Long-Term Effects of Bariatric Surgery on Gut Microbiota

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Obesity is a worldwide disease characterized by an excessive body fat accumulation and by the presence of a subclinical chronic inflammatory status, which is associated with high morbidity and mortality rates. There are multiple pharmacological and non-pharmacological (exercise or dietary interventions) therapeutic strategies to face this disease. However, when these therapies failed, bariatric surgery is the most efficient treatment for obesity. In the last few years, different research studies have demonstrated a key role of gut microbiota, defined as all the microorganisms that habit in the digestive tract, in the development and progression of obesity. For that reason, going deepen in the knowledge of the link between bariatric surgery and gut microbiota could elucidate mechanistic and therapeutic approaches.

bariatric surgery gut microbiota obesity metagenomics metabolomics short-chain fatty acids

1. Introduction

Obesity is one of the main public concerns worldwide, linked to increased rates of morbidity and mortality besides high resources demanding for public health systems [1]. Bariatric surgery is considered the gold standard treatment when non-surgical alternatives have failed, with a great performance to remedy the pathology in the short and in the long term [2][3].

The preponderant role of intestinal microbiota in the development of obesity is undoubtedly accepted in the current knowledge of the disease [4]. Under this perspective, the capacity of bariatric surgery to reshape gut microbiota as one of the mechanisms underlying its therapeutic success has been proposed and several findings reported in this sense. For example, a greater microbial gene richness and bacterial diversity, features associated to a healthy microbiota, have been observed after bariatric surgery [5]. Moreover, the causal role of bariatric surgery-mediated changes in gut microbiota composition in its anti-obesity effect has been demonstrated by the reduced fat mass gain in germ-free mice colonized with faecal microbiota from operated donors [6]. In fact, one of the main contributions of the gut microbiota to the instauration of obesity resides in energy extraction from the dietary nutrients. Weight loss by means of dietary interventions have demonstrated to modify gut microbiota, for example, counteracting the extensively reported increased Firmicutes/Bacteroidetes ratio in obesity and increasing beneficial

Verrucomicrobia phylum [7], but also to promote functional changes in the microbiota and alter its derived metabolites [8][9]. Likewise, bariatric surgery could drive a shift of the metabolic capacity of the gut microbiota towards a lean-like phenotype both from a composition and from a functional point of view, related to the good outcomes of the procedure.

For the above-mentioned reasons, the main aim of this study is to evaluate the long-term effects of bariatric surgery in the faecal metagenome and metabolome of patients with severe obesity.

2. Methods

To reach the proposed aim of this study, as it is shown in the figure below, faecal and blood samples were collected before and 4 years after bariatric surgery from patients with severe obesity and were processed for metabolomics and metagenomic analysis. Gut bacterial communities were identified by 16S rRNA *Illumina* MiSeq sequencing. Polar metabolites were detected and quantified by liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry were employed to determine the concentration of short chain fatty acids (SCFAs).

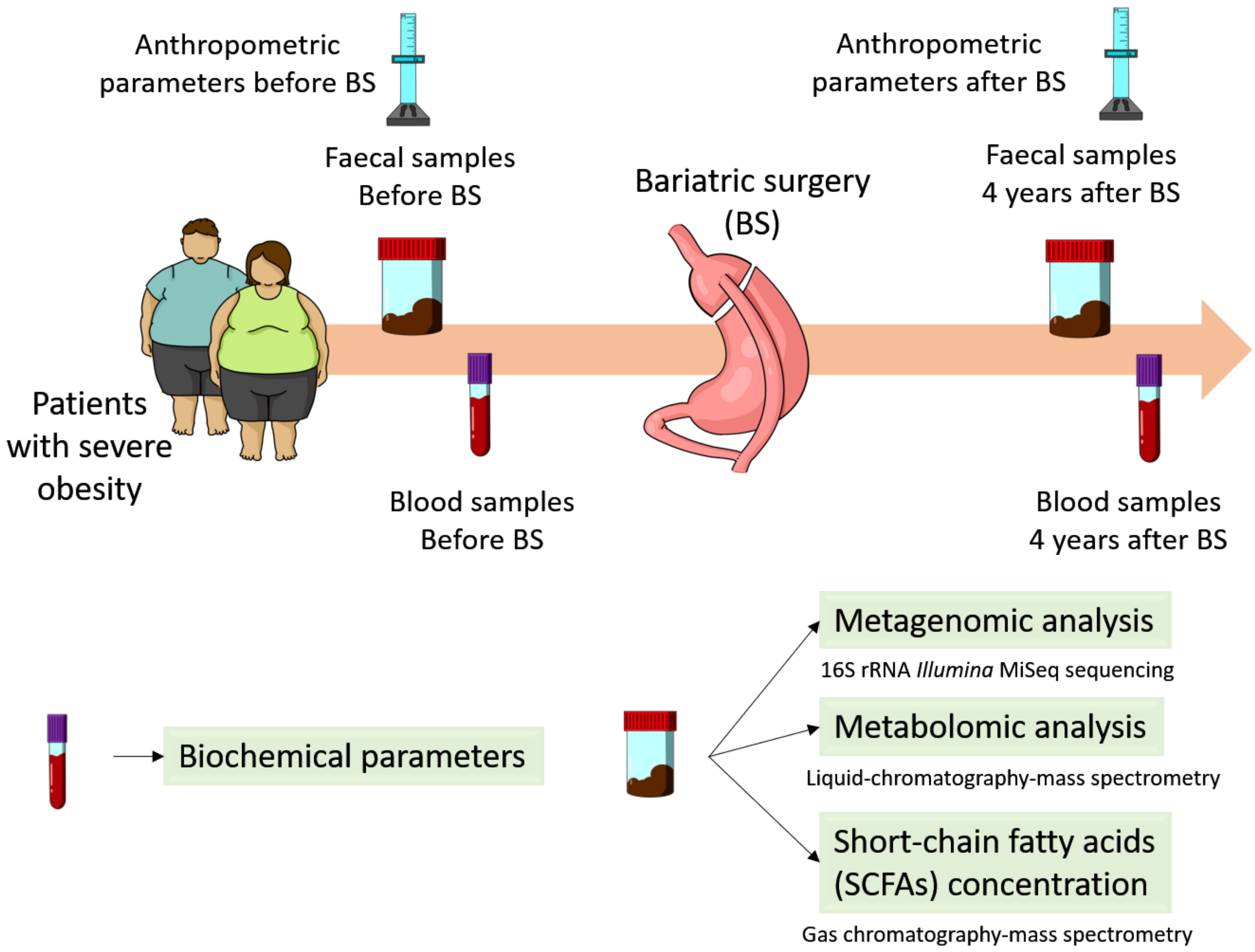

Figure 1. Experimental design.

3. Results and Discussion

Our results showed that bariatric surgery had a profound effect on biochemical and anthropometric parameters and modified the gut microbiota profile. The intervention increased Proteobacteria and Lenthispaerae phyla, whereas Firmicutes was reduced. Proteobacteria phylum has been associated with a beneficial profile characterized by decreased systemic inflammation and improved glucose homeostasis [5], and correlated with weight loss [10]. At family level, our results showed an increase in the abundance of *Enterobacteriaceae*, which has been negatively correlated with cholesterol levels in humans [11][12] as well as positively correlated with weight loss in animal models [13]. The abundance of the *Lachnospiraceae* family members has been positively correlated with BMI, suggesting that the decreased abundance of this family in our study may be related to weight loss [14].

Bariatric surgery also modified gut microbiota composition at the genus level. *Butyricimonas, Parabacteroides* and *Slackia* genera were increased and *Coprococcus, Lachnospira, Lactococcus* and *Phascolarctobacterium* showed an opposite pattern. High levels of *Lactococcus* have been associated with obesity and fasting plasma insulin [15]. Moreover, *Acinetobacter* overgrowth was present in patients under failed bariatric surgery [16], and in our study was positively correlated with LDL plasma concentration, so the significant reduction of this genus could indicate a more successful treatment. *Parabacteroides* has been negatively correlated with serum insulin concentration after bariatric surgery [17] and with BMI in our study, whereas high levels of *Slackia* have been detected in patients after Roux-en-Y gastric bypass [12]. Furthermore, increased abundance of *Butyricimonas* has been associated with less food addiction after bariatric surgery. Finally, *Lachnospira* decreased significantly in operated patients and was positively correlated with BMI, body fat and insulin levels.

The faecal metabolome of the patients with severe obesity was also modified due to bariatric surgery. Methyl acetoacetate, carbamoyl aspartate and serine phosphate increased, whereas metabolites such as 5-aminolevulinic acid, choline, citric acid, malic acid, taurine, TMAO and tropic acid decreased in faeces. Moreover, surgical intervention reduced the tricarboxylic acid cycle, glycine, serine and threonine metabolism, glyoxylate and dicarboxylate metabolism and tyrosine metabolism. These results suggest that branched-chain amino acids (BCAAs) and aromatic amino acids, as well as energetic metabolism, were downregulated with bariatric surgery, findings that have previously reported [18][19][20][21][22]. The reduction in BCAA levels as a consequence of bariatric surgery could be a normalization of the altered amino acid profile associated with obesity [18][19][20], which has been linked to an impairment of glucose homeostasis [18][23].

SCFAs are metabolites produced by gut microbiota fermentation from carbohydrates involved in various physiological process. High levels of these metabolites have been related to cardiometabolic and hepatic health [24][25][26], but also have been associated with gut dysbiosis, gut permeability and excess adiposity [27][28]. In our study, the SCFA faecal profiles of the patients after bariatric surgery were modified, with significant decreases of acetate, butyrate and propionate concentrations, in accordance with previous reports [29][30]. These SCFAs all positively correlated with BMI, reinforcing their reported role in obesity. Moreover, acetate, butyrate and propionate had a negative correlation with *Butyricimonas* and *Parabacteroides* genera, and a positive correlation with the *Lachnospira* genus.

Altogether, correlation analysis showed a metagenomic and metabolomic profile related to bariatric surgery that could be involved in the beneficial effects observed on biochemical and anthropometric parameters.

4. Conclusion

In conclusion, as it is summarized in the figure below, our findings point to bariatric surgery as a long-term modulator of gut microbiota, not only on its composition but also its functionality, promoting less efficient energy extraction from the diet as a possible mechanism linked to the persistent beneficia metabolic effects of a successful intervention.

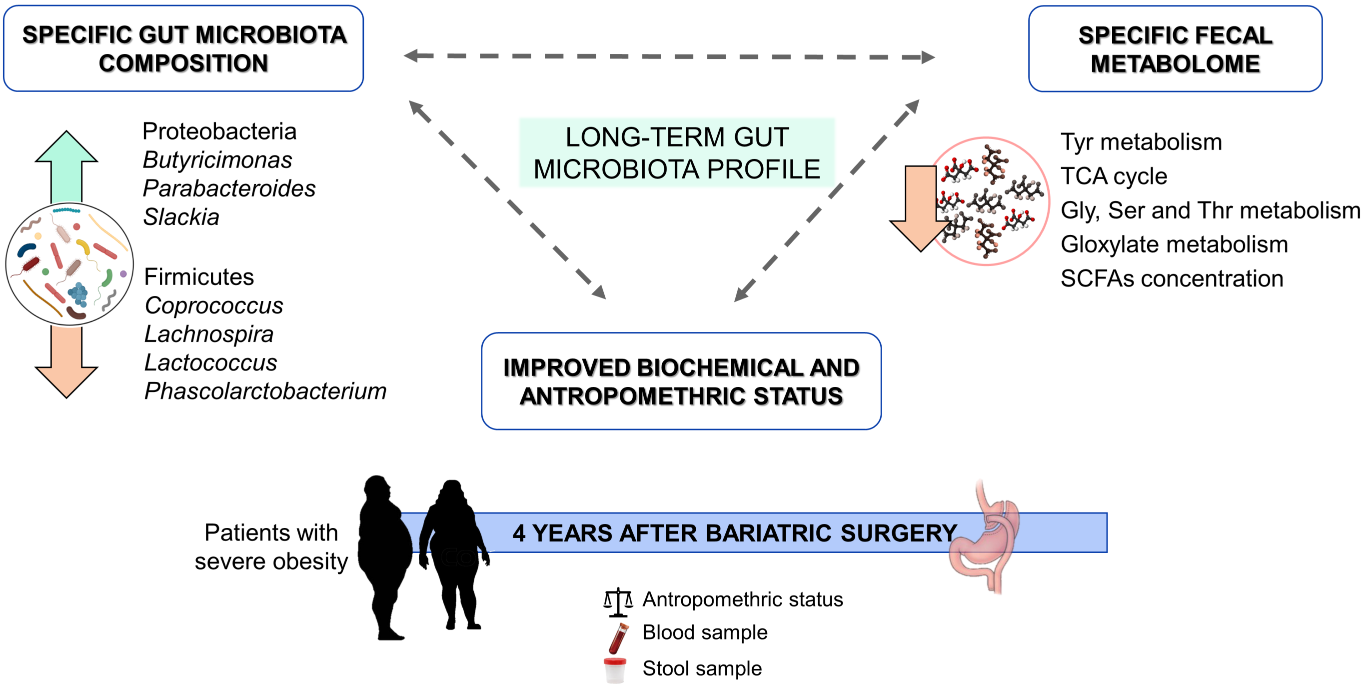

Figure 2. Graphical abstract.

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