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 have allowed phylogenetic exploration and quantitative analyses of gut microbiome and improved our current understanding of the gut microbiota in health and disease. Its role in obesity and its changes following bariatric surgery have been highlighted in several studies. According to current literature, obesity is linked to a particular microbiota profile that grants the host an augmented potential for calorie 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.

Key Words: Bariatric surgery; Obesity; Gut microbiota; Micronutrient deficiency; Probiotics
Core Tip: Obesity represents a major cause of morbidity and mortality globally. Current knowledge suggests a connection between gut microbiota characteristics and obesity, while bariatric surgery has been shown to promote a healthier microbiota composition. However, the exact effects of these procedures remain unclear. In general, an increase in members of the phylum Bacteroidetes and Proteobacteria, and a decrease in members of the phylum Firmicutes is a common finding. This field of research can also inform clinicians’ predictions of outcomes before and after bariatric surgery through analysis of patterns in gut microbiota.

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INTRODUCTION

Obesity represents a huge health burden in society, and is linked with an increase in mortality rates[1]. Recent data suggest a crosstalk between gut microbiota (GM) and obesity, while obesity itself seems to be both a cause and a result of GM alterations[2]. In health, the GM 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 GM 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 have identified important qualitative and quantitative changes in the 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 phyla that includes gut microbiome modulations (and of their by-products) in obese subjects who undergo BS as treatment, are the aim of this review.

OBESITY

Obesity represents the discrepancy between caloric intake and energy expenditure 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 severity and is calculated by dividing the body weight (kg) by the square of height (m²) 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 classified by the World Health Organization into three categories; class I corresponds to a BMI of 30.00 to 34.99; class II between 35.00 and 39.99 and class III is a BMI that exceeds 40[14]. Additionally, a BMI > 50 kg m⁻² is termed superobesity. Regarding the treatment of obesity, it has been shown that in a time period of 2 years, most subjects reach 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 directly recovered from a sample such as from 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 microbiome concentrations are found in the intestine, the skin, and the oral cavity[20]. Of these sites, the GIT 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) cells[21]. However, more recent estimates suggest that the number of gut bacteria is of 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 GIT from 10^3 to 10^8 microbes in the stomach to 10^10 to 10^12 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 few[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 largest 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 collectively yield 2 million genes (100 times the number of human genes. 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 GM along with the host’s genotype and lifestyle, affect the pathophysiology of the disease and thus research interest in these associations has 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 in 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 high-fat diet for 28 d, 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 thus contributing to obesity and T2DM[34,35].

BARIATRIC SURGERY

Bariatric surgery modalities
When lifestyle and/or medication-based approaches are ineffective, BS is an option, as it is a highly effective therapeutic procedure for the treatment of obesity[36]. 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, vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BD), and BPD with duodenal switch (BPD/DS)[7,37].

Vertical banded gastroplasty
This is a restrictive procedure. An incision is made on the lesser curvature 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**

This is 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 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].

**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 glycemic control improves in 90% of recipients[44].

**VSG**

This is a restrictive procedure. VSG has increased in popularity as it is relatively easy to perform and a good clinical outcome is 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”), with 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 substantially reduced portion sizes. Sleeve creation has an impact on hormone regulation, decreasing blood ghrelin levels and enhancing a state of satiety. The average weight loss is 60% excess body weight after two years postoperatively, along with an improvement in associated comorbidities[42]. Both short- and medium-term research reports showed that VSG is almost as effective as RYGB in reducing body weight and improving glycemic control[10,47].

**BPD and BPD with duodenal switch (BPD and BPD/DS)**

This is 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].

Of 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 present in the general population[15]. Table 1 shows the 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 trial reported a weight loss following RYGB of 27% in 15 years, while non-operative approaches (lifestyle changes or pharmacological treatment) had no effect over this period. Controlled long-term studies (> 5 years) on 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 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. This increase was probably related to the GM changes observed after BS[50].

**THE MECHANISMS OF GASTRIC BYPASS**

The gastric bypass procedure is an artificial condition in which the intestinal mucosal energy outflow is variable and 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, food bypasses both the stomach and the duodenum, and the release of gut-derived hormones originating from these areas is altered, e.g., the release of glucose-dependent insulino tropic peptide from the duodenum. 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 acid levels and those of the intestinal microbiota: Bile acids regulate glucose metabolism causing the release of GLP-1, provoking the synthesis and release of...
| Roux-en-Y gastric bypass | Vertical sleeve gastrectomy |
|--------------------------|---------------------------|
| **Technique** | (1) Excision of lateral 70%-80% of stomach along the greater curvature; and (3) Approximately 100 mL gastric reservoir (sleeve) |
| **Mechanism of action** | (1) Alterations in: Gut hormones; Bile acids; Neural signaling; Gut microbiota; Gut-brain-endocrine; Adipocyte-brain axes; and (2) Results in reduced food intake, increased satiety and altered food preferences |
| **Advantages** | (1) Significant long-term weight loss (approximately 10% less than RYGB); (2) Glycemic control as effective as RYGB; (3) Maintain percent EWL in the long-term; (4) Hunger reduction and satiety; (5) Food preferences changes; (6) No anatomical rerouting of food; (7) Short length of stay (< 2 d); (8) Technically simpler than RYGB; and (9) Lower complication rate than RYGB |
| **Disadvantages** | (1) Anatomomtic leak can be difficult to manage; (2) Susceptible to long-term vitamin and/or mineral deficiencies (less common than with RYGB); (3) Precautionary lifelong vitamin and/or mineral supplementation; (4) Lifelong dietary changes; (5) Irreversible; and (6) Potential risk of Barrett esophagus |

EWL: excess weight loss; RYGB: Roux-en-Y gastric bypass.

GUT MICROBIOTA AFTER BARIATRIC SURGERY

A plethora of diseases are connected to GM 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 many microbial species of the GM.

Most often, a decrease in Firmicutes and an increase in Bacteroidetes and Proteobacteria, abundance is observed after BS[63]. Both RYGB and vertical banded gastroplasty, have comparable long-term effects on GM function and composition. Moreover, feces from BS patients were transplanted in germ-free mice, and the mice gained less fat when compared to reciprocal mice transplanted with GM from obese subjects. These findings show a causal relationship between GM and BS-induced weight reduction[64].

SIDE EFFECTS OF BARIATRIC SURGERY

The 1-year mortality rate after BS is 1% and the 5-year mortality rate is 6%[34]. 4% of patients after BS experience surgical complications during the first month[55,56]. These include anastomotic leakage, hemorrhage, perforation, infection and inner herniation[55]. However, the latter is considerably decreased when the closure of any mesenteric defect became 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 in a 5-year follow-up, a third of them still experienced pain[58]. It is important to clarify the underlying pathology following BS but its etiology remains 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 patients 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 after BS[61]. Several theories related to this have been proposed including enhanced B cell mass and function, lowered ghrelin levels, improved insulin sensitivity, and inadequate counter regulation[62]. Unfortunately, the side effects of hypoglycemia often persist for years and can decrease the patient’s quality of life.

Circulating exosome miRNAs (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 these, miRNA MiR-7, which has shown the most concrete post-surgical increase in studies, plays a role in the regulation of pancreatic beta-cell function in humans[53].

Fibroblast growth factor 19 which improves insulin sensitivity and glycemic control[51].

These findings show a causal relationship between GM and BS-induced weight reduction.
Another study employed GM transplantation from mice that underwent RYGB to sham-surgery germ-free mice, which provoked weight loss compared to recipients of GM from non-operated mice[65].

The increase in pH (following BS) in 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[67] summarized 14 clinical studies involving 222 subjects (RYGB = 146, VSG = 25, biliointestinal bypass = 30, vertical banded gastroplasty = 7, and adjustable gastric band = 14). Major changes included a reduction in the abundance of Faecalibacterium prausnitzii and an increase in E. coli. Following VSG, a decrease in the abundance of Firmicutes was observed, while after RYGB an increase in Bacteroidetes and Proteobacteria was observed.

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

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

**EFFECT OF BARIATRIC SURGERY ON SMALL INTESTINE BACTERIA**

Obese subjects after BS can develop small intestine bacterial overgrowth (SIBO), which is defined as greater than 10⁵ 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 to 40% following the procedure[72].

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

**EFFECT OF BARIATRIC SURGERY ON GUT HORMONES**

Typically, food 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, increased production of gut satiety hormones such as PYY and GLP-1, and a reduced increase in ghrelin takes place[76].

After a meal, both PYY and GLP-1 are, proportional to the consumed calories, released from the L cells of the distal small intestine[77]. Following BS, the postprandial PYY levels are increased and the new levels are correlated with 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 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, 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 from 24 patients who had undergone bypass surgery at least two years previously 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, Butyribrio, Alkaliphilus, Lachnospira, Pseudodelotonas, 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 microbiota between subjects with successful and poor BMI reduction after RYGB surgery[81]. In the same study,
Table 2 Changes in human gut microbiota following bariatric surgery

| ↑↑ | Akkermansia (Verrucomicrobia) | Bulleidia (Firmicutes) |
| ↓↑ | Escherichia (Proteobacteria) | Roseburia intestinalis (Firmicutes) |
| ↑↑ | Klebsiella (Proteobacteria) | Faecalibacterium prausnitzii (Firmicutes) |
| ↓↓ | Lactobacillus (Firmicutes) | Coprococcus comes (Firmicutes) |
| ↓↓ | Bifidobacterium (Actinobacteria) | Faecalibacterium prausnitzii (Firmicutes) |
| ↓↓ | Faecalibacterium prausnitzii (Firmicutes) | Coprococcus comes (Firmicutes) |

RYGB: Roux-en-Y gastric bypass; VSG: Vertical sleeve gastrectomy.

Table 3 Literature findings on the postoperative changes of gut microbiota

| Ref. | Postoperative GM changes | Increased abundance | Decreased abundance | Comments |
|------|--------------------------|---------------------|--------------------|----------|
| Graessler et al.[71], 2013 | Enterobacter, Citrobacter, Neisseria, Veillonella, Salmonella, Staphylococcus, E. coli | Faecalibacterium, Coprococcus, Helicobacter, Dichelostomum, Epimyces, Anaerostipes, Nakamuraella, Methanospirillum, Therminococcus | - |
| Kong et al [68], 2013 | Bacteroides, Alistipes, Escherichia | Firmicutes (Lactobacillus, Dorea, Blautia) Bifidobacterium | Increased richness of GM after RYGB | |
| Palleja et al [50], 2016 | Escherichia coli, Klebsiella pneumoniae, 10 species belonging to the genus Streptococcus, 4 from Veillonella, 2 from Alistipes, Bifidobacterium dentium, Enterococcus faecalis, F. nucleatum, and Akkermansia muciniphila | Faecalibacterium prausnitzii | - |
| Tremaroli et al.[64], 2015 | GammaProteobacteria; Several Proteobacteria (Escherichia, Klebsiella, Pseudomonas). E. coli tended to increase but was not statistically significant | Faecalibacterium, Clostridium difficile, Gemella sanguinis | - |

GM: Gut microbiota; RYGB: Roux-en-Y gastric bypass.

Fouladi et al[81] transplanted fecal samples from patients with poor weight loss (PWL) and successful weight loss in antibiotic-treated mice, and reported that mice transplanted with PWL feces tended to gain more weight despite exhibiting similar feeding behaviors. Steinert et al[82] reported decreased mycobiotic diversity in fecal samples from patients before and after RYGB surgery.

MICRONUTRIENT DEFICIENCIES AFTER BARIATRIC SURGERY

After BS, the micronutrient status of patients further deteriorates, which, in turn, affects the structure and composition of the 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].

Unfortunately, these deficiencies persist despite vitamin and mineral supplementation. The deficiencies observed after BS are affected by eating behavior, 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, reduced appetite, and gastrointestinal hormones changes are mechanisms for the observed weight loss[85]. VSG promotes gastric emptying, reduces gastroduodenal transit time, and decreases the release of hydrochloric acid and intrinsic factor. These effects, due to gastric fundus resection, affect gastrointestinal motility and therefore, the release and dissolution of several vitamins and minerals are diminished[86].

Vitamin B₁₂

The anatomic alterations of the GIT 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 B₁₂ absorption, as well as to less interaction of gastric content with parietal cells, which produce the intrinsic factor, causing
malabsorption and deficiency of cobalamin\cite{87,88}. It has also been shown that the deficiency of intrinsic factor is the main driver of post-surgical B$_2$ deficiency, although other molecules such as transcobalamin-1 may participate\cite{89}. As expected, RYGB patients display a higher frequency of vitamin B$_2$ deficiency (37%-50%) than VSG patients (10%-20\%)\cite{90}. It has been reported that, despite adequate supplementation with physiological doses, B$_2$ levels are found to decrease within a few months following BS, and therefore, administration of high doses of B$_2$ is recommended right after BS\cite{91}.

**Folic acid**

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

**Vitamin B$_1$ (thiamine)**

Thiamine deficiency symptoms rapidly develop after only 20 d of insufficient oral intake, faster than for any other vitamins\cite{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\cite{95}, which may present a medical emergency.

Bariatric patients may develop vitamin B$_1$ deficiency within six months following surgery. A study reported that in 118 cases of Wernicke encephalopathy detected postoperatively after either RYGB or VSG, almost 90\% had hyperemesis\cite{96}. A study reported that two years after RYGB, thiamine levels were deficient in 18\% of patients\cite{96}. In a recent retrospective study of VSG patients, 25.7\% of subjects showed decreased thiamine levels within one year after VSG\cite{97}.

**Vitamin D and calcium**

Following BS, bariatric patients have an increased risk of developing metabolic bone disease at any time during the rest of their lives. Furthermore, after BS, SIBO can also aggravate vitamin D deficiency\cite{98}. As diminished acid secretion occurs after both RYGB and VSG, impaired dissolution and solubilization of nutrients can develop. Chronic vitamin D deficiency which subsequently leads to decreased bone mineral density has been observed three years after RYGB and VSG\cite{99}.

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

**Iron**

Following RYGB, 18%-53\% of patients develop iron deficiency compared to 1%-53\% of patients after VSG\cite{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, respectively\cite{103}. Following VSG, iron deficiency is dominant and defined by malabsorption secondary to the amount of gastric resection which prevents reduction of Fe$^{2+}$ to Fe$^{3+}$.

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 only form of iron that can be absorbed\cite{104}. Reduced HCl release in the gastric pouch and administration of H$_2$ blockers significantly impair iron absorption\cite{105}. Also, iron-rich alimentation after BS is largely decreased due to caloric restriction and food aversions, especially to red meat\cite{87}.

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**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\cite{7}, but the frequency of these deficiencies is low with rarely reported clinical manifestations\cite{106,107}.

Vitamin A deficiency can be induced by diminished retinol and carotenoid intake due to caloric 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 \cite{107}. Thus, the prevalence of vitamin A deficiency following RYGB is approximately 10\% \cite{108}. However, no changes in serum vitamin A concentration or optical function following RYGB or VSG were reported in a recent study \cite{109}.

**Zinc, copper, and selenium**

A study analyzing micronutrient deficiencies after both RYGB and VSG during a follow-up of five years found reduced serum zinc concentrations in 25.7\% and 12.5\% of patients, respectively \cite{110}.

The prevalence of copper deficiency after RYGB is 10\%. The development of symptomatic hypocu-premia after BS is uncommon among subjects who adhere to the prescribed supplementation \cite{111}.

Selenium is a trace element and an important antioxidant (selenocysteine) \cite{112}. Serum levels of zinc, selenium, and copper were stable following RYGB and VSG in subjects receiving supplementation \cite{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 GM \cite{29}. The most common administered probiotics are *Lactobacillus*, *Bifidobacterium*, and *Sacharomyces general* \cite{114}.

Although probiotic use is common postoperatively, studies on their efficacy after BS are scarce \cite{115}. It is reported that the high pH setting after RYGB, allows 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 \cite{116}.

### CONCLUSION

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

The exact mechanisms that induce GM changes after BS remain unclear as different factors including diet, weight loss, and surgery are involved. Moreover, side effects that are triggered by the SIBO effect may also affect the weight loss process in patients who undergo BS.

The impact of BS is not well described, as microbiota alterations are not consistent, and they should be considered in 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 members of the phylum *Bacteroidetes* and *Proteobacteria*, and a decrease in members of the phylum *Firmicutes* are the most consistently reported findings.

In brief, BS attempts to restore a healthier GM with a leaner metabolic profile, and this microbiota realignment could contribute to the observed reduced adipose tissue reduction, the increase in lean mass, and the reduction in obesity-related morbidity. However, the mechanisms by which microorganisms and their by-products restore the GM are poorly understood. Finally, the prognostic significance of microbiota patterns on long-term outcomes after BS require further elucidation.

### FOOTNOTES

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REFERENCES

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol* 2019; 15: 288-298 [PMID: 30814686 DOI: 10.1038/s41574-019-0176-8]

2. Căitoi AF, Vodnar DC, Corina A, Nikolic D, Citarrella R, Pérez-Martínez P, Rizzo M. Gut Microbiota, Obesity and Bariatric Surgery: Current Knowledge and Future Perspectives. *Curr Pharm Des* 2019; 25: 2038-2050 [PMID: 31298152 DOI: 10.2174/13816128256661907090819037]

3. Pascale A, Marchesi N, Marelli C, Coppola A, Luzi L, Govoni S, Giustina A, Gazzaruso C. Microbiota and metabolic diseases. *Endocrine* 2018; 61: 357-371 [PMID: 29721802 DOI: 10.1007/s12020-018-1605-5]

4. Astrup A, Bügel S. Overfed but undernourished: recognizing nutritional inadequacies/deficiencies in patients with obesity. *Int J Obes (Lond)* 2019; 43: 219-232 [PMID: 29980762 DOI: 10.1038/s41366-018-0143-9]

5. Mohajeri MH, Brunner RJM, Rastall RA, Weersma RK, Harmsen HJM, Faan M, Eggersdorfer M. The role of the microbiome for human health: from basic science to clinical applications. *Eur J Nutr* 2018; 57: 1-14 [PMID: 29748817 DOI: 10.1007/s00394-018-1703-4]

6. Xu G, Song M. Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery. *Surg Obes Relat Dis* 2021; 17: 231-238 [PMID: 33036939 DOI: 10.1016/j.soard.2020.08.028]

7. Lapoli R, Lembo E, Saldalamacchia G, Avola CK, Angrisani L, Capaldo B. Bariatric surgery and long-term nutritional issues. *World J Diabetes* 2017; 8: 464-474 [PMID: 29204255 DOI: 10.4239/wjd.v8.i11.464]

8. Neylan CJ, Kamann U, Dempsey DT, Williams NN, Dunon KR. The Surgical Management of Obesity. *Gastroenterol Clin North Am* 2016; 45: 689-703 [PMID: 27837782 DOI: 10.1016/j.gtc.2016.07.006]

9. Xanthakos SA. Nutritional deficiencies in obesity and after bariatric surgery. *Pediatr Clin North Am* 2009; 56: 1105-1121 [PMID: 19930166 DOI: 10.1016/j.pcl.2009.07.002]

10. Al-Najim W, Docherty NG, le Roux CW. Food Intake and Eating Behavior After Bariatric Surgery. *Physiol Rev* 2018; 98: 1113-1141 [PMID: 29717927 DOI: 10.1152/physrev.00021.2017]

11. Gaddde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: Pathophysiology and Management. *J Am Coll Cardiol* 2018; 71: 69-84 [PMID: 29301630 DOI: 10.1016/j.jacc.2017.11.011]

12. Upadhyay J, Farr O, Perakakis N, Ghaly W, Mantzoros C. Obesity as a Disease. *Med Clin North Am* 2018; 102: 13-33 [PMID: 29156181 DOI: 10.1016/j.mcna.2017.08.004]

13. Björklund P, Fändriks L. The pros and cons of gastric bypass surgery - The role of the Roux-limb. *Best Pract Res Clin Gastroenterol* 2019; 40: 101638 [PMID: 31594646 DOI: 10.1016/j.bpcg.2019.101638]

14. Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, de Gonzalez AB, Cairns BJ, Huxley R, Jackson 2016; 776-786 [DOI: 10.1016/j.soard.2020.08.028]

15. Stefani N, Häring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? *Lancet Diabetes Endocrinol* 2016; 4: 249-258 [PMID: 28919065 DOI: 10.1016/S2213-8587(17)30292-9]

16. Chen EB, Cason C, Gilbert JA, Ho JK. Current State of Knowledge on Implications of Gut Microbiome for Surgical Conditions. *J Gastrointest Surg* 2018; 22: 1112-1123 [PMID: 29623674 DOI: 10.1007/s11605-018-3755-4]

17. Thomas S, Izard J, Walsh E, Batich K, Chongsathidkit P, Clarke G, Sela DA, Muller AJ, Mullin JM, Albert K, Gilligan JP, DiGuilio K, Dilbarova R, Alexander W, Prendergast GC. The Host Microbiome Regulates and Maintains Human Health: A Primer and Perspective for Non-Microbiologists. *Cancer Res* 2017; 77: 1783-1812 [PMID: 28292977 DOI: 10.1158/0008-5472.CAN-16-2929]

18. Knight R, Callewaert C, Marotz C, Hyde ER, Debelius JW, McDonald D, Sogin ML. The Microbiome and Human Health: from Basic Science to Clinical Applications. *Ann Rev Genomics Hum Genet* 2017; 18: 65-86 [PMID: 28375652 DOI: 10.1146/annurev-genom-083115-022438]

19. Li SS, Zha A, Benes V, Costea PI, Hercog R, Hildebrand F, Huerta-Cepas J, Nieuwdorp M, Salojarvi J, Voigt AY, Zeller G, Sunagawa S, de Vos W, Bork P. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. *Science* 2016; 352: 586-589 [PMID: 27126644 DOI: 10.1126/science.aad8552]

20. Sogin ML, Novotny ME, Fisher JL, Alcorn FC, Kier HM, Belev N, Kulyk J, Yokoyama W, Voigt AY, Zeller G, Sunagawa S, de Vos W, Bork P. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. *Science* 2016; 352: 586-589 [PMID: 27126644 DOI: 10.1126/science.aad8552]

21. Fändriks L. Roles of the gut in the metabolic syndrome: an overview. *J Intern Med* 2017; 281: 319-336 [PMID: 27991713 DOI: 10.1111/joim.12584]

22. O’Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, Crosthwaite G, Brown W. Long-Term Outcomes After Bariatric Surgery: A Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obes Surg* 2019; 29: 3-
Seeley RJ. Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity.

Stefanidis A, Belachew M, Scandola DA, Berger J, Toure M, Tschöp M, Woods SC, et al. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different.

Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers.

Stefater MA, Van Hul M, Lefort C, Depommier C, Rastelli M, Everard A. Microbial regulation of organismal energy homeostasis. Nat Metab 2019; 1: 34-46 [PMID: 32694818 DOI: 10.1038/s42258-018-0017-4]

Stefanidis A. Metabolic endotoxemia and diabetes mellitus: A systematic review. Metabolism 2017; 66: 133-144 [PMID: 28183445 DOI: 10.1016/j.metabol.2016.12.009]

Belachew M, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Pontén T, de Vos WM, Zucker JD, Raes J, Hansen T; METABIT consortium, Børgesen B, Wanning A, Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers. Nature 2013; 500: 541-546 [PMID: 23985870 DOI: 10.1038/nature12506]

Gravina G, Ferrari F, Nebbioli G. The obesity paradox and diabetes. Eat Weight Disord 2021; 26: 1057-1068 [PMID: 32954485 DOI: 10.4051/weightdis-020-0101-5]

Gomes JMG, Costa JA, Alfenas RCG. Metabolic endotoxemia and diabetes mellitus: A systematic review. Metabolism 2017; 68: 133-144 [PMID: 28183445 DOI: 10.1016/j.metabol.2016.12.009]

Tuomi K, Logomarsino JV. Bacterial Lipopolysaccharide, Lipopolysaccharide-Binding Protein, and Other Inflammatory Markers in Obesity and After Bariatric Surgery. Metab Syndr Relat Disord 2016; 14: 279-288 [PMID: 27282236 DOI: 10.1089/metbs.2015.0170]

Chioábárca D, Cátai AF, Copescu C, Miere D, Crișan G. Bariatric Surgery in Obesity: Effects on Gut Microbiota and Micronutrient Status. Nutrients 2020; 12 [PMID: 31963247 DOI: 10.3390/nu12102023]

Morino M, Toppino M, Bonnet G, Rosa R, Garrone C. Laparoscopic vertical banded gastroplasty for morbid obesity. Surg Endosc 2002; 16: 1566-1572 [PMID: 12063579 DOI: 10.1007/s00464-001-9196-1]

Goergen M, Arapis K, Limgha A, Schiltz M, Lens V, Azagra JS. Laparoscopic Roux-en-Y gastric bypass versus laparoscopic vertical banded gastroplasty: results of a 2-year follow-up study. Surg Endosc 2007; 21: 659-664 [PMID: 17180269 DOI: 10.1007/s00464-006-9081-z]

Belachew M, Legrand M, Vincent V, Lisonde M, De Docte N, Deschamps V. Laparoscopic adjustable gastric banding. World J Surg 1998; 22: 955-963 [PMID: 9717421 DOI: 10.1007/s002689900499]

Stefanidis A, Forrest N, Brown WA, Dixon JB, O’Brien PB, Juliane Kampe, Oldfield BJ. An investigation of the neural mechanisms underlying the efficacy of the adjustable gastric band. Surg Obes Relat Dis 2016; 12: 828-838 [PMID: 27090808 DOI: 10.1016/j.soard.2015.11.020]

Sawaya RA, Jaffe J, Friedenberg L, Friedenberg FK. Vitamin, mineral, and drug absorption following bariatric surgery. Curr Drug Metab 2012; 13: 1345-1355 [PMID: 22746302 DOI: 10.2174/138920012803341339]

Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut-brain axis. Neuropeptides 2012; 46: 261-274 [PMID: 22979996 DOI: 10.1016/j.npep.2012.08.005]

Sjöstöm L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, Ahlin S, Anveden Ä, Bengtsson C, Bergmark G, Bouchard C, Dahlgren S, Carlsson J, Lindroos AK, Lönnroth H, Narboro K, Näslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term cardiovascular events. JAMA 2012; 307: 56-65 [PMID: 22215166 DOI: 10.1001/jama.2011.1914]

Carlin AM, Zeni TM, English WJ, Haasvili AA, Genaw JA, Krause KR, Schram JL, Kole KL, Finks JF, Birkmeyer JD, Share D, Birkmeyer NJ; Michigan Bariatric Surgery Collaborative. The comparative effectiveness of sleeve gastrectomy, gastric bypass, and adjustable gastric banding procedures for the treatment of morbid obesity. Ann Surg 2013; 257: 791-797 [PMID: 23470577 DOI: 10.1097/SLA.0b013e3182879ded]

Jacobs DM, Gaudier E, van Duynhoven J, Vaughan EE. Non-digestible food ingredients, colonic microbiota and the impact on gut health and immunity: a role for metabolomics. Curr Drug Metab 2009; 10: 41-54 [PMID: 19149512 DOI: 10.2174/138920009787048353]

Stefater MA, Pérez-Tilve D, Chambers AP, Wilson-Pérez HE, Sandoval DA, Berger J, Toure M, Tschöp M, Woods SC,Seeley RJ. Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. Gastroenterology 2010; 138: 2426-2436, 2436.e1 [PMID: 20226189 DOI: 10.1053/j.gastro.2010.02.059]

Fontana MA, Wohlgemuth SD. The surgical treatment of metabolic disease and morbid obesity. Gastroenterol Clin North Am 2010; 39: 125-133 [PMID: 20202585 DOI: 10.1016/j.gtc.2009.12.010]

Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYG and SG: similar, yet different. J Endocrinol Invest 2019; 42: 117-128 [PMID: 29730732 DOI: 10.1007/s40618-018-0892-2]
Lamounier-Zepter V, Lohmann T, Wolf T, Bornstein SR. Metagenomic sequencing of the human gut microbiome before amino acids in obese women independent of weight loss or the presence of type 2 diabetes. 

Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Dane A, Harms A, Vreeken R, Hankemeier T, Smit JW, Y, Gu W, Deng X, Shen B, Yang H, Xu G, Bi Y, Lai S, Wang J, Qi L, Madsen L, Ning G, Kristiansen K, Wang W. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose microbiome and serum metabolome alterations in obesity and after weight-loss intervention. 

Ying X, Zhao X, Li W, Jia H, Lan Z, Li F, Wang R, Sun Y, Yang M, Shen Y, Jie Z, Li J, Chen X, Zhong H, Xie H, Zhang L, Kong LC. Roux-en-Y Gastric Bypass and Vertical Banded Gastroplasty Induce Long-Term Changes on the Human Microbiota. 

Davies NK, Donahoo WT. Chronic opioid use emerging after bariatric surgery. 

Raebel MA. Gastric Bypass Surgery for Obesity. 

Gribsholt SB, Pedersen AM, Svensson E, Thomesen RW, Richelsen B. Prevalence of Self-reported Symptoms After Gastric Bypass Surgery for Obesity, 151: 504-511 [PMID: 26747510 DOI: 10.1001/jamasurg.2015.5110] 

Greenstein AJ, O’Rourke RW. Abdominal pain after gastric bypass: suspects and solutions. 2011; 201: 819-827 [PMID: 21333269 DOI: 10.1067/j.amjsg.2010.05.007] 

Raebel MA, Newcomer SR, Bayliss EA, Boudreau D, DeBar L, Elliott TE, Ahmed AT, Pawloski PA, Fisher D, Toh S, Donahow WT. Chronic opioid use emerging after bariatric surgery. Pharmacoepidemiol Drug Saf 2014; 23: 1247-1257 [PMID: 24373580 DOI: 10.1002/pds.3625] 

Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, Kashyap SR; STAMPEDE Investigators. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med 2017; 376: 641-651 [PMID: 28199805 DOI: 10.1056/NEJMoa160869] 

Abdeen G, le Roux CW. Mechanism Underlying the Weight Loss and Complications of Roux-en-Y Gastrointestinal Bypass. Review. Obes Surg 2016; 26: 410-421 [PMID: 26350712 DOI: 10.1007/s00130-015-1945-7] 

David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Badinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014; 505: 559-563 [PMID: 24363217 DOI: 10.1038/nature12820] 

Tremaroli V, Karlsson F, Werling M, Ståhlman M, Kovatcheva-Datchary P, Obbers T, Fründers L, le Roux CW, Nielsen J, Backhed F. Roux-en-Y Gastric Bypass and Vertical Banded Gastric Restriction Induce Long-Term Changes in the Human Gut Microbiota Contributing to Fat Mass Regulation. Cell Metab 2015; 22: 228-238 [PMID: 26244932 DOI: 10.1016/j.cmet.2015.07.009] 

Liu AP, Pazuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass lead weight loss and adiposity. Sci Transl Med 2013; 5: 178ra41 [PMID: 23536013 DOI: 10.1126/scitranslmed.3005687] 

Medina DA, Pedreros JP, Turiel D, Quezada N, Pimentel F, Escalona A, Garrido D. Distinct patterns in the gut microbiota after surgical or medical therapy in obese patients. PeerJ 2017; 5: e3443 [PMID: 28649469 DOI: 10.7717/peerj.3443] 

Davies NK, O'Sullivan JM, Plank LD, Murphy R. Altered gut microbiome after bariatric surgery and its association with metabolic benefits: A systematic review. Surg Obes Relat Dis 2019; 15: 656-665 [PMID: 30824335 DOI: 10.1016/j.soard.2019.01.023] 

Kong LC, Tap J, Aron-Wisniewsky J, Pelloux V, Basdevant A, Bouillot JL, Zucker JD, Clément K. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr 2013; 98: 16-24 [PMID: 23719559 DOI: 10.3945/ajcn.113.108743] 

Liu R, Hong J, Xu X, Feng G, Zhang D, Gu Y, Shi J, Zhao S, Liu W, Wang X, Xia H, Liu Z, Cui B, Liang P, Xu L, Jin J, Ying X, Zhao X, Li W, Jia H, Lan Z, Li F, Wang R, Sun Y, Yang M, Shen Y, Jie Z, Li J, Chen X, Zhong H, Xie H, Zhang Y, Gu W, Deng X, Shen B, Yang H, Xu G, Bi Y, Lai S, Wang J, Qi L, Madsen L, Ning G, Kristiansen K, Wang W. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat Med 2017; 23: 859-868 [PMID: 28628112 DOI: 10.1038/nm.4358] 

Lips MA, Van Klinken JB, van Harmelen V, Dhari HK, ’t Hoen PA, Laros JF, van Ommen GJ, Janssen IM, Van Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Danes A, Harms A, Vreeken R, Hankemeier T, Smit JW, Pijl H, Willemsen van Dijk K. Roux-en-Y gastric bypass surgery, but not calorie restriction, reduces plasma branched-chain amino acids in obese women independent of weight loss or the presence of type 2 diabetes. Diabetes Care 2014; 37: 3150-3156 [PMID: 25152504 DOI: 10.2337/diabetes.2014-0195] 

Grässler J, Qin Y, Zhang H, Zhang J, Licinio J, Wong ML, Xu A, Chavakis T, Bornstein AB, Ehrhart-Bornstein M, Lamouir-zepter V, Lohmann T, Wolf T, Bornstein SR. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters.
Pharmacogenomics J 2013; 13: 514-522 [PMID: 23022991 DOI: 10.1038/tpj.2012.43]

DiBiase JK. Nutritional consequences of small intestinal bacterial overgrowth. *Practical Gastroenterology* 2008; 32: 15-28

Adike A, DiBiase JK. Small Intestinal Bacterial Overgrowth: Nutritional Implications, Diagnosis, and Management. *Gastroenterol Clin North Am 2018*; 47: 193-208 [PMID: 29413012 DOI: 10.1016/j.gtc.2017.09.008]

Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol (N Y)* 2007; 3: 112-122 [PMID: 21960830]

Grace E, Shaw C, Whelan K, Andreyev HJ. Review article: small intestinal bacterial overgrowth--prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther 2013*; 38: 674-688 [PMID: 23097561 DOI: 10.1111/apt.12456]

Goldstone AP, Miras AD, Scholtz S, Jackson S, Neff KJ, Penicaud L, Geoghegan J, Chihina N, Duriguel G, Bell JD, Meillon S, le Roux CW. Link Between Increased Satiety Gut Hormones and Reduced Food Reward After Gastric Bypass for Obesity. *J Clin Endocrinol Metab 2016*; 101: 599-609 [PMID: 26580235 DOI: 10.1210/jc.2015-2665]

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature 2002*; 418: 650-654 [PMID: 12167864 DOI: 10.1038/nature00887]

Meguid MM, Glade MJ, Middleton FA. Weight regain after Roux-en-Y: a significant 20% complication related to PYY. *Nutrition 2008*; 24: 832-842 [PMID: 18725080 DOI: 10.1016/j.nut.2008.06.027]

Russell-Jones D, Gough S. Recent advances in incretin-based therapies. *Clin Endocrinol (Oxf)* 2012; 77: 489-499 [PMID: 22804841 DOI: 10.1111/j.1365-2265.2012.04483.x]

Gutiérrez-Repiño CaM, Isabel and de Hollanda, Ana and Martin-Nuñez, Gracia and Vital, Josep and Tina, Francisco. Gut microbiota specific signatures are related to the successful rate of bariatric surgery. American journal of translational research 2019; 11: 942-952

Fouldi F, Brooks AE, Fodor AA, Carroll IM, Bulik-Sullivan EC, Tsilimigras MCB, Sioda M, Steffen KJ. The Role of the Gut Microbiota in Sustained Weight Loss Following Roux-en-Y Gastric Bypass Surgery. *Obes Surg 2019*; 29: 1259-1267 [PMID: 30604078 DOI: 10.1007/s11695-018-03653-y]

Steinert RE, Rehman A, Sotoo Lima EF, Agamennone V, Schuren FHJ, Gero D, Schreiner P, Vonlanthen R, Ismaeil A, Tzafos S, Hosa H, Vetter D, Misselwitz B, Bueter M. Roux-en-Y gastric bypass surgery changes fungal and bacterial microbiota in morbidly obese patients-A pilot study. *PloS One 2020*, 15: e0236936 [PMID: 32735609 DOI: 10.1371/journal.pone.0236936]

Bal BS, Finelli FC, Shope TR, Koch TR. Nutritional deficiencies after bariatric surgery. *Nat Rev Endocrinol 2012*; 8: 544-556 [PMID: 22525731 DOI: 10.1038/nrendo.2012.48]

Ogata H, Goto S, Sato K, Fujibuchi W, Bono H, Ikenhisa M. KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Res 1999*; 27: 29-34 [PMID: 9847135 DOI: 10.1093/nar/27.1.29]

Patel JJ, Mundis MS, Hurt RT, Wolfe B, Martinbire RG. Micronutrient Deficiencies After Bariatric Surgery: An Emphasis on Vitamins and Trace Minerals [Formula: see text]. *Nutr Clin Pract 2017*; 32: 471-480 [PMID: 28696642 DOI: 10.1177/0884533617712226]

Ferraz AAAB, Carvalho MRC, Siqueira LT, Santa-Cruz F, Campos JM. Micronutrient deficiencies following bariatric surgery: a comparative analysis between sleeve gastrectomy and Roux-en-Y gastric bypass. *Rev Col Bras Cir 2018*; 45: e2016 [PMID: 30504099 DOI: 10.1590/0100-6991-e-20182016]

Nielsen MJ, Rasmussen MR, Andersen CB, Nexo E, Moesrup SK. Vitamin B12 transport from food to the body's cells--a sophisticated, multistep pathway. *Nat Rev Gastroenterol Hepatol 2012*; 9: 345-354 [PMID: 22547309 DOI: 10.1038/nrgastro.2012.76]

Decker GA, Swain JM, Crowell MD, Scolapio JS. Gastrointestinal and nutritional complications after bariatric surgery. *Am J Gastroenterol* 2007; 102: 2570-81 [PMID: 17660325 DOI: 10.1111/j.1572-0241.2007.01421.x]

Sala P, Belarmino G, Torrinhas RS, Machado NM, Fonseca DC, Ravacci GR, Ishida RK, Guarda JF, de Moura EG, Sakai P, Santo MA, da Silva ID, Pereira CC, Logullo AF, Heymsfield S, Giannella-Neto D, Witzberg DL. Gastrointestinal Transcriptomic Response of Metabolic Vitamin B12 Pathways in Roux-en-Y Gastric Bypass. *Clin Transl Gastroenterol 2017*; 8: e212 [PMID: 28055029 DOI: 10.1038/ctg.2016.67]

Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A 2006*; 102: 11070-11075 [PMID: 16038367 DOI: 10.1073/pnas.0509478102]

Kornarou LS, Hvas CL, Abild CB, Richelsen B, Nexo E. Early changes in sleeve gastrectomy and Roux-en-Y gastric bypass. *Clinical Transl Gastroenterol* 2019; 10: 23287118

Visentin M, Diop-Bove N, Zhao R, Goldman ID. The intestinal absorption of folates. *Annu Rev Physiol 2014*; 76: 251-274 [PMID: 24512081 DOI: 10.1146/annurev-physiol-020911-153251]

Milman N. Intestinal absorption of folic acid - new physiologic &amp; molecular aspects. *Indian J Med Res 2012*; 136: 725-728 [PMID: 23287118]

Stroh C, Meyer F, Manger T. Beriberi, a severe complication after metabolic surgery - review of the literature. *Obes Facts 2014*; 11: 246-252 [PMID: 25095897 DOI: 10.1159/000366012]

Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. *Ann Surg 2008*; 248: 714-720 [PMID: 18948797 DOI: 10.1097/SLA.0b013e3181884308]

Becker DA, Balker LF, Galeta SL. The Neurological Complications of Nutritional Deficiency following Bariatric Surgery. *J Obes 2012*; 2012: 608534 [PMID: 22970351 DOI: 10.1152/2012.608534]

Clement RH, Katsanis VG, Palepu R, Leeth RR, Leath TD, Roy BP, Vickers SM. Incidence of vitamin deficiency after laparoscopic Roux-en-Y gastric bypass in a university hospital setting. *Am Surg 2006*; 72: 1196-202; discussion 1203 [PMID: 17216818 DOI: 10.1177/000313480607201209]

Williams SE. Metabolic bone disease in the bariatric surgery patient. *J Obes 2011*; 2011: 636416 [PMID: 21274274 DOI: 10.1155/2011/634614]
99 Diaz de Barboza G, Guizzardi S, Tolosa de Talamoni N. Molecular aspects of intestinal calcium absorption. World J Gastroenterol 2015; 21: 7142-7154 [PMID: 26109800 DOI: 10.3748/wjg.v21.i23.7142]

100 Schafer AL, Weaver CM, Black DM, Wheeler AL, Chang H, Szefc GV, Stewart L, Rogers SJ, Carter JT, Posselt AM, Shoback DM, Sellmeyer DE. Intestinal Calcium Absorption Decreases Dramatically After Gastric Bypass Surgery Despite Optimization of Vitamin D Status. J Bone Miner Res 2015; 30: 1377-1385 [PMID: 25640580 DOI: 10.1002/jbmr.2467]

101 Schafer AL. Vitamin D and intestinal calcium transport after bariatric surgery. J Steroid Biochem Mol Biol 2017; 173: 202-210 [PMID: 28027914 DOI: 10.1016/j.jsbmb.2016.12.012]

102 Gletsu-Miller N, Wright BN. Mineral malnutrition following bariatric surgery. Adv Nutr 2013; 4: 506-517 [PMID: 24038242 DOI: 10.2986/adv.4.5.1204 [PMID: 24185753 DOI: 10.1016/j.jand.2012.11.013]

103 Jericó C, Breton I, García Ruiz de Gordejuela A, de Oliveira AC, Rubio MÁ, Tinahones FJ, Vidal J, Vilarrasa N. [Diagnosis and treatment of iron deficiency, with or without anaemia, before and after bariatric surgery]. Endocr Nutrit 2016; 63: 32-42 [PMID: 26611153 DOI: 10.1016/j.endonu.2015.09.003]

104 Santiago P. Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview. ScientificWorldJournal 2012; 2012: 846824 [PMID: 22654638 DOI: 10.1100/2012/846824]

105 Engebretsen KV, Blom-Høgestøl IK, Hewitt S, Risstad H, Moun B, Kristinsson JA, Mala T. Anemia following Roux-en-Y gastric bypass for morbid obesity; a 5-year follow-up study. Scand J Gastroenterol 2018; 53: 917-922 [PMID: 30231804 DOI: 10.1080/03655521.2018.1489892]

106 Poitou Bernert C, Ciangura C, Coupaye M, Czernichow S, Bouillot JL, Basdevant A. Nutritional deficiency after gastric bypass: diagnosis, prevention and treatment. Diabetes Metab 2007; 33: 13-24 [PMID: 17258928 DOI: 10.1016/j.diabet.2006.11.004]

107 Zalesin KC, Miller WM, Franklin B, Madugai D, Rao Buragadda A, Boura J, Nori-Janoss K, Chengelis DL, Krause KR, McCullough PA. Vitamin a deficiency after gastric bypass surgery: an underreported postoperative complication. J Obes 2011; 2011 [PMID: 20871833 DOI: 10.1155/2011/760693]

108 Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. Aliment Pharmacol Ther 2014; 40: 582-609 [PMID: 25075533 DOI: 10.1111/apt.12872]

109 Cuesta M, Pelaz L, Pérez C, Torrejón MJ, Cabrerizo L, Matía P, Pérez-Ferre N, Sánchez-Penaute A, Torres A, Rubio MA. Fat-soluble vitamin deficiencies after gastric surgery could be misleading if they are not appropriately adjusted. Nutr Hosp 2014; 30: 118-123 [PMID: 25137270 DOI: 10.3305/nh.2014.30.1.7471]

110 Moizé V, Andreu A, Flores L, Torres F, Ibarzabal A, Delgado S, Lacy A, Rodriguez L, Vidal J. Long-term dietary intake and nutritional deficiencies following sleeve gastrectomy or Roux-En-Y gastric bypass in a mediterranean population. Adv Nutr 2013; 4: 400-410 [PMID: 23438491 DOI: 10.1016/j.ajand.2012.11.013]

111 Myint ZW, Oo TH, Thein KZ, Tun AM, Saeed H. Copper deficiency anemia: review article. Ann Hematol 2018; 97: 1527-1534 [PMID: 29959467 DOI: 10.1007/s00277-018-3407-5]

112 Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for human health. Metallomics 2014; 6: 25-54 [PMID: 24185753 DOI: 10.1039/c3mt0185g]

113 Papamargaritis D, Asheim ET, Sampson B, le Roux CW. Copper, selenium and zinc levels after bariatric surgery in patients recommended to take multivitamin-supplementation. J Trace Elem Med Biol 2015; 31: 167-172 [PMID: 25271186 DOI: 10.1016/j.jtemb.2014.09.005]

114 Azad MAK, Sarkar M, Li T, Yin J. Probiotic supplements in the modulation of Gut Microbiota: An Overview. Biomed Res Int 2018; 2018: 9478630 [PMID: 29854813 DOI: 10.1155/2018/9478630]

115 Sherf-Dagan S, Zelber-Sagi S, Zilberman-Schapira G, Webb M, Buch A, Keidar A, Raziel A, Sakran N, Gottstein D, Goldenberg N, Mahdi JA, Pevsner-Fischer M, Zmora N, Dori-Bachash M, Segal E, Elinav E, Shibolet O. Probiotics administration following sleeve gastrectomy surgery: a randomized double-blind trial. Int J Obes (Lond) 2018; 42: 147-155 [PMID: 28852205 DOI: 10.1038/s41366-017-210]

116 Woodard GA, Encarnacion B, Downey JR, Peraza J, Chong K, Hernandez-Boussard T, Morton JM. Probiotics improve outcomes after Roux-en-Y gastric bypass surgery: a prospective randomized trial. J Gastrointest Surg 2009; 13: 1198-1204 [PMID: 19381735 DOI: 10.1007/s11605-009-0891-x]
