



Obesity and Microbes: The Role of Bariatric Surgery

Giovanni Pellegrino*

School of Medicine, University of Bari, Bari, Italy

Obesity is defined as the accumulation of excess fat in the body that can compromise health: this corresponds to a BMI equal to or greater than 30 kg/m², with three different likely levels that are class I (BMI = 30.0 – 39.9 kg/m²), class II (BMI = 40.0 – 49.9 kg/m²) and class III (BMI > 50 kg/m²) [1].

Obesity is considered a risk factor for various chronic illnesses such as cardiovascular diseases and hypertension, type 2 diabetes and thyreopathies, non-alcoholic fatty liver disease, and cancer. Over the past thirty years, the prevalence of obesity is rapidly getting higher not only in developed countries but also in developing countries. Even though physical inactivity and excessive food intake are usually thought of as the cause of obesity, its etiology is quite complex. There are many factors to be taken into account, such as environment, genetics, and lifestyle [2]. Besides, the microbiota has been reported as one of the key factors in obesity etiology [3-6].

Obesity is one of the easiest diseases to diagnose but one of the hardest to treat and it should be treated effectively to avoid its consequences on health. Obesity management must be planned in a personalized way [7]. At the moment, treatment methods for obesity are behavior modification therapy, diet therapy, medical treatment, and surgical treatment [8]. Surgery is not always the first choice and it should be applied only if the appropriate indications are present; after its application, body weight loss occurs with changes in the metabolism of bile acids, gastric pH, the metabolism of hormones, and in microbiota [9].

Bariatric Surgery

Bariatric surgery is one of the most effective therapeutic treatments for obesity and complications [10]. Thanks to it, long-term permanent body weight loss is achieved, metabolic effects of obesity are reduced, many diseases are prevented and quality of life is markedly increased [11]. Body weight loss with bariatric surgery is fulfilled through the change of food preferences, reduction of nutrient digestion, acceleration of gastric void, regulation of hormonal secretion (e.g. glucagon-like peptide 1, GLP-1, and peptide tyrosine tyrosine, PYY), and alterations in the metabolism of bile acids. In spite of the fact that bariatric surgery is suitable for obesity treatment, some complications can rarely occur and they should be taken into account in evaluating surgical risk. These are gastroesophageal reflux, nutritional deficiencies, gastric outlet obstruction, mesh erosion and marginal ulcerations, slippage, and internal herniation [12]. Indications for bariatric surgery were established by the United States National Institute of Health in 1991 (Table 1) [13].

There are various bariatric surgical methods according to their effect mechanisms (Figure 1) [14].

***Corresponding author:** Giovanni Pellegrino, School of Medicine, University of Bari, Bari, Italy, E-mail: g.pellegrino21@studenti.uniba.it

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part of the stomach can be tailored by filling it with sterile 0.9% saline solution injected through the abdominal wall. Adjustment of the band

Obesity can affect the human immune system in a significant way and gut microbiota is likely to express a notable function. This is a controversial statement because there is much disagreeing evidence in scientific literature. For example, it has been outlined that a higher BMI compromises immunization following COVID-19 vaccination [44] but other studies, instead, have reported that there is no relationship between BMI and COVID-19 severity, even in the most critical cases [45]. Moreover, it has been stated that obesity could have a protective role against infectious diseases: that is the case of pouchitis by *Clostridioides difficile*. [46]

What is true is far from easy to be defined. This is mostly due to the fact that obesity is complex to the extent that it cannot be evaluated as a single variable. In any case, intestinal microbiota modification may be a therapeutic treatment for the prevention or even reversal of obesity.

Bariatric Surgery and Gut Microbiota

It is reported that significant changes in gut microbiota occur after bariatric surgery; the most likely mechanisms include changes in food choices and preferences, reduction of food intake, and nutrient malabsorption [47].

First of all, short-term dietary changes may cause fast changes in the composition of intestinal microbiota. As an example, it has been outlined that *Prevotella* enterotypes are associated with complex carbohydrate-rich and simple carbohydrate-rich diets, whereas *Bacteroidetes* enterotype is correlated with a typical "Western diet", full of animal protein and saturated fatty acids [48]. In detail, some diets can affect the quantity of specific strains of gut microbiota, such as diets low in fats and high in carbohydrates but also diets high in carbohydrates with a low glycemic index [49].

A second factor regulating the change in gut microbiota after bariatric surgery has been stated to be bile acids [8]. Bile acids can rule their synthesis and their intestinal reabsorption through modulation of the nuclear-located farnesoid X receptor (FXR). Another pathway of auto regulation is the G-linked protein TGR5, but this pathway is yet to be 100% understood [50]. Recently, the physiological role of bile acids has been associated with pancreatic beta cell function and thus glucose homeostasis but also energy consumption. Even these roles of bile acids are correlated with FXR and TGR5 pathways [8]. Bile and pancreatic secretions are separated from nutrients in RYGB and they come together only in the more distal part of the intestine; as a result, the distal jejunum and proximal ileum are excessively exposed to the nutrients. Dietary lipids are surrounded by the bile acids, while bile acids cycling in the upper intestine become blunted: this leads to an increase of serum bile acids level and of serum FGF15/19 levels that normalize the postprandial bile acids answer after surgery [51]. The pathway underlying the beneficial effects of bariatric surgery has been outlined to be changes in bile acids metabolism [43]. The change in bile acids flow has a definite effect on the alterations in gut microbiota after bariatric surgery, too. In the proximal jejunum, the absence of nutrient transit and the decrease in mobility alter the number of bacteria [24]. The changes in bile acids flow also change the 7α -dehydroxylation capacity of the intestinal microbiota, which is implied in the synthesis of the secondary (intermediate) bile acids. In these terms, administration of a diet supplemented with the primary bile acid colic acid to rats increases the presence of Firmicutes, which contains the enzyme 7α -hydroxylase such as *Clostridium* spp [52].

Even hormones, such as leptin and ghrelin, may change after bariatric surgery. Hormonal changes are linked to both energy metabolism and microbiota [53]. Despite the relationship between

gut microbiota and ghrelin is not clearly comprehended, prebiotics are reported to modulate gut microbiota and decrease serum ghrelin levels [54]. On the other hand, leptin has a controversial role. Serum leptin levels have been outlined to have a positive correlation with *Mucispirillum*, *Lactococcus*. Another study stated that leptin has a positive correlation with *Bifidobacterium* and *Lactobacillus* whilst a negative correlation with *Bacteroides*, *Clostridium*, and *Prevotella* [55]. Researchers have emphasized that further studies are necessary, even though hormones have been reported to influence the intestinal microbiota [38, 56-58].

Another important factor affecting microbiota is changes in pH. After surgery, pH increases as the volume of the stomach decreases. The changing pH influences every part of the gastrointestinal system after the stomach. Increased pH can affect microbiota at an important level. It has been reported that *Bacteroidetes* decrease due to pH fluctuations after surgery, while Firmicutes and Actinobacteria increase [59].

After bariatric surgery, microbiota diversity changes due to the reasons mentioned above. Table 3 briefly shows how microorganisms are affected by bariatric surgery [8].

Bariatric surgery is one of the main treatments of obesity. It is considerably effective in achieving and protecting weight loss. The effectiveness of obesity treatments after bariatric surgery is not only related to food consumption but also to microbiota alteration.

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