Bariatric procedures and microbiota: patient selection and outcome prediction

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Abstract: Obesity is a major health issue throughout the world and bariatric surgery plays a key role in its management and treatment. The role of microbiota in determining the pathogenesis of obesity has been widely studied, while its role in determining the outcome of bariatric surgery is an emerging issue that will be an outcome in near future studies. Studies on mice first showed the key role of microbiota in determining obesity, highlighting the fat mass increase in mice transplanted with microbiota from fat individuals, as well as the different microbiota composition between mice undergone to low-fat or high-fat diets. This led to characterize the asset of microbiota composition in obesity: increased abundance of Firmicutes, reduced abundance of Bacteroidetes and other taxonomical features. Variations on the composition of gut microbiome have been detected in patients undergone to diet and/ or bariatric surgery procedures. Patients undergone to restricting diets showed lower level of trimethylamine *N*-oxide and other metabolites strictly associated to microbiome, as well as patients treated with bariatric surgery showed, after the procedure, changes in the relative abundance of Bacteroidetes, Firmicutes and other phyla with a role in the pathogenesis of obesity. Eventually, studies have been led about the effects that the modification of microbiota could have on obesity itself, mainly focusing on elements like fecal microbiota transplantation and probiotics such as inulin. This series of studies and considerations represent the first step in order to select patients eligible to bariatric surgery and to predict their outcome.

Keywords: bariatric endoscopy, bariatric surgery, gut microbiota, obesity

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Introduction

Obesity has become one of the most relevant health issues all over the world. It is defined by World Health Organization (WHO) as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in meters). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight.

In 2016, about 1.7 billion subjects older than 18 years, were overweight and 700 million were obese. Moreover, 51 million children under the age of 5 were overweight or obese in 2016. In developed countries, obesity can kill more than malnutrition but it is preventable.

Several factors concur in defining the etiology of obesity, among which excessive food intake, incorrect diet, sedentary and passive lifestyle, bad sleep habits, genetics and gut microbiome.

Among these factors, rising attention has been focused on gut microbiome, both as an etiologic factor of obesity and as a determining factor in the outcome of therapies. We conducted our research on PubMed searching "obesity and microbiota" and "bariatric surgery and microbiota." We selected studies and trials concerning this topic

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considered "the most interesting and relevant," based on our expertise in the field of microbiota.

Gut microbiota is the given name to the community of microbes living in our intestine. Gut microbiota contains tens of trillions of microorganisms, including at least 1000 different species of known bacteria with more than 3 million genes (150 times more than human genes). Microbiota can weigh up to 2 kg in total. One third of our gut microbiota is common to most people, while two thirds are specific to each one of us. Among physiologic functions, microbiota acts as a crucial regulator of metabolic functions directly and indirectly acting on enterocytes and other cells of the intestinal mucosa.[1,2] Such functions are particularly relevant also in obesity as shown by several reports including emerging data from fecal transplantation.

Furthermore, key therapies for obesity, like the bariatric and also endoscopic surgery, have been extensively associated to microbial signature in case of therapeutic success or failure. In this review, we will focus on relationship between obesity and microbiome, relationship between microbiome and outcome of therapeutic intervention and also on the potential role on microbial signature for patient selection.

Relation between microbiome and obesity

Alterations in gut microbial composition and function, defined dysbiosis, are associated with many clinical conditions including obesity, in both human or mice studies. Pioneering studies from Walker and Parkhill[3] showed that the transplantation of fecal microbiota from an obese woman to recipient mice led to increased mice's adiposity. On the contrary, microbiota transplantation from a lean twin of the obese woman didn't lead to the same result, thus demonstrating the key role of gut microbiota in determining the amount of fat mass.

An interesting study of Zhang and colleagues[4] compared the microbiome composition in mice treated with low fat diet (LF), diet-induced-obese mice (DIO) and diet-resistant mice (DR). It was shown that LF and DR mice present higher richness and diversity of microbiome than DIO. At the same way, DIO, presented higher abundance of Firmicutes and Actinobacteria, lower concentrations of Bacterioidetes and Proteobacteria than DR and LF; what's more, the Firmicutes to Bacterioidetes ratio in DIO was the highest one, followed by DR and LF. This study also showed significant differences in the colon and liver inflammation, and in the expression of tight junction proteins between DIO and DR/LF.

Some evidence found the existence of a mouse strain, HLB444, carrying an *N*-ethyl-*N*-nitrosourea (ENU)-induced mutation in a highly conserved C2 H2 zinc-finger DNA binding motif of the transcriptional regulator KLF15, resistant to diet-induced obesity. In high fat diet, HLB444 shows decreased body fat, lower hepato-steatosis and glucose, and improved insulin sensitivity compared to controls. Gut microbial profiles in HLB444 derived from 16S rRNA sequencing of fecal samples differed from controls under both chow and high fat diets.

Generally, dysbiosis contributes to obesity-related and metabolic conditions like hyperglycemia and hyperlipidemia. In an aged mouse administered with a high fat diet that induced obesity, the modulation of gut microbiota by statins atorvastatin and rosuvastatin was studied, in order to find associations between gut microbiota and immune response: Atorvastatin and rosuvastatin significantly ameliorated the abundance of Bacteroides, Butyricimonas and Mucispirillum Genera, also correlated to levels of IL-1β and TGFβ1 in the ileum. In addition, oral fecal microbiota transplantation with fecal material collected from rosuvastatin-treated mice ameliorated hyperglycemia.

To determine the success of microbiota transplantation on obesity and gut-induced microbial dysbiosis, the effect of a hypercaloric diet on the gut microbial composition was evaluated and combined with antibiotic treatment to deplete the microbiota before fecal microbiota transplantation (FMT). Among the high fat diet (HFD) group and the low-fat diet (LFD) group, the former showed an increased Firmicutes to Bacterioidetes (F/B) ratio; there were no differences in the phylum level or alpha diversity or the Shannon and Simpson indexes, but, regarding the order, Clostridiales were not very high, despite they were strongly affected by diet and responsible for microbiota unbalances.

On the second hand, mice administrated with a high dose of dexamethasone, the species of anaerobic bacteria in the ileum increases, and this suggests a relevant and acute effect of glucocorticoids (GC) exposure on gut microbial composition. In

Table 1. Microbiota and obesity: its role in pathogenesis, how it changes after bariatric surgery and its possible role in predicting response to bariatric surgery.

GENERE/PHYLA	PATHOGENETIC ROLE IN OBESITY	VARIATION AFTER BS	PREDICTIVE ROLE OF RESPONSE?
Firmicutes	↑	↑ SG	↑
Actinobacteria	↑	↓ SG	
Bacterioidetes	↓	↑ SG ↓ GB	
Proteobacteria	↓	↓ SG	↑
Firmicutes/Bacterioidetes	↑	↑ SG ↑ GB	
Verrucomicrobia (*Akkermansia*)	↓	↑ GB	
Faecalibacterium Prausnitzii	↓		
Prevotella/Bacterioidetes		↓ SG ↑ GB	

fact, GC signaling owns part of its activity to interactions with gut microbes, influencing innate immune responses in the intestine.

The biodiversity in individuals with GC-induced obesity is strongly decreased. Some evidence shows how the bacterial communities of GC-induced obesity subjects are rich with *Firmicutes* (genus *Streptococcus*) and depleted in *Bacteroidetes*. Moreover, Small Chain Fatty Acid (SCFA) were lower in GC-induced obesity: they enhance sensitivity to insulin and induce the release of satiety hormone. In addition, through lipopolysaccharides (LPS), component of the bacterial membranes, GC triggers inflammatory processes associated with obesity and insulin resistance.

Melatonin as well is known to play a role in determining weight gain and obesity. Melatonin's levels are somehow thought to be related to gut microbiota composition, though this relationship still remains unclear. Melatonin reduces body weight, liver steatosis and low-grade inflammation and improves insulin resistance in mice fed with HFD. HFD alters several operational taxonomic units (OTUs) comparing to normal chow diet (NCD), and melatonin supplementation reversed this unbalance decreasing the *Firmicutes/Bacteroidetes* ratio and increasing the relative abundance of *Akkermansia*, a mucin degrading bacteria associated with healthy mucosa. This demonstrates that melatonin can be used as a probiotic to reverse HFD-induced dysbiosis. The results shown by studies on mice are quite similar to those emerged by studies on humans.

The increased ratio of Bacterioidetes to Firmicutes is linked to a diminished body mass.[5] At the same time, a high fat intake increases LPS level, related to increased general inflammation.[6]

To sum up (Table 1), it can be stated that obesity in humans can be related to some precise features of gut microbiota composition[7] including:

- An increase in Firmicutes phylum;
- Reduced abundance of Bacterioidetes;
- Higher level of Actinobacteria phylum;
- Lower proportion of Verrucomicrobia (which most relevant species is Akkermansia Muciniphila);
- Lower proportion of Faecalibacterium Prausnitzii.

Microbiome in correcting obesity

Several changes in microbiota composition have been detected, both treating obesity with diet and surgery (Table 1).

Effects of diet on microbiota composition have been studied. Studies from Zhou and colleagues[8] investigated the effects of a low calories diet on microbiota by analyzing the concentrations of tri-methylamine *N*-oxide (TMAO), a metabolite

produced my gut microbiota strongly associated with diabetes and insulin resistance. According to both studies, 6 months after the dietary intervention, patients who underwent a low-fat intake presented lower levels of TMAO, choline and carnitine (precursors of TMAO). These biochemical features, strongly dependent on microbiota, were associated to better glucose fasting and insulin resistance, suggesting that changes in microbiota composition determine such improvement in the metabolic profile.

The role of gut microbiome in correcting and treating obesity by surgery has been studied as well, with rising interest. Several alterations in microbiome's diversity and taxonomic composition have been detected throughout the years. In particular, several differences of microbiome composition have been showed among patients treated with different surgical approaches.

Studies[9,10] detected an increase of alpha diversity in patients eligible for bariatric surgery after the surgical procedure, especially after laparoscopic gastric bendage. At the same way, they showed different variations of taxonomic composition of microbiota before and after sleeve gastrectomy (SG) and laparoscopic gastric bendage (LGB). In particular, SG led to a decrease in Proteobacteria and Actinobacteria, with an increase of Firmicutes; on the contrary, LGB led to a decrease in Bacterioidetes. Another interesting data was the one concerning the Prevotella/Bacterioidetes ratio: according to the study, this ratio tends to decrease after SG, whereas to increase after LGB. The same group of research showed (2018), in another though similar trial, interesting data about Firmicutes/Bacterioidetes ratio: this was shown to be increased both after SG and LGB.

Interestingly, the *Prevotella*/*Bacterioidetes* ratio resulted decreased after Roux-en-Y gastric bypass (RYGB) according to a study by Furet and colleagues.[11]

The relative abundance of Firmicutes and Bacterioidetes, though, looks like showing different patterns according to the kind of surgical procedures: in a study of *2017* by Murphy and colleagues,[12] it was showed, further than the usual increase of diversity and richness after surgery, an increase in *Firmicutes* and decrease in *Bacterioidetes* after RYGB, whereas an increase of *Bacterioidetes* after SG.

Another interesting profile to be studied is Akkermansia Muciniphila, belonging to Verrucomicrobia phylum. Its anti-inflammatory properties are well known, especially in the pathogenesis of inflammatory bowel disease. It seems to play an important role in obesity as well, where its role as a marker of metabolic health is well characterized. In this field, evidence[13,14] showed a lower relative abundance of A. Muciniphila in patients with severe obesity compared to less obese and normal weight patients. They then monitored the levels of A. Muciniphila after surgery, thus showing an increase of this spec after surgery (though only significant after RYGB and not after LGB).

Similar results came out from a de Jonge and colleagues,[15] that highlighted these changes in microbiome composition (increased alpha diversity according to Shannon Index, increased relative abundance of *Proteobacteria* and *Firmicutes*, especially Lactobacilli) focusing on patients operated of duodenal jejunal exclusion (DJBL), that is considered a "no surgical bariatric procedure" that mimics the effects of RYGB.

Still recent evidences[16] highlighted an increase of Bacterioidetes both after SG an RYGB, a decrease of Firmicutes only after RYGB, a decrease of Proteobacteria both after SG and RYGB and a decrease of Verrucomicrobia after both procedures.

Substantially, from all the studies above, it emerged that bariatric surgery can induce microbiome shifting toward a healthier and "lean-like" composition, correcting the relative abundance of *Firmicutes, Bacterioidetes, Proteobacteria* and *Verrucomicrobia*. These four major phyla are thus supposed to be the main influencers and modulator of the response to bariatric surgery.

Microbiome modulation to treat obesity and its complications

Once stated the role that microbiota plays in the development of obesity, it's reasonable to try to impact on its composition in order to treat obesity. This can be achievable by using probiotics (or prebiotics) or performing FMT. FMT is the procedure by which fecal microbiota from a healthy donor is transplanted to an obese patient.

This was the aim of a study by Lai and colleagues,[17] that showed that beneficial effects of

diet and exercise is transmissible through fecal microbiota transplantation from mice under low-fat diet to mice under high-fat diet.

At the same way, a study from Guirro and colleagues[18] performed fecal microbiota transplantation upon rats, showing that, the microbiota transplantation from rats on a low-fat diet to rats on a high fat diet (previously treated with antibiotics) restored the relative abundance of *Firmicutes, Bacterioidetes* and *Proteobacteria.*

A possible role could be played by probiotics. A basic science study from Bubnov and colleagues[19] focused on the role of *Lactobacillus* and *Bifidobacteria* as probiotics to determine a significative weight loss (and circulating cholesterol levels) in obese mice, showing a significant reduction of total and free cholesterol in obese mice treated with these agents.

Another possible probiotic agent that could be taken into consideration in the treatment of obesity is inulin. A study on rats from Weitkunat and colleagues[20] showed the effects of inuline and SCFA (proprionate and acetate) on rats with high-fat diet induced obesity. Both the agents reduce blood glucose concentration 4 hours after a meal and lead to a reduction of adipocyte hyperplasia, thus increasing insulin resistance and leading to a final body weight comparable to the one of mice under low-fat diet. Last but not least, both inulin and SCFA reduce total liver weight due to a reduced fat accumulation, underpinned by reduced activity of fatty acid synthase, that leads to a reduced lipogenesis.

Microbiome as predictor of response to therapy?

If much (though not enough) is known about the relationship between microbiota and obesity, and about the changes in microbiota composition after bariatric surgery procedures, still very little is known about how we can use the knowledge of microbiota composition to predict clinical outcomes of bariatric surgery and rates of maintenance. Finding microbiota "signatures" that can address physician to take up or not bariatric surgery is an impellent need in modern medicine, considering the high costs and (rare but still possible) collateral effects that bariatric surgery after all requires. Few studies have been started on this topic (Table 1).

One of them[21] characterized microbiota in a group of patients divided into responders to BS, primary failure and weight regain (secondary failure). If no significative differences in alpha diversity and clustering of fecal communities emerged from the analysis, interesting data emerged from the taxonomic analysis. Some genera presented statistically significant differences among groups for success, primary failure and weight regain groups: within the Firmicutes genera Sarcina (0.06, 0.03% and 0.00 % respectively), Butyviribio (0.79, 0.84% and 0.61%), Lachnospira (2.85, 2.63, 2.11 %); Pseudoalteromonas (success group abundance 0.14%) from Proteobacteria phylum; and from Fusobacteria phylum the genus Cetobacterium (success abundance 2.33%). While within Bacterioidetes only two minor genera registered differences: 57N15 (0.31, 0.23% and 0.05% respectively) and AF12 (success group abundance was 0.05%). Furthermore, significant differences were found studying the core microbiota of each group, with group of success showing more genera from *Proteobacteria* and *Firmicutes* than groups of primary failure and weight regain.

No further evidence has been found so far, to our knowledge.

For these reasons, we consider very important to focus on this field of research. Defining an identikit of the microbiota of a perfect patient for bariatric surgery would allow gain money, raise the success rate of BS and lower the rate of surgery side effects. Furthermore, it can be hypothesized that protocols aimed to modify microbiota composition in dysbiotic candidates o recipients to bariatric procedures, could perhaps optimize its results.

Conclusion

As emerged from the discussion above, there is still much to do in characterizing the role of microbiota in the pathogenesis and correction of obesity. Still a lot of aspects about this topic are unclear: above all, there are a lot of opposite data about the role of Firmicutes/Bacterioidetes ratio and Prevotella/Bacterioidetes ratio. Neither the role of Bacterioidetes and Firmicutes itself is much clear.

Many certainties we have, instead, about Proteobacteria and Verrucomicrobia (especially A. Muciniphila), whose role as protectors from

obesity and enhancer of response to bariatric surgery looks certain.

For this reason, it is quite difficult, at the moment, to fully depict the role of microbiota as predictor of response to surgical therapy of obesity. Consequently, more studies are needed to make a clear portrait of the perfect patient to candidate to surgical management of obesity.

Finally, several associations between microbiota components and clinical outcomes presented in this review does not fall in a cause-effect relation but actually in a more complex multiparametric interaction which will require novel models to be fully understood in order to be applied in clinical setting.

Conflict of interest statement

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