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Gut Microbiota in Obesity and Bariatric Surgery: Where Do We Stand?

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Contents

Ευχαριστίες

Ευχαριστώ πολύ τον κύριο επιβλέποντα αυτής της διπλωματικής εργασίας Ομότιμο Καθηγητή κ. Ε. Λέανδρο, για την ηθική συμπαράσταση και την εμπιστοσύνη που μου έδειξε με την ανάθεση του θέματος της παρούσας διπλωματικής εργασίας. Το προσωπικό του ενδιαφέρον και η επιστημονική του συμβολή έπαιξαν καθοριστικό ρόλο σε όλα τα στάδια αυτής της εργασίας, της οποίας η πραγματοποίηση θα ήταν ανέφικτη χωρίς την ενεργό του συμπαράσταση.

Ιδιαίτερα θα ήθελα να εκφράσω την ευγνωμοσύνη μου προς την Καθηγήτρια Βιολογίας κ. Μ. Γαζούλη και τους Καθηγητές Χειρουργικής κ. Κ. Τούτουζα και κ. Γ. Θεοδωρόπουλο, οι οποίοι συμμετείχαν ενεργά σε πολλά από τα στάδια της προσπάθειάς μου αφιερώνοντας μεγάλο μέρος του πολύτιμου χρόνου τους και προσφέροντάς μου εξαιρετική καθοδήγηση. Η συνεισφορά τους στην ερευνητική διαδικασία διαδραμάτισαν πολύ σημαντικό ρόλο στην εκπόνηση της παρούσας διπλωματικής εργασίας.

Ευγνώμων επίσης είμαι προς τους διευθυντές αυτού του μεταπτυχιακού προγράμματος Καθηγητές Χειρουργικής κ. Γ. Ζωγράφο και Δ. Θεοδώρου γιατί μου επέτρεψαν να συμμετάσχω στο Πρόγραμμα Μεταπτυχιακών Σπουδών (Π.Μ.Σ.) «Προηγμένη Λαπαροσκοπική – Βαριατρική Χειρουργική», δίνοντάς μου τη δυνατότητα να διευρύνω τους ερευνητικούς και γνωσιακούς μου ορίζοντες. Θερμά τους ευχαριστώ για όλες τις εποικοδομητικές συζητήσεις που είχα μαζί τους.

Εύχομαι αυτή η διπλωματική εργασία να συνεισφέρει, έστω και ελάχιστα, στην αποτελεσματικότερη κατανόηση της επίδρασης του μικροβιώματος του εντέρου στην παχυσαρκία και στη βαριατρική χειρουργική με σκοπό τη βελτίωση της ποιότητας ζωής του πάσχοντα.

Περίληψη

Στη μεταβιομηχανική εποχή μας, ο επιπολασμός της παχυσαρκίας εκρήγνυται παγκοσμίως, με αυξανόμενη νοσηρότητα και θνησιμότητα.

Το μικροβίωμα του εντέρου του ανθρώπου διαδραματίζει βασικό ρόλο στις φυσιολογικές, διατροφικές, μεταβολικές, και ανοσολογικές λειτουργίες του ανθρώπινου σώματος, και λόγω αυτής της σε πολλαπλά επίπεδα δράσης του ορισμένοι συγγραφείς το θεωρούν σαν ένα νέο, αυτοδύναμο, ανεξάρτητο εικονικό όργανο. Χάρις στη μεγάλη πρόοδο στη φυλογενετική έρευνα και τον ποσοτικό προσδιορισμό του μικροβιώματος του εντέρου μέσω της σύγχρονης αλληλουχίας υψηλής απόδοσης, η κατανόησή μας για το μικροβίωμα του εντέρου τόσο στην υγεία όσο και τις ασθένειες προχωρά γρήγορα και αρκετές μελέτες έχουν εξετάσει το ρόλο του στην παχυσαρκία και τις αλλαγές που επισυμβαίνουν μετά από βαριατρική χειρουργική επέμβαση.

Υπάρχουν αυξανόμενες ενδείξεις ότι η παχυσαρκία σχετίζεται με ένα συγκεκριμένο προφίλ του μικροβιώματος του εντέρου που παρέχει στον ξενιστή μια αυξημένη ικανότητα έκλυσης θερμίδων και μειωμένη μικροβιακή ποικιλότητα του εντέρου. Ωστόσο, ο μηχανισμός μέσω του οποίου τα μικρόβια του εντέρου και τα υποπροϊόντα τους επηρεάζουν την παχυσαρκία παραμένουν βασικά ανεξερεύνητοι και επομένως απαιτείται περισσότερη έρευνα για την καλύτερη κατανόηση της εμπειρικά παρατηρούμενης σχέσης μεταξύ των μεταβολών των μικροβίων του εντέρου και της παχυσαρκίας.

Από την άλλη πλευρά, οι βαριατρικές χειρουργικές επεμβάσεις, όπως η γαστρική παράκαμψη Roux-en-Y και η επιμήκης γαστρεκτομή, είναι οι πλέον αποτελεσματικές παρεμβάσεις για την επίτευξη έντονης και παρατεταμένης απώλειας βάρους και για την ομαλοποίηση του μεταβολισμού της γλυκόζης σε παχύσαρκους ασθενείς. Η βαριατρική χειρουργική φαίνεται να αποκαθιστά ένα υγιέστερο μικροβίωμα με πιο λιτή μεταβολική κατατομή και αυτή η αναδιάταξη των μικροβίων συμβάλλει ενδεχομένως στη μειωμένη μάζα λιπώδους ιστού, στην αύξηση της μη λιπώδους μάζας και στην επίλυση συμπαρομαρτούντων νοσημάτων, μεταβολές όπως αυτές που παρατηρούνται μετά από επέμβαση βαριατρικής χειρουργικής. Ο ακριβής μηχανισμός δεν είναι γνωστός, αλλά θα

μπορούσε να δρα τροποποιώντας τη δομή του χολικού οξέος και επίσης να μεταβάλλει την κυκλοφορία του εντεροηπατικού χολικού οξέος. Επιπλέον, ο μεταγραφικός παράγοντας ενεργοποιημένου χολικού οξέος Farnesoid X (FXR), είναι ζωτικής σημασίας για τις θετικές επιδράσεις της βαριατρικής χειρουργικής στην απώλεια βάρους και τη βελτίωση του γλυκαιμικού ελέγχου. Ωστόσο, πρόσφατα δεδομένα έδειξαν ότι το μικροβίωμα του εντέρου δεν αποκαθίσταται πλήρως μετά από επέμβαση βαριατρικής χειρουργικής. Επιπλέον, μη αναγνωρισμένοι δευτερεύοντες στόχοι, όπως το πεπτίδιο FGF15/19 που προέρχεται από το έντερο, ενδέχεται να μπορούν να ερμηνεύσουν τα θετικά μεταβολικά αποτελέσματα της βαριατρικής χειρουργικής.

Συμπερασματικά, απαιτούνται περισσότερες τυχαιοποιημένες ελεγχόμενες δοκιμές και μεγαλύτερες προοπτικές μελέτες, που να συμπεριλαμβάνουν σαφώς καθορισμένες ομάδες ασθενών για τον καλύτερο προσδιορισμό των συσχετίσεων μεταξύ του μικροβιώματος του εντέρου, της παχυσαρκίας και της βαριατρικής χειρουργικής.

Abstract

The prevalence of obesity is exploding worldwide in our post-industrial era, with increasing morbidity and mortality.

The human gut microbiome exhibits a cardinal role in nutritional, physiological, metabolic, and immunological functions of the human body, and due to this multiplexity some authors consider it as an independent virtual organ by itself. Due to the big progress in phylogenetic investigation and quantification of gut microbiome through modern high-throughput sequencing, our understanding of the gut microbiome in health and diseases is rapidly advancing, and several studies have examined its role in obesity and its changes that occur following bariatric surgery.

There is growing evidence that obesity is associated to a specific profile of the gut microbiome which confers to the host an augmented ability for calories extraction, and reduced gut microbial diversity. However, the mechanism through which the gut microbiota and their by-products affect obesity remain mainly undiscovered and therefore more research is required to better comprehend the empirically observed connection between gut microbiome alterations and obesity.

On the other hand, bariatric surgery procedures, such as Roux-en-Y gastric bypass and vertical sleeve gastrectomy, are the most effective interventions for achieving pronounced and sustained weight loss and to normalize glycemic metabolism in obese patients. Bariatric surgery interventions are restoring a healthier microbiome, a leaner metabolic profile and this microbe rearrangement potentially contributes to the observed fat mass reduction, lean mass increase, and resolution of co-morbidities such as those observed following bariatric surgery. The exact mechanism is not certain, but it could be mediated by altering the enterohepatic bile acid circulation as well as altering the bile acid structure. Moreover, the bile acid activated farnesoid X transcription factor (FXR), is crucial for the beneficial effects of bariatric surgery on weight loss and glycose control improvement. However, recent data showed that the gut microbiota is not fully restored after bariatric surgery. Additionally,

unidentified downstream targets such as the gut derived peptide FGF15/19, may potentially explain the positive metabolic effects of bariatric surgery.

More randomized controlled trials and larger prospective studies including well-defined cohorts are necessary to better identify the associations between the gut microbiome, obesity, and bariatric surgery.

Keywords: bariatric surgery; obesity; gut microbiota; micronutrient deficiency; probiotics.

Introduction

Obesity is an enormous health problem in our modern society as it is associated with increased morbidity and mortality(1). Recently, research produced a vast amount of data suggesting a bidirectional interplay between gut microbiota (GM) and obesity, with the latter considered as both a cause and/or a consequence of gut microbiota disorders(2). In the healthy human, gut microbiota is involved in energy intake, adjustment of glucose and lipid homeostasis, as well as in the micronutrients and vitamins composition(3). This GM balance is disrupted in obesity thus presenting with a series of pathological manifestations, such as chronic inflammation, increased insulin resistance, and metabolic disturbances(2,3). Furthermore, obesity is associated with significant vitamins and minerals deficiencies, which aggravate gut microbiota synthesis and function(4,5).

Bariatric surgery (BS) is, for the time being, the sole long-term successful therapeutic option treatment of morbid obesity(6). Several studies report a significant change in the structure and diversity of GM after BS. Additionally, subjects who underwent BS, present some micronutrient deficiencies which could result to serious deficiency related syndromes(7,8), the most common being anemia (10–74%) and neurological disfunctions (5–9%)(9).

However, except the substantial GM alteration after BS, several other factors coexist impairing the postoperative nutritional status of the bariatric patients: the significantly energy-restricted higher protein intake and adequate nutritional supplementation diet, and the anatomical and physiology impairment of the gastrointestinal tract (GIT) with explicit alterations in food digestion and absorption induced by the type of procedure performed(6,7). Therefore, after BS, these patients require a consistent follow-up focused on the prevention of the above side effects, by modulating gut microbiota and prescribing appropriate nutritional supplementation.

The complicated interaction between obesity and GM phylae, and the modulation of the gut microbiota and of their by-products balance produced in obese subjects who undertake bariatric surgery as a therapeutic measure, represent the main focus in this thesis.

Obesity

Recent research is showing that each human body hosts a unique set of associated microorganisms which contribute essentially to maintain health and metabolic balance of the subject.

Due to the contemporary modern living style providing easy access to high energy food consumption and low demanding of physical activity, the prevalence of obesity has exploded. Obesity due to an imbalance of calories ingestion, basal metabolism, and energy expenditure(10). Obesity can be broadly defined as being the end result of the discrepancy between calories consumption and energy expenditure. Numerous genetic, behavioral and environmental factors have been suggested as obesogenic(11). Furthermore, obesity is associated with type 2 diabetes (T2DM), hypertension, dyslipidemia and cardiovascular disease, as well as sleep apnea, musculoskeletal disorders, some forms of cancer, impaired fertility, and with increased incidence of mood disturbances, anxiety, and other psychiatric disorders(12). Obesity increases mortality and its associated comorbidities, so that today in our modern societies, obesity associated diseases kill more individuals than undernourishment and starvation(13). Thus, except the burden that obesity provokes to the individual, it also represents a major health and economic load on the health care systems into both developed and developing countries(14).

Worldwide, the term Body Mass Index (BMI) is used for classifying obesity and is calculated by dividing the body weight (kg) by the square of height (m^2) of the individual. In adults, a BMI between 18.5 to 25 kg m^{-2} is considered as normal; overweight is BMI 25 to 30, while obesity is defined as BMI over 30 kg m^{-2}. The WHO have classified obesity into three classes, where class I relates to a BMI 30.00 to 34.99; class II is between 35.00 and 39.99, while a BMI over 40.00 kg m^{-2} is regarded as class III obesity(12). Additionally, a BMI >50 kg m^{-2} is sometimes termed superobesity.

Regarding obesity treatment, although substantial weight reduction can be achieved by lifestyle alterations such as diet and increased physical activity, it has been shown that those lifestyle changes are hampered on the long term(15). Indeed, the main issue is to keep the

reduced body weight on the long term, as it has been reported that within 1-2 years most subjects reclaim the weight lost, and furthermore, they usually exceed the pretreatment levels. Additionally, the anti-obesity drugs have several limitations due to adverse events and contraindications especially in cardiac and cerebrovascular diseases). Therefore, for morbidly obese patients, BS is the unique, effective in the long term procedure to lose weight, and to reestablish metabolic health(16). The term bariatric surgery is introduced which can be defined as a surgical intervention in the gastrointestinal tract for a weight reducing purpose.

Gut Microbiota in Healthy Subjects

Glossary of microbiome-related terms.

Microbes are found in every surface of the body that is exposed to the external environment, including the skin, respiratory, gastrointestinal, and genitourinary tracts(17).

The ecological community of symbiotic (promoting the health of the host), commensal (neutral to the host health, without benefit nor negative effects), and pathogenic microorganisms that share our body consists the microbiome(18). The term microbiota comprises the sum of all species which form microbial communities, such as bacteria, archea, fungi and protists. When referring to a specific organ, the term is preceded by the said location, for example, the term 'gut microbiota' refers to the intestinal tract(19).

The term 'microbiome' is also commonly referring to the microbiota (i.e., the microorganisms themselves). The study of all microbial DNA of a sample (i.e. the genetic material) directly recovered from a sample such as the gut is called metagenomics. The metagenome, i.e., the collective genome of the microbiota encompasses over 100 times the total amount of genes existing in the human genome, thus containing approximately 10-fold more genes in each microbiome(18). The term 'shotgun metagenomics' describes the process during which the total DNA of a sample is fragmented in a random manner and thereafter subjected to next-generation sequencing. This process generates primer-independent and unbiased sequencing data which can then be analyzed by means of various reference-based and/or reference-free methods. Thus, shotgun metagenomics targets all DNA material in a sample and produce relative abundance information for all genes, functions and organisms(17).

Under normal conditions, the GM is kept under a balanced equilibrium between the organisms involved in promoting the health of the host (symbionts), those holding no benefit or negative effects (commensals) and finally, organisms prone to induce

inflammation (pathobionts)(20). In a healthy state, the GM is in a stable equilibrium while any imbalance of the gut bacterial ecosystem, is called dysbiosis(21).

Gut microbiota under normal conditions.

Under healthy conditions in adult humans the microbial composition appears to remain constant(22). As previously stated, the human microbiota incorporates all the microorganisms that reside in every surface of the body that is exposed to the external environment. The largest microbe concentrations are found in the intestine, the skin and in the oral cavity(23). Among those body sites, the gastrointestinal tract is the most densely colonized organ. It is reported that the gut of a healthy subject contains approximately 1–1.5 kg of microbes, corresponding to about 10^{14} bacteria, i.e. exceeding about 10 times more the number of body cells(24). There are approximately 1000 species of microbes colonizing the gut, with microbial density increasing along the GI tract from 10^{1} to 10^{4} microbes in the stomach and the duodenum, 10^{4} to 10^{8} cells in the jejunum and ileum, to 10^{10} to 10^{12} cells per gram in the colon and feces(18).

Due to the antimicrobial action of hydrochloric acid and nitric oxide, both the stomach and the small intestine contain just a small amount of microbes(25,26). On the contrary, the large intestine is presenting better milieu for symbiotic microbes, achieving better conditions to extract energy as well as essential elements from the lumen bulk after digestion/absorption occurring in the small intestine(27,28). The bigger number of living microbes is located in the colon but due to the impermeable adherent mucus layer, the direct contact with the epithelium is prevented(29).

The microbiome includes bacteria, fungi, and archaea(30). It is estimated that in the gut there are about a thousand bacterial species which have about 2000 genes per species, yielding to approximately 2 million genes, which is 100 times the number of nearly 20.000 human genes. The number above is in line with the actual extent of microbial gene catalogues found in MetaHIT and the Human Microbiome Project(31).

During the whole life, the structure and the function of GM are influenced to a different

degree from many factors starting from birth (such as the delivery method), to the diet followed during childhood and adult age as well as the use of antibiotics(32). An analysis of the LifeLines Deep cohort using metagenomic shotgun sequencing of the GM demonstrated a multifactorial involvement among the microbiome and a plethora of extrinsic and intrinsic parameters, including 60 dietary factors, 31 intrinsic factors, 19 drug categories, 12 diseases, and four smoking categories, all together accounting for 18.7% of the inter-individual variation of the gut microbiota. It was also found that diet plays a significant role that alters GM(33). It is estimated that about 4.5% of BMI is attributable to the GM(5).

The majority of microorganisms in the GIT of humans is a diverse community of bacteria, viruses, archea, fungi and eukaria(34). Gut microbiota are bacteria and belong to two phyla, the *Firmicutes* (64 % encompassing gram-positive genera, e.g., *Clostridium, Ruminococcus, Lactobacillus, Butyrivibrio, Anaerostipes, Roseburia*, and *Faecalibacterium* and the *Bacteroidetes* (23 % containing gram-negative genera, e.g., *Bacteroides, Porphyromonas,* and *Prevotella*)(35). The other phyla occupying the digestive tract include *Proteobacteria (*8 % including gram-negative genera, e.g., *Helicobacter and Escherichia*), *Actinobacteria* (3 % encompassing gram-negative genera, e.g., *Bifidobacterium*), and smaller amounts of *Fusobacteria*, *Spirochaetes*, *Verrucomicrobia* (gram-negative species Akkermansia muciniphila) and *Lentisphaerae* phyla(36). The methanogens, *Methanobrevibacter* and *Methanosphaera* are the most dominant archaeal groups(37,38). Finally, archaea and fungi are less than 1 % of the GM. The two common fungal phyla in the gut include *Ascomycota* (which includes the genera *Candida* and *Saccharomyces*) and *Basidiomycota*(39,40). Overall, the highest concentrations are found into the colon with the majority of bacteria being anaerobes such as *Bacteroides, Porphyromonas, Bifidobacterium, Lactobacillus*, and *Clostridium* (genera that belong to the most abundant phyla: *Bacteroidetes, Actinobacteria*, and *Firmicutes*)(41). The GM has also its own energy demands and consumes energy from the contents of the gut lumen thus enhancing energy utilization(42). Collectively, the gut microorganisms, are considered to constitute a powerful 'organ' capable to influence most physiological functions of the human body(37,42).

GI microbiota are of crucial importance in the nutritional, physiological, metabolic, and immunological procedures of the entire human body. The GM encompasses different genes

involved in carbohydrates metabolism (glucose, galactose, fructose, arabinose, mannose, xylose, starch and sucrose), thus producing important nutrients which could not be synthesized otherwise, such as short-chain fatty acids (SCFA)(43)**,** vitamins (vitamin K, vitamin B_{12}, folic acid), certain amino acids(44,45), neurotransmitters(46), and regulation of gastrointestinal hormones(47,48). The above properties of the GM have pushed some authors to regard it as an independent virtual organ by itself(49). The microbiome encodes specific enzymes capable to provoke fermentation of the indigestible carbohydrates mentioned above, that is 10–30% approximately of the ingested energy as well as the main fermentation products i.e. SCFAs (e.g., acetate, propionate, and butyrate), which are at about 90–95% absorbed in the colon representing approximately about 6–10% of the energy needs of the human body(50).

SFCA is then transferred to the liver where it is converted to triacylglycerols and finally deposited in adipocytes by mediation of fasting-induced adipose factor (FIAF) or angiopoietin-like protein 4 (ANGPTL4), which is a lipoprotein lipase (LPL) inhibitor(40). Normally, the GM downregulates the expression of FIAF/ANGPTL4 from the intestine, which subsequently increases LPL activity, and therefore the breakdown of triacylglycerol into free fatty acids is occurring thus advocating the deposition of triglycerides into the fat cells(51). Therefore, beneficial GM are essential to maintain the immune homeostasis of the human gut and preventing infections. Furthermore, beneficial GM can enhance the proliferation of epithelial cell, angiogenesis within the intestine, and key metabolic functions(42).

The G protein-coupled receptors (GPCRs), such as GPR41, GPR43, and GPR109A can be bind to various molecules and ligands and this action is triggered by SCFA(52). Thus, through stimulation of the GPR41 and GPR43 receptors by SCFA, a triggering of the anorexigenic hormones production occurs, i.e. of peptide YY (PYY) and glucagon-like peptide 1 (GLP-1), which are launching the gut to brain communication (53,54). Additionally, GM participate in the metabolism of glycans, amino acids, xenobiotics and biosynthesis of vitamins and isoprenoids(37).

The GM, through induction of the insulin-like growth factor 1 (IGF-1), is also involved in promoting bone formation and resorption(55).

Between 2013 and 2017, more than 12.900 publications were published studying the GM, a number highlighting that this field of research is blossoming and that a necessity for advancement is underway(56). Human microbiome investigations are focusing to understand the underlying mechanisms, and to develop novel clinical interventions(57).

The human microbiome is not constant, but rather changes with age, diet, and health status. It has been reported that the GM interacts with the host both in health and disease in a lot of ways, including:

1. Modulating the inflammatory host response to the gut
2. Synthesizing small molecules and proteins that are absorbed by the host.
3. Changing the amount of available energy in the diet.

The research of GI microbiota has blossomed enormously recently. This is due to the big progress in phylogenetic investigation and quantification of GM through modern high-throughput sequencing. The recent use of cost-effective, culture-independent molecular techniques (i.e., 16s rDNA sequencing or whole-genome sequencing/metagenomics) on fecal samples enabled for the first time to study accurately and reliably the dynamics of the host–GM interactions. In whole-genome shotgun sequencing**,** the entire DNA in a given sample is fragmented, sequenced, and then remapped into the original genome(58). This information is then compared with preexisting databases to identify species and genes. This method has the advantage of identifying all present species and genes. This method is computationally intense, requiring a considerable amount of bioinformatic mapping(58). One such freely available knowledge base for systematic analysis of gene functions in terms of the networks of genes and molecules is the Kyoto Encyclopedia of Genes and Genomes (KEGG) (http://www.genome.ad.jp/kegg/). It uses different databases to assign functional meanings to genes and genomes and thus predicts the higher level functional changes as KEGG pathway maps(59). However, these studies are valuable since they may provide the most clinically relevant data because they are able to identify gene networks that may be overexpressed in a particular microbiome, for instance vitamin synthesis or decomposition, giving important clues to the physiology changes of the host. However, basic scientific research is based mainly on rodent models and cell cultures, but their relevance for human

physiology and clinical conditions remains unknown as very few studies have validated the translation of rodent-based data to a human context in a 'head-to-head' fashion.

In contrast to human genetics which have been unsuccessful to explain the obesity epidemic, the GM can classify individuals as lean or obese with over 90% accuracy, although this result depends on using the correct methods(60,61). Also, it is worth to note that recent findings support that GM could be implemented as a new marker of cardiovascular disease(62).

Additionally, the GM exhibits a significant role in the defense against pathogens as the high microbial content found in the large bowel poses a major challenge to the mucosal immune system. In fact, the intestinal mucosa must tolerate commensal microbiota as well as dietary antigens and eliminate pathogens successfully. The GM products are crucial in order to protect the host from various diseases(63) as well as shaping systemic immune homeostasis(64). In a healthy state, GM, by producing antimicrobial compounds, keeps the barrier intact and it present anti-inflammatory action which protects the epithelial cells against pathogens(32,41). This action is intermediated through Toll-like receptors (TLR) which can induce the pro-inflammatory factors production and delivery, for instance as the tumor necrosis factor alpha (TNFα) and interleukins 1 and 6 (IL1 and IL6)(65). The development of this peripheral production requires the presence of GM in the colon. Although the exact mechanism of this anti-inflammatory process is not well clarified, several microbe components have been detected to increase their expansion and function, including SCFAs (especially butyrate) and polysaccharide A of *Bacteroides fragilis*(64).

The mechanism on how the beneficial bacteria prevent dysbiosis and maintain balance in healthy state is not known. An example is *Clostridium difficile* which under normal conditions is present in the large intestine in a commensal state not causing any disease. *Clostridium difficile* colonize and release the exotoxins TcdA and TcdB which can trigger colitis appearance in susceptible subjects(66). Recently, a study showed that microcins, which are small size proteins released by numerous bacteria, can restrict the expansion of competing *Enterobacteriaceae* and thus avoiding inflammatory bowel disease(67).

Indoleamine 2,3-dioxygenase-1 (IDO1) is a metabolic enzyme which provides a beneficial effect in combating infections and acts as a mediator of acquired immune tolerance. There are indications that IDO1 is likely to exhibit an integral but circumstantial role in the balance between homeostasis and dysbiosis(68). Dysbiosis can affect oncogenesis, tumor progression, and the response to cancer therapy. One well-studied model of the dysbiosis/cancer connection is that after repeated intra-abdominal infections, the use of antibiotics, or both, they are leading to an increased incidence of colorectal cancer(67). Thus, the metabolic potential of the GM is considered as vital to the process of transformation to malignancy.

GM is both a producer and a consumer of vitamins: Prototrophs (”producers”) are microbes which are able to synthesize vitamins de novo, in contrast to other microbes that require exogenous vitamins provision, called auxotroph (”consumers”)(68). Some common microbes (i.e. *Bacteroides, Enterococcus, Bifidobacterium*) have an auxotrophic behavior although they can produce most of the soluble vitamins of the B complex (cobalamin, thiamine, pyridoxine, biotin, folate, nicotinic acid, pantothenic acid) and vitamin K_2(69). However, it must be noted that the de novo biosynthesis of small micronutrient molecules is demanding a high consumption of energy and therefore bacteria prefer, when available, to absorb those molecules from the surrounding environment(70).

As mentioned before, calorie restriction is causing rapid changes in microbial diversity and function. It has been documented in animal studies that diet develops bacterial phylotypes which are positively correlated with longevity. Moreover, it has been shown that bacteria of the *Lactobacillus* phyla increase in animals which are on low-fat diet, and this leads to a decrease of phylotypes which are negatively correlated with lifespan(71). It has been shown that the GM quickly responds to both directions of weight alterations (gain/reduction) as the structure of the food consumed is of fundamental importance for the composition of GM(65). Notably, it has been shown that short-term consumption of an entirely animal-based diet increased the abundance of bile-tolerant microorganisms, including *Alistipes*, *Bilophila* and *Bacteroides* while it decreased the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia spp*, *Eubacterium rectale* and *Ruminococcus bromii*)(72).

In summary, the gut microbiota has the capacity to cover the human metabolic needs acting as an energy supplier and as a provider of certain vitamins and micronutrients to the host(72). Our understanding of the gut microbiota in health and diseases is advancing rapidly, and several studies have examined the role of the GM in obesity and their change which occurs following BS, although the differences in GM found in obesity and after BS, so far have been mostly limited to simple comparisons(59).

Gut Microbiota in Obese Subjects

It has been found that the gut microbiome together with host genotype and lifestyle, contribute to the pathophysiology of obesity and therefore, there is an increasing research interest exploring possible associations between obesity and GM(73-75).

A lot of scientific evidence has been presented during the last decade on the role of GM in obesity. It seems that an amphidromous interrelation exists between obesity and gut microbiota, and obesity being considered as both a cause and a consequence of the gut microbiota shift. However, the question still remain on what comes first, the microbiota shift or the obesity, as well as the magnitude of this bidirectional correlation(2,76). Several studies performed in mice have shown an interplay between body weight and gut microbiota. It has been demonstrated that this "obese microbiota" pattern is a transferable element, at least in rodents. Thus in a study, a significant increase in body fat of germ-free (GF) mice implanted with microbiota harvested from the cecum of ob/ob mice has been shown, when compared to mice transplanted with a GM from lean rodents(77). Specifically, transferring GM from genetically obese mice provoked within 2 weeks a 47% increase of fat mass, while the inoculation from lean mice augmented fat mass just by 26%(78).

It has been reported that GF mice, i.e., mice born and raised in sterile environment without any commensal bacteria, comprise 42% less total body fat when compared to mice with normal GM, although the GF mice daily diet was 29% more than their counterparts. Moreover, GM transfer from conventionally raised mice to GF ones, resulted in 60% increase of total body fat and insulin resistance despite being on a low food diet(79).

Furthermore, the same group reported that the GM of obese mice showed an increased abundance of sensing and digestion of carbohydrate genes, as well as increased SCFA levels. These findings are suggesting that GM is an added factor contributing to the obesity onset(80). The importance of GM composition in the induction of obesity has been proven as a high-polysaccharide/high-fat diet leading to weight/fat gain, induce a GM shift when compared to rodents on a high-carbohydrate/low-fat diet. Additionally, the same authors

reported that a low in carbohydrate and fat diet which limits weight gain and reduces obesity can increase *Bacteroidetes* abundance, and reduce fat deposition(81)**.** However, those findings are questioned by Fleissner et al. who reported that the absence of GM is not protecting against diet-induced obesity(82).

Additionally, apart the composition, it is the diversity of GM that has been related to obesity. Comparing obese and normal weighted Danish subjects, those who had reduced GM diversity, with microbial gene size less than 480,000 (median 600,000), had more adipose tissue, showed insulin and leptin resistance, and had dyslipidemia when compared to their equivalent group which had huge gene numbers. Also, obese subjects with low gene counts had the tendency to become gradually overweight over time as compared to those with high numbers of genes, indicating that a low GM diversity characterizes a subset of patients at bigger risk for obesity and related comorbidities(79).

There are several factors contributing on how the GM affect obesity, such as the nutrients metabolism. For instance, hippurate, a microbial metabolism of dietary polyphenols derivative, is reported to be associated with *Eubacterium dolichum* and visceral fat mass(82).

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 to act as a contributor to diet-induced obesity(83).

There are still unknown mechanisms of how some factors can influence GM and its association to obesity. For instance we still don't know the effect of gender (84). In addition, sometimes we only have empirical observations: In children before reaching the age of 2 years, the administration of three or more courses of antibiotic therapy that disrupt GM composition, is linked to an augmented risk of early childhood obesity(85).

The disruption of the gut microbiota balance observed in obesity is correlated with insulin resistance, chronic inflammation, and metabolic disturbances which further alter GM structure and are increased by the concomitant shift in GM production of vitamins(4). For instance, it has been shown that metformin (used for type II diabetes management) changes

the rodents' GM and restore the diminished quantities of *Akkermansia muciniphila* which decreases the negative effect of the diet on the gut barrier, and therefore reduces metabolic endotoxemia, and improves insulin sensitivity(32). It has been shown *Akkermansia muciniphila* is decreased in obese subjects and administration of those bacteria is beneficial to the host. It is worth to note that for exercising its beneficial effects only the membrane protein Amuc_1100 of the bacterium is needed(84). Moreover, metformin changes several SCFA producing microbiota including *Butyrivibrio*, *Bifidobacterium bifidum*, *Megasphaera*, and *Prevotella*(86).

Another beneficial bacterium for weight loss is *Christensenella* as it has been shown that its abundance into the human intestine reduces BMI and it can induce weight loss when administered to mice(60).

It has been reported that 75% of patients with severe obesity have low microbial gene richness (MGR), a finding which is related with increased BMI, inflammation and insulin resistance(87). It has been show that in these patients MGR is improved after a short-term energy-restricted diet(88).

Phylogenetic analysis of GM of three groups (normal weight, obese, and post-RYGB subjects) revealed the presence of six main bacterial phyla. Most of the bacteria were *Firmicutes* and *Bacteroidetes*, while the remaining dispersed among *Proteobacteria, Actinobacteria, Fusobacteria*, and *Verrucomicrobia*. The distribution of these bacteria in the intestines of the study groups differs greatly. More specifically, *Prevotellaceae* from the *Bacteroidetes* family and *Erysipelotrichaceae* from *Firmicutes* phyla, are mostly abundant in obese subjects. As *Prevotellaceae* is only found in obese individuals it is considered "obese specific" while in contrast, *Fusobacteria* and the family *Enterobacteriaceae* within Proteobacteria were found only in the RYGB group(89).

All these data provide evidence that obesity is related to a change of the GM structure and to a disorder deviating from the normal function, with both leading to an augmented energy production from the ingested food. Since this GM dysbiosis is involved from the onset of

obesity, it is reasonable to expect that restoring the disturbed GM could result to a metabolic state improvement(2).

Regarding humans, a milestone study showed that 12 obese subjects were initially exhibiting less *Bacteroidetes* and more *Firmicutes* than their lean counterparts(90). When the subjects assigned to caloric-restricted diet (fat- or carbohydrate-restricted), an increase of *Bacteroidetes* and a concomitant decrease of *Firmicutes* occurred, regardless of the kind of diet implied. Most importantly, the increased richness of *Bacteroidete*s showed a good correlation with the percentage of weight loss observed and not with the diet switch(91). A recently published study showed that 75% of the candidates to BS, displayed a low GM gene abundance and this finding correlated with increased fat mass of the trunk and related comorbidities (T2DM, hypertension etc.)(92).

Apart from the decreased diversity of GM observed in obese subjects, it seems that they carry more aerotolerant bacteria, which are capable to produce products which can be easily converted to SCFAs. An imbalanced GM is capable to result in weight gain through its potential to extract calories from non-digestible nutrients which escape from ingestion into the small bowel and can then be transformed into digestible forms that are either excreted in feces or finally reabsorbed and subsequently transferred and stored to the liver until needed(11,93). Bacterial fermentation of carbohydrate and proteins within the large bowel produces SCFAs mainly butyrate, propionate, and acetate(94,95). Both butyrate and propionate can be used as energy sources of the epithelial cells, and furthermore, they are both able to activate intestinal gluconeogenesis (IGN)(96). Additionally, acetate plays a role for the growth of other bacteria which are involved in cholesterol metabolism and lipogenesis. Furthermore, acetate may be engaged in central regulation of appetite(97). Therefore, although under normal conditions the involvement of gut microbiota in energy supply is rather small(80), it seems that through SCFA production, it can provide additional energy to the host, thus resulting in the expansion of adipose tissue mass(11).

Several studies in obese rodents support the above GM mechanism leading to augmented fermentation and increased SCFA production and therefore to the development of obesity(98,99). However, the hypothesis of bigger SCFA production acting as a trigger for

the onset of obesity is still on debate as some studies showed the opposite, i.e. the increased fermentation produced by the GM plays a protecting role against fat mass increase and obesity appearance(2).

Additionally, the GM is inhibiting adenosine monophosphate-activated protein kinase (AMPK) which stimulates fatty acid oxidation in peripheral tissues(100). Thus, AMPK inhibition downregulates fatty acid oxidation, causes decrease of insulin sensitivity and increases lipogenesis, cholesterol and triglyceride synthesis(100). Additionally, the increased AMPK activity seems to prevent GF mice from diet-induced obesity(101). The ability to regulate the choline bioavailability, an essential nutrient for the synthesis of phosphatidylcholine, that in turn is a major component of very-low-density lipoproteins (VLDL), makes the GM a secondary indirect player in triglycerides storage into the liver(102). Therefore, when choline metabolism is disrupted, its bioavailability becomes decreased, resulting to an impairment of phosphatidylcholine biosynthesis in the liver, and consequently to significantly reduced levels of circulating VLDL(103). Therefore, the GM except acting as a caloric extractor from the diet, it also intervenes to the lipid metabolism of the host through various pathways.

Obesity is also characterized from a low-grade chronic inflammation. It has been found that a high fat diet for four weeks, increased up to two or three times the systemic lipopolysaccharide (LPS) levels and the LPS-containing GM, thus presenting a condition termed “metabolic endotoxemia”. Thus, the circulating high LPS levels may trigger inflammation which could then be the contributing factor for obesity and T2DM(104).

In obesity and in high fat diet, because of GM disturbance due to a *Bifidobacteria* decrease, a markedly enhanced gut permeability is established. This break of the intestinal barrier, provokes at first a mucosal inflammation and then follows a migration of bacteria and/or their metabolites from the gut lumen to the mesenteric lymph nodes(105). Consequently, the leakage of LPS and of bacteria metabolites, as SCFA, and trimethylamine N-oxide (TMAO), result to the induction of “metabolic endotoxemia” followed by additional cellular inflammatory responses. Lastly, this produces systemic low-grade inflammation, insulin resistance and hyperplasia of fat cells (106). Lately, two more mechanisms have been suggested to participate in gut permeability and bacterial migration: The first implies that

the glucagon-like peptide-2 (GLP-2), an anti-inflammatory as well as an intestinal growth factor, is inhibited by the altered GM. The other one refers to the endocannabinoid system, associated in both maintenance of epithelial barrier integrity and the permeability of the intestine(107).

Both these mechanisms reveal the link that exists between dysbiotic GM, disruption of the gut barrier function, and “bacterial translocation” associated to a state of low grade gut inflammation, i.e., “metabolic endotoxemia” which finally resumes to systemic inflammation and consequently to the pathogenesis of obesity(108).

Opposite to the previous findings, it has been shown that the *Firmicutes/Bacteroidetes* ratio changed in favor of *Bacteroidetes* in overweight and obese subjects(109). Furthermore, other studies reported that the Bacteroidetes and Firmicutes amounts are substantially augmented in the obesity group when compared to the normal-weight one(110). Interestingly enough, some researchers were unable to detect any differences between obese and normal-weighted individuals in the proportion of *Bacteroidetes* abundance(111). Furthermore, they did not discover any association between BMI and the main phyla population(112).

Recently, two more mechanisms seem to be involved in gut permeability and bacterial translocation, namely one that refers to **glucagon-like peptide-2** and the other one to the endocannabinoid system. A disrupted GM seems to be the culprit for the suppression of GLP-2, which otherwise is an anti-inflammatory and an intestinal growth factor. In addition, the endocannabinoid system, implicated in both maintenance of epithelial barrier integrity and gut permeability, is inhibited by the altered GM(113).

In summary altogether these data provide support that the dysbiotic GM and its associated genes contribute to the onset of obesity along with an unhealthy diet. Therefore, the gut microbiome should be considered as a set of genetic factors that together with host genotype and lifestyle contribute to the pathophysiology of obesity. However, in normal conditions, the involvement of GM in energy supply is small(81).

BS candidate obese patients have impaired nutritional status characterized by poor-quality food choices with a diet with low diversity and essential nutrients intake, thus contributing to intestinal dysbiosis(113,114). The most common nutritional deficiencies and their prevalence before BS are Vitamin D (65–93%), Iron (13–47%) and Vitamin B_{12} (4–13%)(115). Those results are indicating that diet might be the main contributor in shaping the GM. Some studies reported that diet change accounts for 57% of the total structural shift of GM, while genetic mutation accounts for less than 12%.

Finally, up to now, it is still challenging to answer whether the GM changes are a cause or a consequence of obesity. However, given that obese phenotype can be installed after obese microbiota inoculation, it is logical to assume that GM alterations could be one reason in inducing obesity(2). In summary, there is growing evidence that obesity is attributed to a specific GM profile which confers the host with an increased ability for calories extraction. It seems that GM imbalance contributes to the onset of obesity in tandem with an unhealthy diet. Therefore, the GM should be considered as a set of genetic factors that together with host genotype and lifestyle contribute to the pathophysiology of obesity.

Bariatric Surgery

Bariatric Surgery modalities

When the lifestyle and/or medication-based approaches for losing weight in obese patients have proven ineffective, then bariatric surgery is an option, as it has been shown to be a highly effective therapeutic procedure for treating obesity(116). Thanks to its capability to encourage substantial and sustainable weight loss, bariatric surgery became an increasingly prevalent intervention for obesity treatment(49).

Bariatric surgery (BS) interventions have been developed over the years and can be classified as either being restrictive or malabsorptive, both reducing food intake and promoting weight loss(117). The different bariatric procedures started from the 1950s with radical small bowel operations such as the jejunal-ileal bypass, to the gastric bypass in the 1960s(118–120), gastric banding in the 1990s(121), and the more recently widely spread vertical sleeve gastrectomy(122). Lately, the whole spectrum of bariatric procedures but especially gastric bypass and sleeve gastrectomy are referred as metabolic surgery procedures, thus emphasizing the health benefits associated with weight loss rather than simply weight loss itself(123).

The armamentarium of metabolic surgery procedures includes laparoscopic adjustable gastric band (LAGB), vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) and BPD with duodenal switch (BPD/DS)(117,124).

Vertical banded gastroplasty (VBG). A restrictive procedure. Before the introduction of LAGB, VBG was the most frequently performed restrictive operation in the past(125 -127). An incision is made on the lesser curve of the stomach 6 cm from the esogastric junction. The lesser omentum is dissected followed by a 2 cm opening of the lesser sac. Dissection continues downward to 1 cm above the upper most 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(128,129). Poor weight loss and complications results in 25%–54% of patients seeking revision surgery usually converted to other surgical constructions, most often RYGB(130).

Laparoscopic adjustable gastric band (LAGB). A restrictive procedure, more widely performed in the past, but its use has declined in popularity in the last 5 years(128). 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(131). Today, it has been proved that most of the procedure's efficiency is due to the pressure applied on the Intraganglionic Laminar Endings (IGLES) which convey afferent signals resulting in hunger reduction(132). The gastric band causes a delayed bolus transit into the infra band stomach but does not change the overall gastric emptying half-time. When food or liquid is ingested, the pouch expands creating a pressure sensation signaling satiety. The average weight loss is about 45%–47% of the excess weight by 4–5 years postoperatively(117).

Roux-en-Y gastric bypass (RYGB). Both a combined restrictive and malabsorptive procedure. Over the last 30 years it is the most commonly performed procedure due to its effectiveness in weight loss and to maintain this loss over the long term(133). RYGB is a two-step approach: At first, a 15-30 mL small tubular gastric pouch is created just below the gastroesophageal junction and subsequently the small intestine is split at 30-50 cm distally to the Treitz ligament. Then, the newly constructed gastric pouch is anastomosed to a Roux (alimentary) limb created from the division of both the proximal and the distal jejunum(134). Thus, a large lower gastric remnant is excluded from contacting with food as the Roux limb bypasses the stomach, duodenum, and proximal jejunum encouraging malabsorption. This anatomical rearrangement permit the immediate transfer of ingested food to the small intestine and prevents the mixing of food with digestive enzymes as it travels the Roux limb: Gastric, pancreatic, and biliary secretions flow to the jejunal transection and are mixed with chyme in a common canal shaped by side-to-side anastomosis of the biliopancreatic limb 100 –150 cm distally to the gastrojejunal

anastomosis(131). Thus, except the mechanical restriction of calories intake, RYGB is also impairing nutrients absorption. The average weight loss for RYGB at 1 year is 70–75% of excess body weight, whereas in three years is about 67%(122) and a 15–30% of the weight loss is maintained for at least 20 years after RYGB(48). Moreover, after RYGB the glycemic control improves in 90% of recipients(135).

Vertical Sleeve Gastrectomy (VSG). A restrictive procedure. VSG has increased in popularity due to its relative ease to perform as well as the good clinical outcome achieved(136). In VSG, a vertical excision of 70 –80% of the stomach lengthwise the great curvature, including fundus, corpus, and antrum, with preservation of the pylorus is performed. It aims to make a small gastric pouch ("sleeve"), having a volume of approximately 100 mL and create a high pressure chamber that easily produces sufficient pressure to overcome the tone of the pyloric sphincter thus resulting in rapid gastric emptying(97). This decreased gastric reservoir does not permit any distention and therefore provokes premature satiety, resulting in to substantially reduces portion sizes. Furthermore, restriction is further initiated by the natural band effect applied by the preserved pylorus(137).

Initially, VSG was used as the initial phase of a staged bariatric procedure for patients who had BMI greater than 60 kg/m^2. After initial weight loss, a revision surgery followed, converting VSG to RYGB or to biliopancreatic diversion with duodenal modification, but soon this second step was abandoned, as it became clear that VSG alone can accomplish substantial loss of weight without the malabsorption complications(137,138).

The sleeve creation has an impact on hormone regulation, decreasing blood ghrelin levels and enhancing a state of satiety. The average weight loss of 60% excess body weight after two years postoperatively, along to an improvement in associated comorbidities(117). Both short- and medium- term research papers showed that VSG is almost as effective as RYGB in reducing body weight and improving glycemic control(49,139).

Biliopancreatic diversion (BPD) and **BPD with duodenal switch (BPD and BPD/DS).** A malabsorptive procedure. It is used occasionally, being a radical procedure. BPD/DS may still be performed in morbid obesity cases having major complications(125). 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 combination of biliopancreatic diversion and duodenal switch was originated shortly after the introduction of BPD. The BPD-DS involves a VSG with the pylorus still left intact. A duodenal ileostomy is created resulting in a 150 cm limb and a common channel of 100 cm. The weight loss achieved via BPD and/or BPD/DS is the greatest among any of the other bariatric procedure with excess weight loss of 70%–80% postoperatively(117,124).

From all the above-mentioned procedures the most commonly performed worldwide are RYGB and VSG(125). Currently, about 50% of the bariatric procedures are VSG and around 40% are RYGB(140). However, although VSG became more popular during recent years, RYGB has been performed over decades and therefore it is estimated that millions of RYGB patients are residing worldwide in the general population(13).

Table 1 presents a comparison among those two common bariatric procedures.

Today, BS is considered as the only effective treatment for achieving a pronounced and sustained weight loss(13). The Swedish Obese Subject (SOS) trial reports a weight loss following RYGB of 27 ± 12% after 15 years, whereas non-surgical interventions (lifestyle changes and/or pharmacological treatment), have principally no effect over this time span. Controlled long term studies (>5–8 years) regarding the effects of VSG on weight loss are still a few, but weight loss up to 5 years is reported to be similar to that occurring after RYGB(13).

Additionally, many studies have reported improvements in obesity related comorbidities like T2DM, hypertension, metabolic syndrome, sleep apnea and overall mortality after weight loss(13). It is worth to note that some of these metabolic improvements manifest well before the reduction of body weight, thus indicating a direct action on metabolic control due to the modified gastrointestinal anatomy and function(140). As an example, it has been shown that after both RYGB and VSG, glucose levels decrease significantly, well before any considerable weight loss is achieved, due to weight-independent

mechanisms(141) such as the faster gastric emptying occurring following RYGB and VSG(142,143).

Furthermore, insulin levels are also found considerably lower following BS, probably due to the excessive weight loss, the serum glucose regulation, and/or the improvement of insulin sensitivity. Into the same framework, HbA1c and the homeostatic model assessment-insulin resistance (HOMA-IR) were drastically augmented before BS. In accordance with the above, the intestinal hormones correlated with glucose homeostasis, such as GLP-1 and PYY, are found increased, and therefore, lower glucose and insulin levels combined with glucagon suppression is reported. The above findings may be attributed to the faster influx of food into the ileum before being completely digested(144).

In 2016, a joint statement by multiple international diabetes organizations asserted that BS should be recommended in patients with class II and III obesity and considered as an option in patients with class I obesity with poor glycemic control(143).

Additionally, after BS, total cholesterol, triglycerides, and LDL were significantly lower, along with increased HDL, implying a normalization of the lipoprotein profile, possibly due to the loss of weight(145). In a comparison study among RYGB and VSG patients, glucose, triglycerides, and HDL levels were comparable between the two groups, while insulin levels were significantly increased in the VSG group. Therefore, it is evident that both BS procedures are metabolically efficient, a finding parallel with their similar efficiency in weight loss(146).

Lastly, branched-chain amino acids (BCAAs) were significantly reduced after BS, a finding associated with alleviation of the “metabolic overload” observed in some tissues(144). Trimethylamine-n-oxide, a metabolite proposed as a cardiovascular marker, was found increased following BS. Probably, this increase is related to the GM changes observed after BS(147,148).

All the above data demonstrate the significant amelioration of metabolic and lipidemic profiles of patients undergoing bariatric surgeries.

The mechanisms of gastric bypass

Gastric bypass procedures are considered as an artificial condition where the intestinal mucosal energy outflow is a physiological variable which could impact both body weight and glycose levels.

Contrary to an old assumption, the weight loss after a BS procedure is not achieved neither by malabsorption, nor by a mechanical restriction of food intake. Instead, the main driving force for weight reduction is instead a modified eating behavior which reduces energy intake(149). Also, regarding the old belief that reduced meal size is due to the limited size of the gastric pouch is not valid anymore, as the current surgical procedure leaves a minimum gastric pouch (20-30 mL) but followed by a gastroenteroanastomosis (GEA) of sizable caliber without any outflow restriction. Therefore, the small pouch together with the Roux-limb can be considered as a common cavity, so any possibility for the GEA to act as a restriction site can be excluded. Using high-resolution manometry, it has been confirmed that during eating there is no intraluminal pressure gradient between the pouch and the Roux-limb(150). However, it has been reported that RYGB exhibits a restrictive element with the restriction site situated to the Roux limb(150). Until now, the actual clearance rate of the Roux-limb has not been assessed and therefore it remains to be investigated to what extent a dynamic flow restriction of the Roux limb has any significance in the regulation of food intake.

Two potential working theories have been proposed as gastric bypass mechanisms: The foregut and the hindgut theories.

The **foregut theory** suggests that as food bypasses both the stomach and the duodenum, the secretion of gut-derived hormones originating from them is altered, e.g., the release of glucose-dependent insulinotropic peptide (GIP) from the duodenal mucosa.

The **hindgut theory** states that since the more distal parts of the intestine, i.e., the jejunum and the ileum, due to the created bypass are now exposed to nutrients and contact food sooner than normal, this provokes faster humoral responses.

Thus, it has been reported that after RYGB, the concentration of gut derived hormones i.e. peptide YY(PYY), glucagon-like peptide 1(GLP-1), ghrelin, GIP, oxyntomodulin and

cholecystokinin (CCK) change dramatically. It is well known that PYY and GLP-1 are secreted from L-cells in the ileum and colon and act as satiety promoting hormones, while hunger is stimulated by ghrelin which is secreted from P/D1 cells in the gastric fundus. It has been shown that in RYGB patients, eating induces increased delivery of PYY and GLP-1, from subnormal levels as those seen in obesity, to more normalized levels capable to decrease food intake(151).

In addition to regulating energy intake, different studies revealed an expanded energy expenditure in RYGB patients. Remarkably, it seems that it is not the basal metabolic rate (BMR) which becomes upregulated, but it seems that the thermogenesis associated to meal intake might be the causative process(152). The exact mechanism involved is unknown, but according to experiments in rodents, it might be due to a reprogrammed mucosal metabolism in the Roux limb.

Another two mechanisms of RYGB effect are the observed changes of the circulating bile acids levels as well and those of the intestinal microbiome: More specifically, it is assumed that bile acids regulate glucose metabolism through an action of the TGR5 receptor on L-cells, causing release of GLP-1, as well as provoking the synthesis and secretion of fibroblast growth factor 19 (FGF19) which improves insulin sensitivity, thus leading to an improved glycemic control(153).

It has been reported that transferring feces from RYGB-treated to GF mice caused a substantially bigger loss of weight as compared to mice receiving feces from sham-surgery treated mice(149). Additionally, GF mice inoculated with fecal microbiota from BS patients added less fat than mice transplanted with microbiota originating from obese subjects(154). Theoretically, it is expected that the jejunum mucosa into the Roux limb becomes irritated by the new intraluminal milieu and, in turn, responds starting an antiingestive signaling. Nevertheless, a study performing a thorough inspection of the postoperative mucosa did not support this hypothesis, and although some proinflammatory signs were present, the Roux-limb mucosa did not manifest any inflammation(155).

In summary, it seems that the bio-mechanic properties of the Roux limb wall regulate both food intake and intestinal sensing. Thus, the proposed hypothesis that “big-eaters” have a low-threshold for inducing Roux limb clearance motility awaits confirmation(13).

Side effects of Bariatric Surgery

The perioperative mortality rate of BS is very low with an average value of 0.3%(156).

Bariatric surgery has some unwanted consequences, thus requiring a cost-benefit analysis for every individual candidate. About 4% of patients after BS manifest surgical complications within the first 30 postoperative days(157,158). Typical postoperative complications include anastomotic leakages, bleeding, perforation and infections, as well as inner herniations(157), although the herniation incidence has been dramatically lowered after the closure of any mesenteric defect became a standard routine practice during the BS operation(159). Late surgical complications are also detected in 15–20% of patients and they include obstruction of the small intestine, anastomotic stenosis, and marginal ulceration(156). Both early and late surgical complications can be diagnosed and treated by means of endoscopy or surgery. Additionally, except typical surgical complications, some other procedure-dependent side effects may be present, such as excess skin requiring additional cosmetic surgery, dumping symptoms and postprandial hypoglycemia, as well as micronutrients deficiency(13).

Unexplained chronic abdominal pain is a common negative side effect seen in patients after RYGB(160). It is reported that 54% of RYGB patients suffer from abdominal pain and in a 5-year follow up, 34% of these patients still experience abdominal pain(161,162). It is of paramount importance to elucidate the underlying pathology of chronic abdominal pain following BS but its etiology remains still obscure(163). The long term consumption of morphine or its analogs for pain relief in RYBG patients may provoke to opioid induced bowel dysfunction which presents with constipation, nausea and vomiting, and to the narcotic bowel syndrome(164). Furthermore, it is estimated that 4% of patients who were not on opioids before, became chronic opioid users after BS(165) and therefore the

attending physician of a RYGB patient who develops chronic postprandial nausea and pain, must bear in mind the risk of iatrogenic opioid associated symptom aggravations.

Hypoglycemia in patients without diabetes appears in 64 – 82% of patients during the first 5 years of BS(166). The underlying mechanism is not clear and several theories have been proposed including enhanced B cell mass and function, diminished ghrelin levels, improved insulin sensitivity, and failure of counter regulation(167). The consequent side effects of hypoglycemia often persist throughout the years and can thus worsen the quality of life.

Sometimes, in RYGB operated patients, a series of symptoms occurs and termed as the Roux stasis syndrome (RSS) which presents with pain, nausea and vomiting that is worsening after food ingestion(168). However, the RSS seems to not be related with a stasis in the Roux limb(13).

Gut Microbiota after Bariatric Surgery

Many surgical diseases are related to gut microbiota alterations. So far, obesity, atherosclerosis, non-alcoholic fatty liver disease, inflammatory bowel disease, intestinal anastomotic leaks, and colorectal cancer have been reported(17).

As mentioned previously, BS is the treatment of choice to accomplish and maintain in the long term a normal weight to morbidly obese patients. Those patients who undergo BS are losing weight significantly, and they restore their metabolic health regarding T2DM, dyslipidemia, hypertension and cardiovascular risk(169,170).

It has been shown that BS plays a cardinal role by altering the abundance of several microbial species of the GM. However, the available data regarding the changes of GM after BS are highly heterogeneous and insufficient to be included in quantitative analysis(171).

The exact mechanisms underlying the post-surgical restructuring of the GM have not yet been elucidated and must yet to be explained. However, it is certain that the dramatic anatomical alterations induced by BS, contribute significantly to the substantial metabolic changes observed following BS(172). Additionally, several factors coexist that can alter the postoperative status of the BS patients: Caloric restriction (substantially energy restricted diet with higher protein intake), alterations in the secretion of gut hormones and bile acids, and changes of the GM composition have been proposed as possible mechanisms(173). Thus, due to the multiple metabolic and hormonal changes which coincide during the early postoperative period, it is rather difficult to establish underlying relationships between factors related to BS and changes in GM composition and function after performing BS(174).

Several studies have shown that bariatric surgery provokes alterations to the GM which can be installed as early as the first week after surgery and in any case as soon as the first three months postoperatively (175,176) and this consequence can be sustained up to nine years(154).

Additionally, late complications include severe deficiency-related disorders, such as anemia (10–74%) and neurological dysfunctions (5–9%)(9). Therefore, the patients who underwent BS are in need of a rigorous follow-up aiming to prevent those side effects through GM modulation and adequate nutritional supplementation(177).

It has been observed that a major alteration in the structure and diversity of GM is taking place after BS. A recent meta-analysis included 22 studies and 562 patients who underwent different types of BS. Despite that the different studies reported a substantial variety of the bacterial species, the overall findings showed a change of the GM postoperatively(178). Therefore, this GM change might not be the result but rather the reason of weight loss after BS, as it has been recently suggested that metabolic regulation is starting from the gut which then is signaling to the brain and other endocrine organs to adapt to this change(179,180).

The most common change observed after BS procedures is a decrease of *Firmicutes* and an increase of *Bacteroidetes, Proteobacteria*, especially of *Gammaproteobacteria* (genus *Escherichia*) abundance(75). In another study, a decrease of the *Firmicutes/Bacteroidetes* ratio was reported following BS in subjects with morbid obesity, accompanied with a substantial change of the structure and function morbidly of the GM. However, the whole subject is still under debate(154). It is also worthwhile to note that additional GM changes following BS have been reported in a study: An increase in the phyla *Verrucomicrobia* and *Fusobacteria*, as well as a diminished amount of *Actinobacteria*(181).

Some articles focused on fecal microbiota transfer experiments. A well-planned study showed that both RYGB and VBG, have similar long-term effects on the composition and functions of the gut microbiome. It is worth to note that the GM changes were independent from BMI or from the magnitude of weight and fat mass loss, thus suggesting that BS can cause specific shifts in the GM. In the same study, feces from BS patients were transplanted to GF mice; two weeks after transplantation, the mice gained less fat as compared to reciprocal mice transplanted with GM from obese subjects. Those findings suggest a causal relationship between GM and to BS induced weight loss(154). The same results are reported in another study which showed that GM transplantation from mice which underwent RYGB

to sham-surgery germ free mice, provoked weight loss and decrease of adipose tissue when compared to recipients of GM from non-operated mice(182).

A similar GM transplantation study was done in a group of females who, nine years previously, were randomly assigned to undertake RYGB or VSG: Both types of surgery recipients showed similar GM profiles of their fecal samples (as assessed by means of 16S rRNA amplicon sequencing analysis) and furthermore, they were substantially different from the profiles of non-operated obese women. When feces from BS patients were inoculated to GF mice, the recipients had decreased fat mass as compared to reciprocal mice that received GM from obese, non-operated subjects. Additionally, the recipient mice which were transplanted with human post-RYGB GM, showed the bigger increase of lean body mass. Therefore, it seems that the human GM can directly trigger the reduction of adipose tissue seen after BS(154).

In another longitudinal study of obese individuals, it was found that *Bacteroidetes* were reduced prior to surgery, but three months post-RYGB, the *Bacteroidetes* abundance was returned to pre-surgery levels, being remarkably similar to that of lean control group. Additionally, the observed abundance in *Bacteroidetes* following RYGB, correlated with a substantial decrease of adipose tissue and an increased serum leptin levels(183).

Methanogenesis facilitates the fermentation of dietary fibers through the consumption of hydrogen and acetate and methanogenic archaea are found in abundance in obese subjects. In a study comparing the 16S rRNA sequences in the feces of three groups, namely normal weight, morbidly obese, and post-RYGB subjects, distinct differences were found in the GM between the three cohorts: Methanogenic archaea were found in abundance in the obese group, but they were found below detection levels in normal weighted or all-but-one post-RYGB patient(184).

The same changes in the GM are also observed after sleeve gastrectomy: In mice which became obese through increased food intake and subsequently underwent VSG, a substantial and sustained increase of *Bacteroidetes* together with a relative decrease in *Firmicutes* is reported. Additionally, GM metabolism is related to that of the host. Thus, three months after VSG, several metabolic processes of the patients, such as carbohydrate

fermentation, citrate cycle, and amino acids production, as determined by shotgun metagenomic sequencing, became more analogous to those of normally weighted control group(185). However, regarding the metabolic improvement or the degree of weight loss, it seems that BS itself is more important factor relatively to the feces transplantation, indicating that apart from GM, BS and other pathways are involved in those positive results(186).

Several other gut bacteria are proliferating after BS: Due to the increased pH into the lumen and high levels of dissolved oxygen, both been observed after BS, the growth of facultative aerobic microorganisms (such as *Proteobacteria*) and inhibition of anaerobic microbes is observed(172). In tandem, the diminished gastric volume resulting after BS, increases the pH of both the stomach and distal intestine and the resulting gastrointestinal acidity leads to microbial overgrowth and promotes the abundance of *Akkermansia muciniphila, E. coli,* and *Bacteroides spp*. or of the oral microbiota bacteria(187).

However, there is a couple of studies using sequencing methods, described a high MGR and bigger GM diversity following both RYGB and VSG as well as a change from “obese” to a “lesser obese” microbial species profile(91,95). Nevertheless, despite profound weight loss and improvement of metabolic markers after both types of surgery, the MGR may not be fully restored one year after RYGB and remain unchanged even after 5 years(187). The absence of complete repair of GM after BS could explain the observed delayed regain of weight and the recurrence of obesity related comorbidities observed in some patients after BS. The fact that BS alone cannot reestablish MGR, indicates that other contributing mechanisms (i.e., diet, weight loss, inflammatory and metabolic improvement) are also involved. Therefore, after BS surgery, specific interventions to restore the correct microbial balance and improving the interactions among gut microbiota and the host are required(91).

However, the two BS surgeries might exhibit different functionality due to the different surgical techniques as well as to resulting different intestinal environmental conditions. With that in mind, one would anticipate more profound changes in the intestine after RYGB

as contrasted to VSG, as besides caloric restriction, it involves more radical and complex anatomical changes and more functional modifications of the GI tract(2).

Below are listed some studies exploring the GM related outcomes of the different surgical BS procedures.

Administration and/or abundance of *Akkermansia muciniphila* is related to enhanced gut barrier function and diminished metabolic endotoxemia as a result of decrease of the circulating levels of systemic lipopolysaccharide(188). Also, the administration of *Akkermansia muciniphila* rose L cells numbers which, when stimulated, induce GLP-1 release which is implicated in glucose homeostasis(189) and GLP-2, an important intestinal growth factor(191). It has been reported that after RYGB, the *Akkermansia muciniphila* increases(192) which has been negatively correlated with body mass(193).

Furthermore, following RYGB, *Escherichia coli* abundance is enhanced and, independently of food intake changes, it is inversely correlated with adipose mass and leptin levels, in contrast to *Faecalibacterium prausnitzii*, which is found to decrease after RYGB(183).

Several factors have been advocated to play a role for the vast GM restructuring observed after RYGB as the disrupted anatomy (small gastric remnant and shortened small intestine) result in decreased food ingestion. Additionally those severe anatomic changes also have some physiological consequences like changes in pH, transit time, and input of dissolved oxygen which promotes the relocation of some of the typically residing in the small bowel microbiota, to the large intestine(184). Additionally, the observed GM change after RYGB could also be attributed to altered bile acid metabolism which is regulated by BS as well(191).

Two recent meta-analyses reported that although after BS the diversity and richness of GM greatly fluctuated across studies, certain bacterial phylae such as *Bifidobacteria* was strongly correlated with BMI(171,192).

A study investigated whether the GM changes after RYGB are preserved and whether inoculation of RYGB modified microbes can provide a weight loss effect transferable to other recipients. Using a mouse RYGB model which resembles many of the metabolic

outcomes seen in humans, fecal samples of three groups were collected for 16*S* ribosomal RNA gene sequencing: after RYGB surgery, sham surgery, or sham surgery coupled to caloric restriction. The sequential analysis showed that distal gastric, ileal, cecal, and colonic microbiota were substantially altered after RYGB. A rapid and sustained increase in the relative abundance of *Enterobacteriales* and *Verrucomicrobiales* was found. Three phyla increases are prevailed: In *Bacteroidetes*, *Verrucomicrobia*, and *Proteobacteria*, with resolution to the genus level of *Alistipes, Akkermansia*, and *Escherichia*. The observed GM alterations were unbiased of weight alteration and calories restriction and were found along the entire length of the GIT but mostly evident distally from the surgical manipulation site. The recipient lean GF mice transplanted with feces from RYGB-operated rodents had reduction of fat mass which was not observed after inoculation of GM from mice that had lost weight due to food restriction. The above findings provide evidence to the assumption that GM changes contribute to reduced host weight and fat mass following RYGB surgery(182).

A study performed in morbidly obese individuals within 3 months after they underwent RYGB, found that their GM featured an increased relative abundance of 31 species, including *Escherichia coli*, *Klebsiella pneumoniae*, *Veillonella spp*., *Streptococcus spp*., and *Alistipes spp*., while *Akkermansia muciniphila and Faecalibacterium prausnitzii* decreased in their relative abundance. Furthermore, an augmented potential for oxygen tolerance as well as for microbial utilization of macro- and micro-nutrients was reported and those changes were still present one year after RYGB(176).

The phylogenetic analysis of GM of three groups (healthy, obese, and post-RYGB subjects) showed six main bacterial phyla to be present but distributed differently in the GI of the study groups. Interestingly enough, *Prevotellaceae* was explicitly detected only in obese subjects and therefore it is considered as obesity specific bacteria. To the contrary, *Fusobacteria* and the *Enterobacteriaceae* within *Proteobacteria* family were found only in the RYGB group(49).

Tremaroli et al(154) performed shotgun sequencing of the fecal metagenome to analyze the GM of weight-stable women 9 years post-RYGB. Furthermore, they performed human-to-

mouse GM inoculation. After RYGB, an increased abundance of Gamma-proteobacteria was detected, while in contrast, lower levels within the *Firmicutes* phylum of *Clostridium difficile, Clostridium hiranonis*, and *Gemella sanguinis* were detected. In contrast, facultative anaerobes within *Proteobacteria* (*Escherichia, Klebsiella*, and *Pseudomonas*) family were found augmented in the RYGB recipient mice. The metabolomic comparisons performed after BS showed an inhibited SCFA/branched-chain fatty acid ratio, a finding suggesting an enhanced amino acid fermentation. The genetic marks for microbe enzymes participating in the synthesis of secondary bile acids were enhanced in parallel to a shift of secondary to primary bile acid profiles ratio, suggesting that modified bile acid profiles may contribute in the reduction of fat mass following BS(49).

In a study comparing the impact of both RYGB and VSG on GM, an important increase of *Proteobacteria* was found. The same altered pattern (a *Roseburia* abundance) was also shown in T2DM patients who underwent RYGB or VSG when a T2DM remission was achieved. In contrast, six months postoperatively, despite similar weight loss, the *Bacteroidetes* increased in RYGB group of patients, while it decreased in the VSG group(194).

Additionally, as RYGB provokes greater rearrangements of the digestive tract than VSG, a significantly lower body weight and a greater shift on GM were produced from RYGB as compared to VSG, nine weeks postoperatively(195). It is postulated that the differences observed between the two techniques could be due to the fact that VSG involves much less intestinal manipulations than RYBG. The above results were also confirmed by a study which revealed that RYGB provoked increased *Firmicutes* and *Actinobacteria* but decreased *Bacteroidetes*, but the later been found increased after VSG. Thus, one year following RYGB surgery, more significant functional GM alterations were found as compared to VSG, despite similar diet, weight loss, or remission of T2DM(196).

It has been reported that sleeve gastrectomy provokes both early (one week after surgery) and prolonged (one month after surgery) changes of the GM. Furthermore,, the same article demonstrated that the altered microbial composition of VSG operated rodents is persisting and does not change even when re-exposure to obesity associated GM occurs(184). The

same findings are also reported regarding the functional capacity of GM after VSG in 23 obese patients. It was found that three months post-VSG the microbial activity was similar to that of lean subjects and a marked increase of *B. thetaiotaomicron*, an anti-obesogenic substance, was observed(197).

In a recent systematic review Davies et al., summarized 14 clinical studies, with a total of 222 subjects (RYGB = 146, VSG = 25, biliointestinal bypass = 30, vertical banded gastroplasty = 7, and adjustable gastric band = 14). Major switches comprise a reduction of the relative abundance of *Faecalibacterium prausnitzii* and an increase of *E. coli*. After VSG, a decrease in the relative abundance of *Firmicutes* while following RYBG an increase in *Bacteroidetes* and *Proteobacteria* was also noticed(194).

Their findings are summarized in Table 2. It was found that the different types of BS result in dramatic changes of gut microbiota, but the impact of those alterations to the metabolic benefits achieved is still unclear(195).

Table 2. **Changes of human gut microbiota following different Bariatric Surgeries.**

A systematic review and meta-analysis reviewed the impact of BS in metabolic and GM profiles, of 22 articles published between 2008 and 2016. However, they found that only two studies were randomized, the rest being prospective ones(154,197,198). The total sample size was 562; 411 patients had RYGB, and 97 underwent VSG(199).

Table 3 summarizes the literature findings regarding the postoperative changes of gut microbiota following bariatric surgery.

As shown in **Table 3** several microbes are affected by BS. As can be seen from this Table, some authors found increased Bacteroides while Firmicutes and Bifidobacterium had lower abundance in the post-RYGB subjects(190,199).

More specifically, regarding RYGB, two studies found lower *Firmicutes* abundance after RYGB(189,198) while two other studies showed the opposite(200,201). Additionally,

another study showed that *Lactobacillus*, been part of the *Firmicutes* family, was in higher abundance after biliointestinal bypass(202). The discrepancies observed among the results of those studies can be explained from the different clinical protocols applied using varying levels of calorie restriction. Furthermore, another couple of studies showed an increased Bacteroides abundance in RYGB patients and the higher was the Bacteroides increase after RYGB, the bigger the decrease in body fat mass and leptin(192,199). It is worth to note that the same findings were also reported in less obese subjects(203).

In another study, an increased *Bacteroidetes* abundance was found after VSG, while after RYGB a decrease for the same phylum was observed(200). Regarding *E. coli* population, it was found enhanced in five studies(190,200 -204). The increase in abundance of *Escherichia coli* could be due to anatomical readjustments causing higher oxygen concentrations in the distal intestine(205).

Obviously, these data are not sufficient to arrive to a solid conclusion as certain methodological differences and limitations regarding the different administered antibiotics, diet, and demographic parameters are coexisting.

In summary, it appears that BS reestablishes a healthier microbiome together with a slimmer metabolic profile, and possibly this microbiome readjustment contributes to a diminished fat mass, an increased lean mass, and disappearance of BS associated co-morbidities. Nevertheless, the mechanisms through which the gut microbiota and their by-products affect obesity are still obscure, and robust microbe manipulations that interfere with the host-bacteria interactions for the treatment or prevention of obesity are still in need to be developed(17).

Bariatric Surgery Related Diet on Gut Microbiota

The rearrangement of the gastrointestinal tract following BS leads to alteration of the gut microbial ecology. The post-surgery food intake of patients submitted to RYGB or VSG, has major quantitative and qualitative changes: In a matter of days the calories restriction alters the bacterial structure of the bacterial community(180). Whether diet dominates overweight modification following BS in shaping GM or if GM change is a direct consequence of BS per se are still matters of debate(206).

It has been postulated that the observed GM shift after VSG (i.e., the reduction of the *Firmicutes/Bacteroidetes* ratio) might be the adaptive response of bacteria to the caloric constraint imposed by surgery. More precisely, the *Firmicutes* decrease results to diminished fermentation to subsequent reduced energy intake, and finally, to concomitant SCFAs production, the latter being substrates for gluconeogenesis and lipogenesis. A study showed that VSG, but not a strict dietary regimen with low calories, enhanced the obesity related GM synthesis towards a lean microbiome phenotype(207). Moreover, it has been shown that, in a mouse model, when only food restriction is applied there are no early changes in GM after RYGB, and therefore, the loss of weight appears to be one among the least important factors involved in the GM shift(206).

Thus, in 45 subjects submitted to either RYGB (n = 23) or VSG (n = 22), GM composition and diversity changes were assessed before following a two-week crash diet (baseline), by the end of it, as well as one week, three months, and six months postoperatively. A substantial but temporary alteration in GM was noticed after the baseline crash diet, but BS provoked more persistent changes in GM composition and to restoration of microbial diversity well before any significant weight loss, irrespectively of the type of BS performed. Both RYGB and VSG groups exhibited the same magnitude GM changes in all phases of the study(207).

Bariatric Surgery Effect on Small Intestine Bacteria

Obese patients after bariatric surgery, may present small intestine bacterial overgrowth (SIBO), a condition defined as greater than 105 bacteria (colony-forming units)/mL of proximal jejunal aspiration(208). SIBO is a common manifestation of obesity and a recent prospective study including 378 patients with morbid obesity, reported that 15% of patients before undergoing RYGB had SIBO, and that this figure increased up to 40% after the operation(207).

In clinical practice, SIBO diagnosis is made from small intestine aspirate test, but this is an invasive and expensive test, and therefore the most practical detection method is the "therapeutic trial", by empirically administering treatment with antibiotics upon the presence of the clinical manifestations associated with SIBO(209).

SIBO interferes to the weight loss process and increases the micronutrient deficiencies risk. It manifests with several gastrointestinal symptoms, including bloating, diarrhea, and malabsorption of nutrients, all depending from the specific type of bacteria that overgrow into in the small intestine(210). Mechanical stasis is frequently associated with RYGB and creation of blind loops. SIBO bacteria bear a resemblance to those typically observed in the colon, either gram-negative aerobes and/or anaerobes species, such as *E. coli, Enterococcus spp*., *Klebsiella pneumonia*, or *Proteus mirabilis*, capable to metabolize undigested carbohydrates into SFCA and gas. The disproportionate growth of atypical bacteria in the proximal small intestine permits their competition with the human host for nutrients harvesting. Additionally, the inflammatory response following SIBO provokes alterations of the epithelial cells and provoke villous atrophy and/or stimulate the synthesis of inflammatory cytokines resulting to mucosal injury(211).

Also, it has been shown that SIBO restricts the absorption of vitamins B_1 and B_{12}: In a retrospective analysis of 80 RYGB patients, 39 of them had lower B_1 levels than the reference range(212). Twenty-eight of these patients, had elevated folate levels in plasma, a marker suggesting the SIBO presence, and also another 15 were diagnosed with SIBO by undertaking glucose-hydrogen breath testing. After treating SIBO with antibiotics, the

persistent B_1 deficiency rapidly resolved (213). Secondary megaloblastic anemia may be present following RYGB due to impaired B_{12} absorption. A case report article reported two patients which were positive for SIBO after been submitted to RYGB. After antibiotic treatment their hemoglobin levels were improved, but mean cell volume was still increased and B_{12} levels were below normal range(211).

The malabsorption of fat-soluble vitamins, like A, E, and D arises due to the bacterial deconjugation of bile acids by small intestine bacteria leading to the formation of toxic lithocholic acid, which further aggravates the intestinal epithelial cell disfunction and subsidizes carbohydrate and protein malabsorption as well(212). In contrast, in patients with SIBO, the vitamin K levels are within normal limits or even increased since bacteria are capable to synthesize menaquinone(213).

The reduced brush border enzyme activity as well as the substrate readiness generate impaired carbohydrate uptake, which small bowel bacteria are able to metabolize prematurely. Also, increased numbers of small bowel bacteria compete with the host for intraluminal protein, thus disturbing the amino acids and peptides absorption. Furthermore, patients with SIBO demonstrate reduced enterokinases levels which result to impaired proteolytic reactions and subsequently to impaired activation of pancreatic zymogens(213).

Bariatric Surgery on Gut Hormones

In healthy conditions, meal intake suppress the hunger hormone ghrelin; however, in obese subjects this mechanism might be disrupted. It has been suggested that ghrelin release is sensitive to BS, but contradictory results are reported regarding both physiological ghrelin release as well as the effect of BS on its excretion(214). Thus it has been reported that within days after BS, as a more quick release of nutrients to the distal small intestine starts to occur, an increased production of gut satiety hormones such as PYY and GLP-1, and a reduced increase of ghrelin is taking place(215).

After a meal, both PYY and GLP-1 are, proportionally to the consumed calories, released from the L cells of the distal small intestine(216). Following BS, the postprandial PYY levels are increased with the new ones correlating to the postoperative weight loss(217). Also, the role of PYY in the regulation of feeding after RYGB has been assessed using octreotide, which blocks the secretion of most of the gut hormones and therefore increases food consumption(218).

Although the effects of PYY and GLP-1 on gastric emptying, glucagon secretion, and insulin release from the pancreas are well understood, however, the appetite change after BS seems to be a synergistic response of more than one gut hormones(219,220).

Bile Acids and Gut Microbiota Interactions

Primary bile acids (cholic and chenodeoxycholic acid) are synthesized by the liver from cholesterol, and conjugated with glycine and taurine becoming bile salts, subsequently stored within the gallbladder, and ultimately excreted in the duodenum by contraction caused by cholecystokinin. When they reach the ileum, they are reabsorbed, enter the portal circulation, and are transported back to the liver. Only a little quantity of bile salts is escaping from enterohepatic circulation and arrive in the colon where they are deconjugated and dehydroxylated by the GM to secondary bile acids (deoxycholic and litocholic acids). Lastly, about 95% of primary and secondary bile acids are reabsorbed and return backwards to the liver(218).

The gut bacteria contribution in deconjugation and fermentation of primary bile acids to secondary ones, has different impacts on human metabolism: The primary bile acids foster metabolism improvement, while secondary bile acids do not but rather seem to initiate carcinogenic processes(221). In addition, GM benefit from the deconjugation of bile acids as it can consume glycine or taurine for its own metabolism(222). Also, bile acids shape the GM population through regulation of their growth and colonization and impacting the structure of their cell membrane. It has been reported that bile acids exhibit antimicrobial effects on certain bacteria while they promote the growth of others(223).

It is well established that bile acids enhance the release of PYY and GLP-1 but inhibit ghrelin. Thus, clinical studies have shown that by administrating bile acids, a number of metabolic parameters are altered, including reduced appetite(224,225), improved glucose control through the increase of insulin and GLP-1(226,227), by increasing energy consumption and brown adipose tissue activity(228).

A wide range of evidence shows that bile acids, beyond their traditional role in lipid absorption, they behave like hormones by interacting with two receptors: The nuclear ligand-activated nuclear farnesoid X receptor (FXR) and a G protein-coupled cell surface receptor (TGR-5) and therefore are considered signaling molecules capable to regulate a number of metabolic pathways. It is interesting to note that primary bile acids principally activate FXR, whereas secondary bile acids mainly activate TGR-5(224).

It seems that FXR play multiple roles in metabolism regulation. FXR is a major regulator of bile acid signaling in both the liver and intestine, controlling the enterohepatic cycle of them by inhibiting hepatic bile acid synthesis and intestinal absorption. Additionally, bile acids serve as a ligand for FXR and appear to control glucose metabolism via FXR-related pathways. In this way, bile acids, expand their molecular repertoire as modulators for both glucose and lipids metabolism(224). Finally, genetic and pharmacological mouse models have demonstrated differential roles of liver and intestinal FXR signaling in glucose metabolism and weight management(224).

Thus, the synthesis of bile acids into the liver is directly inhibited by FXR, or via FXR-mediated release of the hormone fibroblast growth factor 19 (FGF19) and growth factor 21 (FGF21), which in turn mediate simple sugar consumption by reducing the appetitive behavior towards sweet food(24,49). On the other hand, the activation of TGR5 promotes the release of GLP-1 and PYY(49). Moreover, during enterohepatic recirculation, a fraction of bile acids is shunted to the systemic circulation, and therefore, they may influence energy turnover at all biological levels(225).

Bile acid levels are increased in response to BS and it is has been advocated that they are the mechanism responsible for losing weight as well as for metabolic improvements

observed after BS(226,227). Regarding RYGB, the plasma bile acids are increased due to the fast quantity of undiluted bile to the distal L cells and activation of the TGR5 receptors(228). Additionally, a significant increase in the 12a-hydroxylated/non-12a-hydroxylated bile acid ratio have been described following RYGB(183). In RYGB, bile acids do not mix with food until the final part of the jejunum. Therefore, in obese rodents which underwent RYGB, the procedure produced significant weight loss and amelioration of glucose tolerance independently from the weight(229). This is also reported in a study where increased bile acid levels were found in T2DM patients who underwent RYGB, but they were decreased after a hypocaloric diet that resulted in similar weight loss in T2DM patients, suggesting that the increase in bile acids after BS is weight independent(230).

It has been suggested that FXR is crucial for the positive outcomes of VSG on both weight loss and glycemic control, as FXR-deficient mice despite been submitted to VSG, showed reduced ability to decrease body weight and improve glucose tolerance(231). It is worth to note that increased bile acids levels are also found after VSG(232,233). This implies that this is not simply due to rerouting of bile acid as in the case of RYGB, but rather a physiological change of bile acids regulation than simply an operation related displacement of the bile acids(233). Moreover, FXR is essential for the positive effects of VSG on weight loss and glycemic control(233,234).

The hypothesis that bile acids exhibit a contributory role in mediating the effects of BS is not always granted. For instance, in a study comprising T2DM and normoglycemic patients who underwent RYGB, glucose metabolism improved shortly after surgery, but the total bile levels did not increase until three months post-surgery(235). Another study reported decreased bile acid levels shortly after surgery and an increase at 2 years after it(235). These data reveal the possibility that the relationship between the clinically relevant effects of BS procedures and the alterations of bile acid levels may be more complicated.

The gut-derived peptide FGF15/19 is likely a molecular and therapeutic marker to elucidate the encouraging metabolic effects of BS(224). FGF15/19 is expressed in the enterocytes of the small bowel ileum and is excreted postprandially as a response to the absorption of bile acids. After been released from the ileum, FGF15/19 is directed to the liver through the

portal venous circulation where it binds to its receptor FGFR4 and suppresses the de novo bile acid synthesis via reduction of cholesterol 7a-hydroxylase (*CYP7A1*) and gallbladder filling.

The circulating FGF19 levels increase following BS, indicating that FGF15/19 might be a potential target to mediate the positive effects of BS. However, the mechanism on how the increased levels of FGF19 in patients following BS directly facilitate the beneficial effects of the surgical procedure is not clear yet. Therefore, there is a need for studies which should implement BS in animal models with tissue-specific deletion of FGF15 or FGFR1/4 and thus may provide further insight into understanding the direct role of FGF15/19 signaling in mediating the effects of BS. The literature data indicate the need of more studies to fully understand the plethora of FGF15/19-mediated actions. Understanding these complex actions may help researchers to directly link the FGF15/19 increase with specific metabolic benefits of BS(224).

Micronutrient Deficiencies after Bariatric Surgery

After BS, the micronutrient status of patients further deteriorates, which, in turn, affects the structure and composition of GM(236). Thus, following BS, 30 –70% of patients develop nutritional deficiencies which, if severe, can result to edema, hypoalbuminemia, anemia, and hair loss as well as peripheral neuropathy, Wernicke encephalopathy and beriberi, metabolic bone disease, and anemia(236). Micronutrient deficiencies are common after RYGB and VSG(237), and a prevalence up to 50% in mid- and long-term follow-up has been reported(207). The underlying causes can be due to either surgery- or patient- related reasons(238).

BS may lead to severe postoperative micronutrient deficiencies which persist despite vitamin and mineral supplementation. A variety of factors can contribute to micronutrient deficiency observed after BS including eating behavior, decreased absorption, SIBO, poor compliance to the suggested optimization of diet and to prescribed nutritional supplementation(59).

There is strong evidence that after both RYGB and VSG, the restriction of food intake, the reduced appetite, as well as the changes of gastrointestinal hormones are common mechanisms for the observed weight loss(239). Furthermore, the complications observed after BS, such as nausea, vomiting, food intolerance, or SIBO may result to vitamin and mineral deficiencies(240).

It is of interest to state that micronutrient deficiencies are manifested in a similar degree after VSG and RYGB, although fewer micronutrient deficiencies are expected after VSG, since the small bowel remains intact after this operation(239,241). This observation leads to the assumption that BS related micronutrient deficiencies must be explained by different mechanisms: Namely, VSG accelerates gastric emptying and gastroduodenal transit time and, furthermore, reduces the secretion of hydrochloric acid and of the intrinsic factor. All these changes, due to the gastric fundus resection, affect the gastrointestinal motility and therefore, the release and dissolution of several vitamins and minerals is diminished(242).

On the other hand, after RYGB, the bypass of the remaining stomach as well as of the upper portion of the small bowel, exclude the exposure of the food bolus to the biliopancreatic secretions and therefore affect the vitamins and minerals absorption. It is worth to note that the degree of malabsorption better correlates to the length of the common channel (distal jejunum, ileum, and colon) rather than the length of the Roux limb(243). Additionally, diminished absorption may also occur in the common portion of the small intestine as an asynergia consequence between food bolus, bile acids, and pancreatic enzymes. Finally, following RYGB, the absorption of some micronutrients (especially vitamin B_{12}) can also be reduced attributed to the lower location of gastric output as an anatomic consequence of bypassing the distal stomach(244).

Except the above-mentioned BS related variables of micronutrient deficiency, some patient related causes can alter their postoperative micronutrient status. Thus, it has been reported that patients who underwent BS may exhibit substance and alcohol abuse as well as poor compliance to the nutritional supplementation protocol. Thus, a long term (up to seven years) follow up study of more than 2000 BS patients states that 20% of RYGB patients established an alcohol use related disorder(244). In a recent questionnaire-based survey on 533 patients who underwent bariatric surgery, reported that slightly over half of the respondents showed non-adherence to micronutrient supplementation(245).

The main micronutrient deficiencies reported after both BS include vitamin B_{12}, folic acid, iron, thiamine (vitamin B_1), vitamin D, and calcium(246,247). Other studies on nutritional deficiencies after weight loss surgery, particularly following mixed bariatric procedures, report deficiencies of fat liposoluble vitamins, namely, vitamin A(248), vitamin E(249), and vitamin K(250), as well as for copper(249), zinc, and selenium(251,252). Therefore, lifelong nutritional supplementation, especially regarding protein, iron, folate, calcium, vitamins B_1, and B_{12}, and D is a critical part of the postsurgical management of BS operated patients as those substances are the most affected.

Vitamin B_{12}

The anatomic alterations of the gastrointestinal tract due to BS, has as a consequence the impaired secretion of both HCl and pepsin from the functional part of the remnant. This

results to diminished vitamin B_{12} capture as well as to less food interaction with the cells producing the intrinsic factor, provoking malabsorption and deficiency of cobalamin(253,254). It has also been shown that the impaired intrinsic factor, is the main driver of the B_{12} deficiency observed post-surgery, although other molecules like transcobalamin 1 may participate(255). As expected, RYGB patients present a higher vitamin B_{12} deficiency (37–50%), than VSG patients where it is present in only 10–20%(94). It has been reported that, despite adequate supplementation with physiological doses, B_{12} levels are found decreased within a few months following BS, and therefore, administration of high doses of B_{12} is recommended right after bariatric surgery(256).

Folic Acid

It is expected that after BS folate absorption should be impaired due to hypochlorhydria and altered pH in the proximal jejunum(257). However, it has been reported that folic acid may be also synthetized by bacteria in the colon. It seems that it is absorbed throughout the whole bowel intestine and the colon, with a lowering absorption gradient observed from jejunum to colon. Therefore, following RYGB the administration of physiologic doses of supplement is sufficient to prevent or correct folate deficiency as a compensatory mechanism of intestinal absorptive capacity is present(258).

Vitamin B_1 (thiamine)

The thiamine deficiency symptoms rapidly develop after only 20 days of insufficient oral intake, faster than for any other vitamins(259). Hyperemesis, a symptom rather common after BS surgery, impairs the 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's encephalopathy(260), which may present a medical emergency characterized by sudden onset of nystagmus, ataxia, ophthalmoplegia, and altered mental state(261).

Bariatric patients may present vitamin B_1 deficiency within six months following surgery. A study reported that from 118 cases of Wernicke's encephalopathy detected postoperatively after either RYGB or VSG, almost 90% had hyperemesis(261). A study reported that two years after RYGB, the thiamine levels were deficient in 18% of patients(261), a finding which

is in agreement with later observations which reported the same percentage of clinical thiamine deficiency after surgical follow-up(262). Regarding VSG patients, in a recent retrospective study, within one year after VSG, the 25.7% of subjects showed decreased thiamine levels(263). Furthermore, 5 years after VSG surgery, 30.8% of patients despite routine supplementation, had significantly decreased thiamine serum concentrations(264).

Vitamin D and Calcium

Following BS, the bariatric patients have an increased risk for developing metabolic bone disease at any time for the rest of their lives. Furthermore, after BS, SIBO can also aggravate vitamin D deficiency(265). As diminished poor acid secretion occurs after both RYGB and VSG, an impaired dissolution and solubilization of nutrients becomes present. Chronic vitamin D deficiency which subsequently leads to reduced bone mineral density and bone remodeling have been observed three years after RYGB and, in a lesser degree, after VSG(266).

As active calcium transport in the upper small bowel is bypassed in RYGB, postoperatively, low calcium levels over short (6 months)(267), medium (12 months), or long-term (24 months) have been reported(268) despite adequate supplementation of calcium and adjusting vitamin D levels(269).

After VSG, vitamin D malabsorption might be the result from diminished exposure of nutrients to the digestive mucosa(269). Although VSG does not involve intestinal anatomy, calcium uptake might be hampered through several possible mechanisms such as vitamin D deficiency, reduced caloric intake, hypochlorhidria, or proton pump inhibitors' administration(269). In a large cohort study including 999 subjects, the prevalence of hypocalcemia postoperatively was found in 3.6% of patients, with 15 patients (1.9%) underwent RYGB, and 13 patients (9.3%) were VSG operated. In the same study, the lowest calcium concentrations were observed after 1200 days in the RYGB group, and after 239 days in the VSG group, respectively. The recommended daily calcium intake administered through both diet and supplementation varied between 1500 and 2000 mg(270).

Both vitamin D deficiency and decreased calcium absorption contribute for secondary hyperparathyroidism (sPTH) appearance(271). Already, at three months following RYGB, calcium malabsorption and sPTH develop and bone turnover increases. At one year after RYGB, in 8–11% of patients present decreased bone mineral density (BMD) of the hip, whereas only small reductions of spine BMD have been observed. Adverse skeletal effects following VSG have not been so well documented. However, bone loss has been observed 6 months following this bariatric procedure(272).

Iron

Following RYGB 18–53% of patients develop iron deficiency, and respectively, 1–53% of patients after VSG(273). This is rather expected after RYGB, as the duodenum which is most efficient area for iron absorption is bypassed. A study including 72 post RYGB patients reported that red meat intolerance occurred in 49.2%, 42.2%, 46.4%, and 39% of subjects after 1, 2, 3, and 4 postoperative years respectively(274). Following VSG, the iron deficiency is dominated and defined by the malabsorption secondary to the amount of gastric resection which prevents reduction of Fe^{3+} to Fe^{2+}.

Several mechanisms underlie the pathogenesis of postsurgical iron deficiency: After ingestion, the gastric acidic environment enhances iron absorption by converting it from the ferric state (3+) to the ferrous form (2+), the only form of iron that can be absorbed in the GI(240). The reduced HCl secretion in the gastric pouch as well as decreased intestinal absorptive surface (duodenum and proximal jejunum) and administration of H_2 blockers or proton pump inhibitors significantly impair iron absorption(247). Also, iron-rich food intake after bariatric surgery is considerably decreased due to both caloric restriction and food aversions, especially to red meat(253).

Following BS, iron deficiency results in microcytic anemia(253), a condition which mimics other mineral defects such as vitamin B_{12} and folate deficiencies which may also be present and therefore is rather difficult to establish its diagnosis and subsequent treatment. For this reason, a frequent laboratory monitoring of iron levels and preventive supplementation are recommended after BS(250). The therapeutic administration of iron is better to be delivered

intravenously as the high rate of gastrointestinal side effects, impaired absorption, and poor adherence to oral supplementation can be avoided(274).

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 their malabsorption(7), but generally the frequency of these deficiencies is low and therefore their clinical manifestations are rarely reported(276,277).

Vitamin A deficiency can be induced by the severely diminished retinol and carotenoids' intake due to calorie restriction. Additionally, the recommended low fat diet following BS, further contributes to diminished absorption of vitamin A. Furthermore, non-alcoholic steatohepatitis and cirrhosis, frequently observed in BS patients, might impede vitamin A storage and synthesis(277). Thus, the prevalence of vitamin A deficiency following RYGB ranges between 8% and 11%(278). However, no effects on serum vitamin A concentration or visual function following both RYGB or VSG has been reported in a recent study(279).

Regarding vitamin E and K deficiency after BS we found very few studies(7,272). Thus, vitamin E deficiency reported in 8.7% of patients, after adjustment of serum levels to total cholesterol at one year following RYGB(278). In a review study, the prevalence of vitamin E deficiency after RYGB is between 0% and 22%(280). In another systematic review, it is stated that although rare, a symptomatic vitamin K deficiency may occur in patients submitted to major BS procedures, and therefore, these patients should be closely monitored post-surgery(281).

Zinc, Copper and Selenium

Normally, zinc competes with both iron and copper for absorption in the small bowel. Therefore, it is advised to BS patients to separately dispense these supplements. If zinc and copper are taken together, they should be supplemented in an appropriate ratio(282). A slightly higher post-surgical zinc deficiency was observed a year following RYGB (37%) than

following VSG (34%)(283). A study analyzing micronutrient deficiencies after both RYGB and VSG during a follow-up for five years, found reduced serum zinc concentrations in respectively 25.7% and 12.5% of patients(284). When routinely supplemented after RYGB surgery the zinc deficiency is generally asymptomatic and varies between 8% in short-term and 25.7% in long-term(282).

Copper deficiency after RYGB has a 10% prevalence approximately. The risk of developing symptomatic hypocupremia after BS is scarce among patients who adhere to prescribed supplementation(285). In patients who had VSG surgery, copper concentration tends to decline during the first two postoperative years, and furthermore, five years after, 9.8% of patients have still inadequate copper concentrations(286, 287).

Selenium is a trace element and important antioxidant in the form of selenocysteine, which is the 21st amino acid used in human protein synthesis(288). Serum levels of zinc, copper, and selenium were found to be relatively stable after both RYGB and VSG in patients taking adequate supplementation, although a likelihood for decreased selenium serum levels was observed(289). However, selenium deficiency was not documented in VSG patients following BS(287).

Probiotics and Gut Microbiota: Implications for Bariatric Patients

It is well known that probiotics can be beneficial to the host even without inhabiting the gut or making major changes to gut microbiota(290). The most commonly administered probiotics are bacterial phyla belonging to *Lactobacillus, Bifidobacterium,* and *Sacharomyces genera*(291).

Although probiotics use is common postoperatively, studies on their efficacy after BS is limited(292). It has been reported that the high pH setting achieved after RYGB, allows for higher survival of probiotic bacteria during transition through the acidic milieu of the gastrointestinal tract, thus making BS patients a suitable target group for probiotic therapy. It has been reported that the 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 an optimized micronutrient status(293).

The effects of probiotics following BS have been reported in three studies on patients who underwent RYGB, and in only one performed on VSG patients(294,295). More specifically, in a study of 60 RYGB patients, an improvement of gastrointestinal symptoms and quality of life was observed 14 days after probiotics administration(292). A triple-blind randomized controlled trial on 9 RYGB patients demonstrated that prebiotics administration alone, augmented weight loss(294). Finally, probiotic administration was associated with ameliorations of SIBO and increased weight loss in 44 RYGB subjects. It is also reported that after probiotic administration, significantly increased levels of vitamin B_{12} are observed at three and six months postoperatively, a finding which could be related with reduced bacterial overgrowth, a clinically relevant finding as BS is associated with an increased B_{12} deficiency risk(293,294).

On the other hand, the study on VSG patients did not report any improvements associated with probiotic therapy at six months and one year after BS, implementing that VSG leaves little or no room for an extra beneficial effect by probiotics administration(295,296).

Conclusion

Bariatric surgery, being the most effective treatment of severe obesity, has continuously expanding use in our modern era. From the other hand, the role of gut microbiota on the host's ability to maintain a healthy metabolism and digestion is widely recognized. However, our understanding of the linking mechanisms between obesity and concurrent changes in gut microbiota is not clear as it seems that bariatric surgery cannot fully restore the disrupted microbial balance provoked by obesity. Therefore, there is a growing interest regarding the effects of bariatric surgery on gut microbiota as the weight loss and improvement or remission of obesity related comorbidities after bariatric surgery are associated with significant alterations in gut microbiota composition.

The exact contributing mechanisms which induce the GM alterations after bariatric surgery are not clear as different factors have been suggested namely diet, weight loss, or surgery itself. Moreover, there are some side effects that are triggered from the onset of small intestine bacterial overgrowth, which affect the weight loss process of the patients who underwent bariatric surgery.

Still the impact of bariatric surgery is not well defined, as the microbiota alterations which are detected following surgery are not consistent, and they should be considered in the context of restricted energy intake and altered dietary quality. Moreover, no differences regarding GM modulation were observed among the two most currently performed weight loss surgery techniques, i.e., RYGB and VSG. In general, an increase in members of the phylum *Bacteroidetes* and *Proteobacteria*, as well as a decrease in members of the phylum *Firmicutes* is reported.

In summary, bariatric surgery seems to attempt to restore a healthier gut microbiome with a leaner metabolic profile, and this microbiome re-alignment potentially contributes to the observed reduced fat mass reduction, the increase of lean mass, as well as resolving the obesity related co-morbidities. However, the mechanism by which microbes and microbial by-products restore the gut microbiota remain poorly understood and microbiome

manipulations that exploit the host-bacteria interaction after bariatric surgery still need to be developed.

Tables

Table 1. Comparison of the two main bariatric surgery procedures

	Roux-en-Y gastric bypass (RYGB)	Vertical sleeve gastrectomy (VLS)
Technique	• 15-30 ml gastric pouch • Gastrojejunostomy (GJ) • Jejunojejunal anastomosis (Roux-en-Y) 30-50 cm distal to ligament of Treitz • Remnant disconnected but left in situ	• Excision of lateral 70-80% of stomach along the great curvature • ~ 100 mL gastric reservoir (sleeve)
Mechanism of action	• Instantaneous food transfer to small intestine, altering: - Gut hormones - Bile acids - Neural signaling - Gut microbiota Gut-brain-endocrine Adipocyte-brain axes • Results in reduced food intake, increased satiety and altered food preferences	• Alterations in: - Gut hormones - Bile acids - Neural signaling Gut microbiota Gut-brain-endocrine Adipocyte-brain axes • Results in reduced food intake, hunger, increased satiety and altered food preferences
Advantages	• Significant long-term weight loss • Glycemic control improvement in 90% of cases • Maintain percent EWL in the long term • Hunger reduction and satiety • Food preferences changes • Increases energy expenditure	• Significant long-term weight loss (~ 10% less than RYGB) • Glycemic control as effective as RYBG • Maintain percent EWL in the long term • Hunger reduction and satiety • Food preferences changes • No anatomical rerouting of food • Short length of stay (< 2 days) • Technically simpler than RYGB • Lower complication rate than RYGB
Disadvantages	• Technically complex (two anastomoses) compared with AGB or VSG. • Higher complication rate than AGB or LSG; for example, anastomotic leak or dumping syndrome can occur. • Longer length of stay • Long- term vitamin and/or mineral deficiencies (for example, vitamin B12, iron, calcium or folate) • Requires lifelong vitamin and/or mineral supplementation. • Lifelong dietary changes • Increases alcohol addiction and suicide rates • Postprandial hypoglycemia	• Anastomotic leak can be difficult to manage • Susceptible to long-term vitamin and/or mineral deficiencies (less common than with RYGB) • Precautionary lifelong vitamin and/or mineral supplementation • Lifelong dietary changes • Irreversible • Potential risk of Barrett esophagus
EWL: excess weight loss		

Table 2. **Changes of human gut microbiota following Bariatric Surgeries.**

↑/↓	RYGB	VSG
↑	*Akkermansia* (Verrucomicrobia)	*Bulleidia* (Firmicutes)
↑	*Escherichia* (Protobacteria)	*Roseburia intestinalis* (Firmicutes)
↑	*Klebsiella* (Protobacteria)	*Faecalibacterium prausnitzii* (Firmicutes)
↓	*Lactobacillus* (Firmicutes)	*Coprococcus comes* (Firmicutes)
↓	*Bifidobacterium* (Actinobacteria)	
↓	*Faecalibacterium prausnitzii* (Firmicutes)	
↓	*Coprococcus comes* (Firmicutes)	

Table 3. Literature findings of the postoperative changes of gut microbiota

Author, Reference, year	Postoperative GM changes		
	Increased abundance	**Decreased abundance**	**Comments**
Federico(20), 2016	*Lactobacillus crispatus*	*Butyrivibrio fibrisolvens, Roseburia hominis/faecis, Dorea longicatena, Blautia spp./Ruminococcus spp., Ruminococcus obeum*	Highly heterogenous fecal bacteria profiles, with similarity ranging between 50% -65% in pre-surgery & 30-65% in post-surgery patients
Furet(183), 2010	*Bacteroides/ Prevotella* E. coli	*Bifidobacterium* *Lactobacillus/ Leuconostoc/ Pediococcus*	-
Graessler(190), 2013	*Enterobacter, Citrobacter, Neurospora, Veillonella, Salmonella, Shigella* E. coli tended to increase	*Faecalibacterium, Coprococcus, Helicobacter, Dictyostelium, Epidinium, Anaerostipes, Nakamurella, Methanospirillum, Thermomicrobium*	-
Ishida(294), 2014	-	-	Increased bacterial counts were registered in the gastric pouch
Kong(197), 2013	*Bacteroides* *Alistipes* *Escherichia*	Firmicutes (*Lactobacillus*, *Dorea*, *Blautia*) *Bifidobacterium*	Increased richness of GM after RYGB
Murphy(196), 2017	Firmicutes post-RYGB Actinobacteria post-RYGB Bacteroidetes post-SG	Bacteroidetes post-RYGB	-
Palleja(147), 2016	*Escherichia coli*, *Klebsiella pneumonia*, 10 species belonging to the genus *Streptococcus*, 4 from *Veillonella*, 2 from *Alistipes*, *Bifidobacterium dentium*, *Enterococcus faecalis*, *F. nucleatum*, and *Akkermansia muciniphila*	*E. prausnitzii*	-
Patrone(50), 2016	*Lactobacillus Megasphaera* *Acidaminococcus* *Enterobacteriaceae*	*Lachnospiraceae* *Clostridiaceae* *Ruminococcaceae* *Eubacteriaceae* *Coriobacteriaceae*	31 bacterial groups were differentially abundant.
Tremaroli(154), 2015	Gammaproteobacteria Several Proteobacteria (*Escherichia*, *Klebsiella*, *Pseudomonas*) *E. coli* tended to increase but not statistically significant	3 species of Firmicutes (*Clostridium difficile*, *Clostridium hiranonis*, *Gemella sanguinis*)	-

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