blood ghrelin levels and enhancing a state of satiety. The average weight loss of 60% excess body weight after two years postoperatively, along with an improvement in associated comorbidities[42]. Both short- and medium-term research papers showed that VSG is almost as effective as RYGB in reducing body weight and improving glycemic control[10, 47].

Biliopancreatic diversion (BPD) and BPD with duodenal switch (BPD and BPD/DS).
A malabsorptive procedure. Being a quite radical procedure, it is only used occasionally. The BPD procedure involves a sleeve gastrectomy with the creation of a 200–500 mL gastric pouch. A Roux-en-Y gastroileostomy of 200 cm is formed with a common channel 50 cm from the ileocecal valve joining biliary and digestive enzymes. The weight loss achieved via BPD and/or BPD/DS is the greatest among any of the other bariatric procedures with excess weight loss of 70%–80% postoperatively[42, 48].

From all the aforementioned procedures, half of the bariatric procedures are VSG and approximately 40% are RYGB[49]. RYGB has been the primary choice for decades and thus millions of RYGB patients are residing in the general population[13]. Table 1 shows a comparison between these bariatric approaches.

Today, BS is regarded as the only effective treatment for a pronounced and permanent weight loss[13]. The Swedish Obese Subject (SOS) trial reports a weight loss following RYGB of 27% in 15 years, while non-operative approaches (lifestyle changes or pharmacological treatment) have no effect over this period. Controlled long-term studies (>5 years) about the effects of VSG on weight loss are still scarce, but weight loss up to 5 years is similar to that of RYGB[13].

Lastly, branched-chain amino acids (BCAAs) were significantly reduced after BS, a finding associated with alleviation of the "metabolic overload" observed in some tissues[50]. Trimethylamine-n-oxide, a metabolite proposed as a cardiovascular marker, was found to increase following BS. Probably, this increase is related to the GM changes observed after BS[50].

THE MECHANISMS OF GASTRIC BYPASS

Gastric bypass procedure is an artificial condition in which the intestinal mucosal energy outflow is variable capable of altering BMI and glucose levels.

The main reason behind weight reduction is a modified eating behavior that reduces energy intake. According to the foregut theory suggests that as food bypasses both the stomach and the duodenum, the release of gut-derived hormones originating from them is altered, e.g., the release of glucose-dependent insulinotropic peptide (GIP) from the duodenal. A second theory known as the hindgut theory states that since the more distal parts of the intestine are now (following the procedure) exposed to nutrients and contact food sooner than normal, this provokes faster humoral responses.

RYGB also changes the circulating bile acids levels and those of the intestinal microbiota: bile acids regulate glucose metabolism causing the release of GLP-1, provoking the synthesis and release of fibroblast growth factor 19 (FGF19) which improves insulin sensitivity and glycemic control[51].

Circulating exosome microRNAs (miRNAs) constitute another mechanism that could explain bariatric surgery–associated outcomes[6]. Several studies have identified miRNAs that tend to increase or decrease in expression after bariatric surgery[52, 53]. Of those, miRNA MiR-7, which has shown the most concrete post-surgical increase among studies, plays a role in the regulation of pancreatic beta-cell function in humans[53].

SIDE EFFECTS OF BARIATRIC SURGERY

The 1-year mortality rate after BS is 1% and the 5-year mortality rate is 6%[54]. 4% of patients after BS experience surgical complications during the first month[55, 56]. These include anastomotic leakages, hemorrhage, perforation, and infection and inner herniation[55]. However, the latter is considerably decreased after the closure of any mesenteric defect became a routine practice during the BS approach[57].

Chronic abdominal pain is a common side effect seen in patients after RYGB; half of RYGB patients experience abdominal pain and in a 5-year follow-up, a third of them still experience it[58]. It is of importance to clarify the underlying pathology following BS but its etiology remains still obscure[59]. Furthermore, it is believed that 4% of patients who were not on opioids, became chronic users after BS[60] and therefore the attending physician of such a patient who develops nausea and pain, must bear in mind the risk of iatrogenic opioid addiction.

Hypoglycemia in non-diabetic subjects appears in more than 64% of patients during the first 5 years of BS[61]. Several theories have been developed including enhanced B cell mass and function, lowered ghrelin levels, improved insulin sensitivity, and inadequate counter regulation[62]. Unfortunately, side effects of hypoglycemia often persist throughout the years and can decrease the quality of a patient's life.

GUT MICROBIOTA AFTER BARIATRIC SURGERY

A plethora of surgical diseases are connected to gut microbiota changes including, atherosclerosis, non-alcoholic fatty liver disease, inflammatory bowel disease, and colorectal cancer[16]. BS plays a central role by affecting the abundance of may microbial species of the GM.

Most often, a decrease of *Firmicutes* and an increase of *Bacteroidetes, Proteobacteria*, abundance is observed after BS[63]. Both RYGB and VBG, have comparable long-term effects on gut microbiota function and composition. Moreover, feces from BS patients were transplanted to GF mice. The mice gained less fat as compared to reciprocal mice transplanted with GM from obese subjects. These findings show a causal relationship between GM and BS-induced weight reduction[64]. Another study employed transplantation from mice that underwent RYGB to sham-surgery germ-free mice, provoked weight loss compared to recipients of GM from non-operated mice[65].

The increased pH (following BS) into the lumen and high levels of dissolved oxygen, affect the growth of aerobic microorganisms (such as *Proteobacteria*) and inhibit the growth of anaerobic bacteria[66].

In a recent systematic review, Davies et al. summarized 14 clinical studies, (n=222) subjects (RYGB = 146, VSG = 25, biliointestinal bypass = 30, vertical banded gastroplasty = 7, and adjustable gastric band = 14). Major changes comprise reduction of the abundance of *Faecalibacterium prausnitzii* and an increase of *E. coli*. Following VSG, a decrease in the abundance of *Firmicutes* while after RYBG an increase in *Bacteroidetes* and *Proteobacteria* was observed[67].

Their findings are summarized in Table 2. It was found that the different types of BS result in dramatic changes in gut microbiota.

A systematic meta-analysis investigated the effect of BS in metabolic and GM profiles, of 22 articles. Only two studies were randomized, while the rest were prospective ones[64, 68, 69]. The total sample size was 562; 411 patients had RYGB, and 97 underwent VSG[70].

As shown in Table 3, several microbes are affected by BS: some authors found increased *Bacteroides* while Firmicutes and *Bifidobacterium* had lower abundance in the post-RYGB subjects[70, 71].

In summary, it appears that BS reestablishes a healthier microbiota together with a slimmer metabolic profile, and possibly this microbiota readjustment contributes to a diminished fat mass and an increased lean mass,. Nevertheless, the pathways through

which the gut microbiota and their metabolites affect obesity are still obscure, and robust microbe manipulations that interfere with the host-bacteria interactions for the management of obesity still need to be developed[16].

BARIATRIC SURGERY EFFECT ON SMALL INTESTINE BACTERIA

Obese subjects after BS can present small intestine bacterial overgrowth (SIBO), which is defined as greater than 10^5 colony-forming units per mL of proximal jejunal aspiration[72]. SIBO is a manifestation of obesity and a prospective study including 378 subjects with morbid obesity, reported that 15% of patients before undergoing RYGB had SIBO, and that this figure increased up to 40% following the procedure[72].

SIBO diagnosis is set from a small intestine aspirate test. However, due to the invasive nature of this process the most acceptable detection technique is the "therapeutic trial", by empirically administering antibiotics due to the clinical complications associated with SIBO[73].

The malabsorption of A,D, E, K (the fat-soluble vitamins) is due to the bacterial deconjugation of bile acids by small intestine bacteria while the formation of a toxic compound (the lithocholic acid) further aggravates the intestinal epithelial cell dysfunction and aggravates carbohydrate and protein malabsorption[74]. In contrast, subjects with SIBO, the vitamin K levels are within normal levels or increased since bacteria are capable to synthesize menaquinone[75].

BARIATRIC SURGERY ON GUT HORMONES

Typically, meal intake suppresses the hunger hormone ghrelin; however, in obese subjects, this mechanism might be disrupted. Thus it has been reported that within days after BS, as a more quick release of nutrients to the distal small intestine starts to occur, an increased production of gut satiety hormones such as PYY and GLP-1, and a reduced

increase of ghrelin is taking place[76].

After a meal, both PYY and GLP-1 are, proportionally to the consumed calories, released from the L cells of the distal small intestine[77]. Following BS, the postprandial PYY levels are increased with the new ones correlating to the postoperative weight loss[78]. Also, the role of PYY in the regulation of feeding after RYGB has been assessed using octreotide, which blocks the secretion of most of the gut hormones and therefore increases food consumption[76].

Although the effects of PYY and GLP-1 on gastric emptying, glucagon secretion, and insulin release from the pancreas are well understood, however, the appetite change after BS seems to be a synergistic response of more than one gut hormone[79].

Gut microbiota signatures as predictors of long-term outcomes in bariatric surgery

In a study by Gutiérrez-Repiso *et al*.[80], fecal samples of 24 patients who had undergone bypass surgery at least two years ago were studied. The authors reported that patients who would go on to show greater rates of weight loss and low weight maintenance in the long-term tended to have a higher diversity of core microbiota in the mid-term. Furthermore, the bacterial genera *Sarcina*, *Butyrivibrio*, *Alkaliphilus*, *Lachnospira*, *Pseudoalteromonas*, and *Cetobacterium* were more abundant in stool samples in patients for whom gastric bypass surgery was more successful in the long-term[80]. Nevertheless, another study by Fouladi *et al*.[81] failed to prove a significant difference in the microbiotas between subjects with successful and poor BMI reduction after Roun-en-Y Gastric Bypass surgery[81]. In the same study, Fouladi et al. transplanted fecal samples from patients with poor (PWL) and successful weight loss (SWL) in antibiotic-treated mice, reporting that mice transplanted with PWL feces tended to gain more weight despite exhibiting similar feeding behaviors[81]. Steinert *et al*. have reported a decreased mycobiotic diversity in fecal samples from patients before and after Roun-en-Y Gastric Bypass surgery[82].

MICRONUTRIENT DEFICIENCIES AFTER BARIATRIC SURGERY

After BS, the micronutrient status of patients further deteriorates, which, in turn, affects the structure and composition of GM[83]. Thus, after BS, more than 30% of patients develop nutritional deficiencies that may result in edema, hypoalbuminemia, anemia, and even peripheral neuropathy and Wernicke encephalopathy[83].

Unortunately, these deficiencies persist despite vitamin and mineral supplementation. The deficiency observed after BS including is affected by the eating behavior, the decreased absorption, SIBO, or poor compliance to the suggested optimization of diet[84].

There is strong evidence that after RYGB and VSG, food intake restriction, the reduced appetite, and gastrointestinal hormones changes are mechanisms for the observed weight loss[85]. VSG promotes gastric emptying and reduces gastroduodenal transit time, and decreases the release of hydrochloric acid and intrinsic factor. These effects, due to the gastric fundus resection, affect gastrointestinal motility and therefore, the release and dissolution of several vitamins and minerals are diminished[86].

Vitamin B_{12}

The anatomic alterations of the gastrointestinal tract due to BS lead to impaired release of both HCl and pepsin from the functional part of the remnant. In turn, this leads to diminished vitamin B_{12} absorption, as well as to less interaction of gastric content with parietal cells, which produce the intrinsic factor, causing malabsorption and deficiency of cobalamin[87, 88]. It has also been shown that the deficiency of intrinsic factor is the main driver of post-surgical B_{12} deficiency, although other molecules such as transcobalamin-1 may participate[89]. As expected, RYGB patients display a higher frequency of vitamin B_{12} deficiency (37–50%) than VSG patients (10–20%)[90]. It has been

reported that, despite adequate supplementation with physiological doses, B_{12} levels are found to decrease within a few months following BS, and therefore, administration of high doses of B_{12} is recommended right after bariatric surgery[91].

Folic Acid

It is expected that after BS, folate absorption should be impaired due to hypochlorhydria and altered pH in the proximal jejunum[92]. However, it has been reported that folic acid may be also synthesized by bacteria in the colon. It seems that it is absorbed throughout the small intestine and even the colon, with a lowering rate of absorption. Therefore, following RYGB, the administration of usual doses of supplement is sufficient to prevent or correct folate deficiency, because a compensatory mechanism of intestinal absorptive capacity is plausibly present[93].

Vitamin B_1 (thiamine)

Thiamine deficiency symptoms rapidly develop after only 20 days of insufficient oral intake, faster than for any other vitamins[94]. Hyperemesis, a symptom rather common after BS surgery, impairs B_1 absorption and thus its deficiency can appear despite any oral supplementation. A large variety of pathologies are associated with thiamine deficiency, including beriberi, neuropathy, and Wernicke encephalopathy[95], which may present a medical emergency.

Bariatric patients may present vitamin B_1 deficiency within six months following surgery. A study reported that from 118 cases of Wernicke encephalopathy detected postoperatively after either RYGB or VSG, almost 90% had hyperemesis[96]. A study reported that two years after RYGB, the thiamine levels were deficient in 18% of patients[96]. Regarding VSG patients, in a recent retrospective study, within one year after VSG, 25.7% of subjects showed decreased thiamine levels[97].

Vitamin D and Calcium

Following BS, bariatric patients have an increased risk for developing metabolic bone disease at any time for the rest of their lives. Furthermore, after BS, SIBO can also aggravate vitamin D deficiency[98]. As diminished poor acid secretion occurs after both RYGB and VSG, an impaired dissolution and solubilization of nutrients becomes present. Chronic vitamin D deficiency which subsequently leads to decreased bone mineral density has been shown three years following RYGB and VSG[99].

After VSG, vitamin D malabsorption might be the effect of diminished exposure of nutrients to the digestive mucosa[100]. Although VSG does not involve intestinal anatomy, calcium uptake might be hampered through several possible mechanisms such reduced calory intake, hypochlorhydria, or usage of proton pump inhibitors [100]. In a large cohort study including 999 subjects, the prevalence of hypocalcemia postoperatively was found in 3.6% of patients, with 15 patients (1.9%) undergoing RYGB, and 13 patients (9.3%) undergoing VSG. In the same study, the lowest calcium concentrations were shown after approximately 3 years in the RYGB group, and after 239 days in the VSG group, respectively. The daily calcium intake administered through was pporximately 1750mg[101].

Iron

Following RYGB, 18–53% of patients develop iron deficiency compared to 1–53% of patients after VSG[102]. This is rather expected after RYGB, as the duodenum, which is the most efficient area for iron absorption, is bypassed. A study including 72 post-RYGB patients reported red meat intolerance in 49.2%, 42.2%, 46.4%, and 39% of subjects after 1, 2, 3, and 4 postoperative years correspondingly[103]. Following VSG, the iron deficiency is dominated and defined by the malabsorption secondary to the amount of gastric resection which prevents reduction of Fe^{3+} to Fe^{2+}.

Several mechanisms underlie the pathogenesis of postsurgical iron deficiency: After ingestion, the gastric acidic environment enhances iron absorption by favoring its

ferrous form (2+), the sole state of iron that can be absorbed[104]. The reduced HCl release in the gastric pouch and administration of H_2 blockers significantly impair iron absorption[105]. Also, iron-rich alimentation after BS is largely decreased due to caloric restriction and food aversions, especially to red meat[87].

OTHER MICRONUTRIENT DEFICIENCIES

Fat-Soluble Vitamins

After BS, some deficiencies of fat-soluble vitamin (vitamin A, E, and K) levels in plasma are observed due to malabsorption[7], but the frequency of these deficiencies is low with rarely reported clinical manifestations[106, 107].

Vitamin A deficiency can be induced by diminished retinol and carotenoid intake due to calorie restriction. Additionally, the recommended low-fat diet following BS, contributes to poor absorption. Interestingly, cirrhosis observed in BS subjects may impede vitamin A storage and synthesis[107]. Thus, the prevalence of vitamin A deficiency following RYGB is apporixmately 10%[108]. However, no changes on serum vitamin A concentration or optical function following RYGB or VSG were reported in a recent study[109].

Zinc, Copper, and Selenium

A study analyzing micronutrient deficiencies after both RYGB and VSG during a follow-up for five years found reduced serum zinc concentrations in respectively 25.7% and 12.5% of patients[110].

Copper deficiency after RYGB has a 10% prevalence. The development of symptomatic hypocupremia after BS is uncommon among subjects who adhere to prescribed supplementation[111].

Selenium is a trace element and an important antioxidant (selenocysteine)[112]. Serum levels of zinc, selenium, and copper were stable following RYGB and VSG in subjects taking supplementation[113].

PROBIOTICS AND GUT MICROBIOTA: IMPLICATIONS FOR BARIATRIC PATIENTS

Probiotics are beneficial to the host even without inhabiting the gut or making major changes to gut microbiota[29]. The most administered probiotics are *Lactobacillus, Bifidobacterium,* and *Sacharomyces genera* phyla[114].

Although probiotic use is common postoperatively, studies on their efficacy after BS are scarce[115]. It is been reported that the high pH setting achieved after RYGB, allows for higher survival of probiotic bacteria during transition through the acidic milieu of the GI, thus making BS patients suitable candidates for probiotic therapy. Administration of probiotics appears to offer many beneficial effects to BS patients such as greater weight loss, decreased SIBO, improved vitamin synthesis and availability, and optimized micronutrient status[116].

CONCLUSION

BS, the most effective operation for severe obesity, is continuously expanding its applications. However, the role of gut microbiota on the host's metabolism and digestion is also widely recognized. Nevertheless, current understanding of the mechanisms that link obesity and concurrent changes in gut microbiota remains veiled and current data suggest that bariatric surgery can only partially restore the microbial imbalance.

The exact mechanisms that induce the GM changes after BS remain unclear since different factors including diet, weight loss, and surgery are involved. Moreover, side effects that are triggered from the SIBO effect may affect the weight loss process of the patients who underwent BS.

Still, the impact of BS is not well described, as microbiota alterations are not consistent, and they should be considered under the context of energy intake restriction and altered dietary quality. At the same time, no differences regarding GM modulation

were observed among the two most common weight loss surgery techniques (RYGB and VSG). In general, an increase in the phylum *Bacteroidetes* and *Proteobacteria* members, and a decrease in members of the phylum *Firmicutes* are the most consistently reported findings.

In brief, BS attempts to restore a healthier gut microbiota with a leaner metabolic profile, and this microbiota re-alignment could contribute to the observed reduced adipose tissue reduction, the increase of lean mass, and the reduction in obesity-related morbidity. However, the mechanisms by which microorganisms and their by-products restore the gut microbiota remains rather poorly understood. Finally, the prognostic significance of microbiota patterns for long-term outcomes after bariatric surgery needs further elucidation.

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