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World J Gastrointest Pathophysiol 2022 May 22; 13(3): 59-113



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The primary aim of the *World Journal of Gastrointestinal Pathophysiology* (WJGP, *World J Gastrointest Pathophysiol*) is to provide scholars and readers from various fields of gastrointestinal pathophysiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGP mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal pathophysiology and covering a wide range of topics including disorders of the esophagus, stomach and duodenum, small intestines, pancreas, biliary system, and liver.

INDEXING/ABSTRACTING

The WJGP is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Gastrointestinal Pathophysiology

ISSN

ISSN 2150-5330 (online)

LAUNCH DATE

April 15, 2010

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Kusum K Kharbanda, Tsutomu Nishida, Somchai Amornvotin

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<https://www.wjgnet.com/2150-5330/editorialboard.htm>

PUBLICATION DATE

May 22, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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

Konstantinos Georgiou, Nikolay A Belev, Tilemachos Koutouratsas, Hector Katifelis, Maria Gazouli

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dilek ON, Turkey; Salimi M, Iran; Yang M, United States

Received: November 10, 2021

Peer-review started: November 10, 2021

First decision: December 12, 2021

Revised: December 21, 2021

Accepted: March 25, 2022

Article in press: March 25, 2022

Published online: May 22, 2022



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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.

Citation: Georgiou K, Belev NA, Koutouratsas T, Katifelis H, Gazouli M. Gut microbiome: Linking together obesity, bariatric surgery and associated clinical outcomes under a single focus. *World J Gastrointest Pathophysiol* 2022; 13(3): 59-72

URL: <https://www.wjgnet.com/2150-5330/full/v13/i3/59.htm>

DOI: <https://dx.doi.org/10.4291/wjgp.v13.i3.59>

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, archaeobacteria, 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 microbe 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 10^1 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 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 (BPD), 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 intragastric lamina propria 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 gastrojejunostomy 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[13]. 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 insulinotropic 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

Table 1 Comparison of the two main bariatric surgery procedures

	Roux-en-Y gastric bypass	Vertical sleeve gastrectomy
Technique	(1) 15-30 mL gastric pouch; (2) Gastrojejunostomy (GJ); (3) Jejunojunal anastomosis (Roux-en-Y); (4) 30-50 cm distal to the ligament of Treitz; and (5) Remnant disconnected but left <i>in situ</i>	(1) Excision of lateral 70%-80% of stomach along the greater curvature; and (3) Approximately 100 mL gastric reservoir (sleeve)
Mechanism of action	(1) Instantaneous food transfer to small intestine, altering: 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	(1) Alterations in: Gut hormones; Bile acids; Neural signaling; Gut microbiota; Gut-brain-endocrine; Adipocyte-brain axes; and (2) Results in reduced food intake, hunger, increased satiety and altered food preferences
Advantages	(1) Significant long-term weight loss; (2) Glycemic control improvement in 90% of cases; (3) Maintain percent EWL in the long term; (4) Hunger reduction and satiety; (5) Food preferences changes; and (6) Increases energy expenditure	(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) Technically complex (two anastomoses) compared with AGB or VSG; (2) Higher complication rate than AGB or LSG; for example, anastomotic leak or dumping syndrome can occur; (3) Longer length of stay; (4) Long-term vitamin and/or mineral deficiencies (for example, vitamin B12, iron, calcium or folate); (5) Requires lifelong vitamin and/or mineral supplementation; (6) Lifelong dietary changes; (7) Increases alcohol addiction and suicide rates; and (8) postprandial hypoglycemia	(1) Anastomotic 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.

fibroblast growth factor 19 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 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].

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 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 and 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.

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].

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 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 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 deconjugation 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*, *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 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

↑/↓	RYGB	VSG
↑	<i>Akkermansia</i> (Verrucomicrobia)	<i>Bulleidia</i> (Firmicutes)
↑	<i>Escherichia</i> (Proteobacteria)	<i>Roseburia intestinalis</i> (Firmicutes)
↑	<i>Klebsiella</i> (Proteobacteria)	<i>Faecalibacterium prausnitzii</i> (Firmicutes)
↓	<i>Lactobacillus</i> (Firmicutes)	<i>Coprococcus comes</i> (Firmicutes)
↓	<i>Bifidobacterium</i> (Actinobacteria)	
↓	<i>Faecalibacterium prausnitzii</i> (Firmicutes)	
↓	<i>Coprococcus comes</i> (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 <i>et al</i> [71], 2013	<i>Enterobacter</i> , <i>Citrobacter</i> , <i>Neurospora</i> , <i>Veillonella</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E. coli</i> tended to increase	<i>Faecalibacterium</i> , <i>Coprococcus</i> , <i>Helicobacter</i> , <i>Dictyostelium</i> , <i>Epidinium</i> , <i>Anaerostipes</i> , <i>Nakamurella</i> , <i>Methanospirillum</i> , <i>Thermomicrobium</i>	-
Kong <i>et al</i> [68], 2013	<i>Bacteroides</i> , <i>Alistipes</i> , <i>Escherichia</i>	Firmicutes (<i>Lactobacillus</i> , <i>Dorea</i> , <i>Blautia</i>) <i>Bifidobacterium</i>	Increased richness of GM after RYGB
Palleja <i>et al</i> [50], 2016	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , 10 species belonging to the genus <i>Streptococcus</i> , 4 from <i>Veillonella</i> , 2 from <i>Alistipes</i> , <i>Bifidobacterium dentium</i> , <i>Enterococcus faecalis</i> , <i>F. nucleatum</i> , and <i>Akkermansia muciniphila</i>	<i>E. prausnitzii</i>	-
Tremaroli <i>et al</i> [64], 2015	Gammaproteobacteria; Several Proteobacteria (<i>Escherichia</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>); <i>E. coli</i> tended to increase but was not statistically significant	3 species of Firmicutes; (<i>Clostridium difficile</i> , <i>Clostridium hiranonis</i> , <i>Gemella sanguinis</i>)	-

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[87,88]. It has also been shown that the deficiency of intrinsic factor is the main driver of post-surgical B₁₂ deficiency, although other molecules such as transcobalamin-1 may participate[89]. As expected, RYGB patients display a higher frequency of vitamin B₁₂ deficiency (37%-50%) than VSG patients (10%-20%)[90]. It has been reported that, despite adequate supplementation with physiological doses, B₁₂ levels are found to decrease within a few months following BS, and therefore, administration of high doses of B₁₂ is recommended right after BS[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 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[93].

Vitamin B₁ (thiamine)

Thiamine deficiency symptoms rapidly develop after only 20 d of insufficient oral intake, faster than for any other vitamins[94]. Hyperemesis, a symptom rather common after BS surgery, impairs B₁ 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 develop vitamin B₁ 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[96]. A study reported that two years after RYGB, thiamine levels were deficient in 18% of patients[96]. In a recent retrospective study of VSG patients, 25.7% of subjects showed decreased thiamine levels within one year after VSG [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[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[99].

Following 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 as reduced calorie intake, hypochlorhydria, or the use of proton pump inhibitors[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[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, respectively[103]. Following VSG, iron deficiency is dominant and defined by malabsorption secondary to the amount of gastric resection which prevents reduction of Fe³⁺ to Fe²⁺.

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[104]. Reduced HCl release in the gastric pouch and administration of H₂ 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 approximately 10%[108]. However, no changes in 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 of five years found reduced serum zinc concentrations in 25.7% and 12.5% of patients, respectively[110].

The prevalence of copper deficiency after RYGB is 10%. The development of symptomatic hypocupremia after BS is uncommon among subjects who adhere to the 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 receiving 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 GM [29]. The most common administered probiotics are *Lactobacillus*, *Bifidobacterium*, and *Sacharomyces genera*[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 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[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 re-alignment 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

Author contributions: Georgiou K, Koutouratsas K, and Katifelis H wrote the original draft, Gazouli M, and Belev NA edited and reviewed the final version of the manuscript; all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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S-Editor: Liu JH

L-Editor: Webster JR

P-Editor: Liu JH

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