Association Between the *Blautia/Bacteroides* Ratio and Altered Body Mass Index After Bariatric Surgery

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Abstract

Current evidence support that the gut microbiota plays a potential role in obesity. Bariatric surgery can reduce excess weight and decrease the risk of life-threatening weight-related health problems and may also influence gut microbiota. In this study, we aimed to investigate the changes in gut microbiota before and after bariatric surgery and evaluate the association of the gut microbial shift and altered body mass index (BMI) after bariatric surgery. Between January 2019 and July 2020, stools from 58 patients scheduled for bariatric surgery were collected. Six months after bariatric surgery, stools from 22 of these patients were re-collected, and the changes in gut microbiota before and after bariatric surgery were evaluated. In addition, the differences in gut microbiota between patients with severe obesity (BMI > 35, n=42) and healthy volunteers with normal BMI (18.8 – 22.8, n=41) were investigated. The gut microbiota of patients who underwent bariatric surgery showed increased α-diversity and differed β-diversity compared with those before surgery. Interestingly, *Blautia* was decreased and *Bacteriodes* was increased at the genus level after bariatric surgery. Further, the *Blautia/Bacteroides* ratio showed a positive correlation with BMI. These results were similar regardless of the surgery type (Roux-en-Y gastric bypass or sleeve gastrectomy). To validate these results, we compared the gut microbiota from severely obese patients with high BMI with those from healthy volunteers and demonstrated that the *Blautia/Bacteroides* ratio correlated positively with BMI. In the gut microbial analysis of patients who underwent bariatric surgery, we identified that the *Blautia/Bacteroides* ratio had changed after bariatric surgery and showed a positive correlation with BMI. Based on these results, we suggest that bariatric surgery could change the gut microbiota and specific microbiomes might have a potential role in obese patients.

Introduction

Obesity is defined as excessive fat accumulation with body mass index (BMI) over 30 (defined as a BMI over 25 according to the Asia-Pacific perspective) and presents a risk to health. Globally, a total of 609 million adults were estimated to be obese in 2015[1]. Obesity is associated with cardiovascular disease, diabetes mellitus (DM), several types of cancers, musculoskeletal disorders, and poor mental health[2–5]. The etiologies of obesity are genetic, behavioral, environmental, physiological, social, and cultural, resulting in energy imbalance and promoting excessive fat deposition[6]. Recently, emerging evidence has suggested that gut microbiota plays a role in obesity. Since the first reporting in 2006 about the metabolic potential of mouse gut microbiota with increased capacity for energy harvest[7], there have been numerous studies reporting an association between obesity and gut microbiota. In particular, obese individuals tend to have an elevated *Firmicutes*-to-*Bacteroidetes* ratio compared with lean individuals, and this ratio is similar to that found in children[8–11].

Bariatric surgery is the most effective treatment option for obesity, which archives rapid and durable weight loss and has dramatic effects on remission of type 2 DM. It also can lead to improvements in the atherosclerotic process, hypertension, obstructive sleep apnea, and cardiovascular related mortality[12,13]. Bariatric procedures include laparoscopic sleeve gastrectomy (LSG), which primarily restricts limiting

food intake, and laparoscopic Roux-en-Y gastric bypass (LRYGB), which induces restriction/malabsorption. Both procedures have remarkable metabolic effects, such as increased glucose tolerance, insulin sensitivity, and secretions of incretin and glucagon like peptide-1[14]. Recent studies have reported that bariatric surgery induces significant shifts in gut microbiota and may contribute to weight loss and metabolic changes[15–17]. The anatomic rearrangements of bariatric surgery mainly affect the proximal intestine, and bariatric surgery could impact the composition and activity of the resident gut microbiota[18]. Although there is increasing evidence for the effectiveness of bariatric surgery on gut microbiota, the understanding for the contribution of gut microbiota to the induction and maintenance of weight loss and the resolution of related comorbidities is not fully understood. Most evidence for the relationship between gut microbiota and bariatric surgery has been limited to the Western population; data on the Eastern population has rarely been reported.

In this study, obese Korean patients who underwent bariatric surgery in a single institution were enrolled. Differences in gut microbiota before and after bariatric surgery were evaluated. We hypothesized that the composition and distribution of the gut microbiota changed after bariatric surgery and that these transitions are associated with alteration of BMI. The aim of this study was to investigate the change of gut microbiota before and after bariatric surgery and evaluate the association of gut microbial shift and altered BMI after bariatric surgery.

Results

Baseline characteristics and alteration of body profile after bariatric surgery. The baseline characteristics of 22 patients who provided their fecal samples before and after bariatric surgery are summarized in Table 1. The mean age was 37.8 years and 8 of the 22 patients (36.4%) were male. More than half of the patients had comorbidities, including DM, hypertension, and sleep apnea. Before bariatric surgery, the mean body weight of patients was 106.8 kg (range, 67.3 – 166.0 kg), and the mean BMI was 39.2 kg/m^2 (range, 30.1 – 62.1 kg/m^2). Six months after bariatric surgery, the body weight and BMI of patients decreased to an average 84.2 kg (range, 55.1 – 142.8 kg) and 30.6 kg/m^2 (range, 22.3 – 45.6 kg/m^2), respectively (Fig. 1A).

Table 1
Baseline characteristics of enrolled patients.

Characteristics	Total (n=22)
Age	37.8 (21 – 64)
Sex	
Male	8 (36.4)
Female	14 (63.6)
Comorbidities	
Diabetes Mellitus	14 (63.6)
Hypertension	12 (54.5)
Depression	1 (4.5)
Musculoskeletal pain	4 (18.2)
Sleep apnea	14 (63.6)
Dyslipidemia	7 (31.8)
GERD	2 (9.1)
Body weight (kg)	106.8 (67.3 – 166.0)
BMI (kg/m^2)	39.2 (30.1 – 62.1)
Type of surgery	
LSG	14 (63.6)
LRYGB	8 (36.4)
Data are presented as mean (min – max) or number (percentage).	
GERD, gastroesophageal reflux disease; BMI, body mass index; LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass	

Changes in gut microbial diversity and composition before and after bariatric surgery. Compared with before bariatric surgery, alpha diversity significantly increased and beta diversity differed after surgery (Fig. 1B). After bariatric surgery, *Firmicutes* decreased and *Bacteroidetes* increased at the phylum level, and the taxonomy composition at the genus level was remarkably changed (Fig. 1C). We performed linear discriminant analysis (LDA) effect size (LEfSe) to compare the gut microbial changes at the genus level following bariatric surgery. The LDA scores were computed for features that showed differential abundance of patients before and after bariatric surgery. As shown in Fig. 2A, at the genus level *Blautia*, *Catenibacterium*, and *Clostridiaceae* were enriched in patients before bariatric surgery, whereas *Bacteroides* and *Streptococcus* were the preponderance in patients after bariatric surgery. In addition, we

performed LDA effect size analysis at the species level and identified that *Ruminococcus gnavus* and *Blautia obeum wexlerae* were enriched in patients before bariatric surgery, whereas *Bacteroides thetaiotaomicron, Bacteroides nordii, Bacteroides uniformis*, and *Bacteroides dorei vulgatus* were the preponderance in patients after bariatric surgery (Supplementary Fig. 2A).

Correlation between a specific gut microbiome and BMI. Based on the results of LDA scores, we evaluated the correlation analysis between gut microbiota at the genus level and BMI and found that *Blautia* showed a positive correlation with BMI ($r=0.59$, $p=2.3\times10^{-5}$) while *Bacteroides* had a negative correlation with BMI ($r=-0.65$, $p=1.8\times10^{-6}$) (Supplementary Table 1, Fig. 2B and 2C). The abundance of *Blautia* significantly decreased and the abundance of *Bacteroides* significantly increased after bariatric surgery (Supplementary Fig. 1A and 1B). When converting as a log value, we identified that the log value of the *Blautia/Bacteroides* ratio showed a positive correlation with BMI (Fig. 2D). In addition, we found a correlation between gut microbiota at the species level and BMI; *Ruminococcus gnavus* and *Blautia obeum wexlerae* showed positive correlations with BMI, while *Bacteroides thetaiotaomicron, Bacteroides nordii, Bacteroides uniformis*, and *Bacteroides dorei vulgatus* had negative correlations with BMI (Supplementary Fig. 2B and 2C).

Comparison according to the surgery type. Before surgery, the median body weight and BMI were higher in patients who underwent LSG than those in patients who underwent LRYGB, and these values significantly decreased after both LSG and LRYGB surgery (Supplementary Fig. 3A). Alpha diversity significantly increased in patients who underwent LRYGB, but not in patients who underwent LSG. Further, beta diversity of before and after surgery was significantly differ in both surgery types (Fig. 3A). The taxonomy composition at the phylum and genus levels showed changes after both LSG and LRYGB (Supplementary Fig. 3B). LDA effect size at the genus level showed similar results regardless of the surgery type (Fig. 3B). Further, the log value of the *Blautia/Bacteroides* ratio showed a positive correlation with BMI in both surgery types (Fig. 3C).

Validation in severely obese patients and healthy volunteers. To validate these results, we selected 42 patients with severe obesity (BMI > 35) from the 58 patients who were initially enrolled in this study for scheduled bariatric surgery and compared them to the healthy volunteers with normal BMI (n=41). The baseline characteristics of patients with high BMI and healthy controls are summarized in Table 2. Compared to a healthy person, severely obese patients showed different beta diversity, but alpha diversity was not significantly differed (Fig. 4A). The taxonomy composition of severely obese patients was different than those of healthy volunteers; severely obese patients showed more enriched *Firmicutes* and deficient *Bacteroidetes* at the phylum level and more abundant *Blautia* and deficient *Bacteroides* at the genus level (Fig. 4B).

Table 2
Baseline characteristics between healthy volunteer with normal body weight (BMI, 18.8 – 22.8) and patients with severe obesity (BMI > 35).

Characteristics	Healthy volunteers (n=41)	Patients with severe obesity (n=42)
Age	35.9 (22 – 59)	36.8 (19 – 58)
Sex		
Male	13 (31.7)	19 (45.2)
Female	28 (68.3)	23 (54.8)
BMI	20.9 (18.8 – 22.8)	42.5 (35.1 – 62.1)
Comorbidities		
Diabetes Mellitus	0 (0.0)	19 (45.2)
Hypertension	0 (0.0)	17 (40.5)
Depression	0 (0.0)	5 (11.9)
Musculoskeletal pain	0 (0.0)	6 (14.3)
Sleep apnea	0 (0.0)	36 (85.7)
Dyslipidemia	0 (0.0)	13 (31.0)
GERD	0 (0.0)	7 (16.7)
Data are presented as mean (min – max) or number (percentage).		
BMI, body mass index		

The results of LDA effect size demonstrated that *Blautia*, *Streptococcus, Ruminococcus_0, Catenibacterium, Collinsella, Eubacterium_0, Dorea, Lactobacillus* and *Clostridium* were much more enriched in severely obese patients, whereas *Bacteroides*, *Faecalibacterium, Ruminococcus, Enterococcus, Rhizobium, Oscillospira, Alistipes, Lactococcus, Paraprevotella*, and *Parabacteroides* were enriched in healthy volunteers. These results were similar in the Cladogram analysis (Fig. 5A). In addition, we evaluated the correlation analysis between BMI and gut microbiota of severely obese patients and healthy volunteers, and we found that *Blautia* showed a positive correlation with BMI and *Bacteroides* had a negative correlation with BMI (Fig. 5B and 5C). We also identified that the log value of the *Blautia/Bacteroides* ratio showed a positive correlation with BMI (Fig. 5D).

Discussion

Despite the increasing evidence of relevance between gut microbiota and obesity, the clinical significance for differences in gut microbiota before and after bariatric surgery is under-investigated. This study

provides evidence for the association of gut microbial shift and altered BMI after bariatric surgery.

The gut microbiota has evolved along with humans to form symbiotic relationships that are important for life. Emerging data supports a link between the gut microbiota and obesity, suggesting that specific microbiomes could increase the capacity to harvest energy from the diet, leading to obesity.[7] One study found that cohousing lean and obese mice prevented the development of increased adiposity and body mass and showed that the microbiota's metabolic profile of obese mice transformed to a lean-like state[19]. We collected the fecal samples from 58 obese patients who scheduled bariatric surgery and re-collected samples from 22 patients six months after bariatric surgery. We then evaluated changes in the gut microbiome before and after bariatric surgery. We observed increased alpha diversity and differed beta diversity after bariatric surgery as well as changes in specific microbiomes after bariatric surgery. Compared to previous studies that have described higher *Firmicutes/Bacteroidetes* ratios in obese patients versus their healthy counterparts at the phylum level[20–22], our study shows that the *Blautia/Bacteroides* ratio is associated positively with BMI at the genus level. In addition, we presented that *Ruminococcus gnavus* and *Blautia obeum wexlerae* were enriched in patients before bariatric surgery, whereas *Bacteroides thetaiotaomicron, Bacteroides nordii, Bacteroides uniformis*, and *Bacteroides dorei vulgatus* were enriched in patients after bariatric surgery. These results suggest that gut microbial changes occur after bariatric surgery and that specific microbiomes might be strongly associated with obesity.

A study using next-generation sequencing reported that certain bacterial species including *Blautia huydrogenotorophica, Coprococcus catus, Eubacterium ventriosum, Ruminococcus bromii*, and *Ruminococcus obeum* were significantly associated with obese subjects[23]. A cross-sectional study in Japan reported that *Blautia* was the only genus whose abundance showed a significant negative relationship with visceral fat accumulation in Japanese people regardless of sex[24]. A study for a Chinese population presented that *Blautia wexlerae* and *Bacteroides dorei* were the strongest predictors for weight loss when present in high abundance at baseline[25]. *Blautia* is a taxonomic genus placed in the *Lachnospiraceae* family of the *Firmicutes* phylum. *Blautia* are anaerobic bacteria with the ability to ferment different carbohydrates and are a common acetic acid producer in the intestine, which may inhibit insulin signaling and fat accumulation in adipocytes[26]. Despite the increasing level of knowledge about *Blautia*, it is still poorly understood, therefore further studies are needed to cement the role of *Blautia*.

Regarding the effect of bariatric surgery type on the microbiota profile, several studies found that both LSG and LRYGB resulted in an increase of diversity index and gene richness of gut microbiota, and in parallel with weight loss, another study reported that LRYGB induces greater taxonomic and functional changes in gut microbiota than LSG[27]. Conversely, another study reported no significant differences between surgery types[28]. Following LRYGB, the nutrient-stimulated circulating levels of the gut hormones peptide YY and glucagon-like peptide 1 are markedly elevated as a consequence of increased L cells, which result from the anatomical rearrangement. Thus, these changes might occur more in LRYGB than

LSG[29]. Our study shows that the log value of the *Blautia/Bacteroides* ratio showed a positive correlation with BMI, regardless surgery type.

To validate the correlation between specific microbiomes and BMI, we examined the microbial relationship between patients with severe obesity and healthy volunteers with normal BMI. Similar to the results of bariatric surgery, the microbiomes of severe obese patients differed in diversity from those of healthy person with more enriched *Firmicutes* and deficient *Bacteroidetes* at the phylum level and more abundant *Blautia* and deficient *Bacteroides* at the genus level. Moreover, we found that the log value of the *Blautia/Bacteroides* ratio had a positive correlation with BMI. As mentioned above, the physiological effects of *Blautia* in obesity is controversial. The strength of our study is that the results acquired by analyzing fecal samples before and after bariatric surgery were re-confirmed by the validation comparing fecal samples of severely obese patients and healthy volunteers. However, our study has several limitations. First, we did not re-collect fecal samples after bariatric surgery from all 58 patients who provided their fecal samples at the baseline, therefore we only assessed the data of 22 patients (37.9%) of the initially enrolled 58 patients. Second, further basic experiments to investigate the role of *Blautia* and *Bacteroides* in obesity have not been conducted in this study. In the next step, we plan to perform both in vitro and in vivo experiments to cement our results. Third, this study was carried out for obese patients who underwent bariatric surgery in a single institution. Therefore, these results may not be representative of populations from other institutions and countries. Further studies for large population are needed to corroborate our results.

In summary, we identified that the *Blautia/Bacteroides* ratio had a positive correlation with BMI in the gut microbial analysis of patients who underwent bariatric surgery and verified these results by performing a validation study for patients with severe obesity and healthy volunteers with normal BMI. The altered *Blautia/Bacteroides* ratio after bariatric surgery suggests that bariatric surgery could change the taxonomy composition of the gut microbiota, and that specific microbiomes including *Blautia* and *Bacteroides* might have a potential role in obesity.

Materials And Methods

Participants and Stool Collection. Subjects who were between 18-60 years of age and who scheduled bariatric surgery, either a LSG or LRYGB, were included, and patients who had any cancer or severe lung, liver, kidney, or heart disease were excluded. A study investigator explained the aim and contents of the study in detail to the participants, and all participants (including healthy volunteers) provided written informed consent. Detailed clinical data including age, sex, height, weight, a presence of sleep apnea or gastroesophageal reflux disease (GERD), and history of medication uses for DM, hypertension, dyslipidemia, depression, or musculoskeletal pain were collected through a self-administered questionnaire or medical records. Between January 2019 and July 2020, fecal samples were collected from 58 patients who scheduled bariatric surgery. Six months after bariatric surgery, fecal samples of 22 patients were re-collected, and the change of gut microbiota before and after bariatric surgery was evaluated. The collected samples were stored at -80℃ in a deep freezer and transported to Cell Biotech,

Co., Ltd. (Gimpo, Korea) for analysis. In addition, the differences in gut microbiota between patients who have preoperative severe obesity (BMI > 35, n=42) and healthy volunteers with normal BMI (18.8 – 22.8, n=41) were investigated. The study protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH 2021-08-012). All methods were performed in accordance with the relevant guidelines and regulations.

DNA extraction and sequencing. Microbial DNA was extracted using the FastDNA SPIN Kit for Soil (MP Biochemicals, Santa Ana, CA, USA) according to the manufacturer's instructions. The extracted microbial DNA was purified using DNeasy PowerClean Cleanup Kit (Qiagen, Hilden, Germany), and DNA quality was measured using Nano-drop. The purified DNA was measured for DNA concentration using the Qubit™ dsDNA BR Assay kit (Thermo Fisher Scientific, Carlsbad, CA, USA).

A sequencing library was prepared according to the Illumina 16S Metagenomic Sequencing Library Preparation Guide. The V4-V5 region of the bacterial 16S rRNA gene was amplified for 16S rRNA gene sequencing. The forward primer in the v4 region (CCA GCM GCC GCG GTA ATW C) and the reverse primer in the v5 region (CC GTC AAT TYY TTT RAG TTT) were used for PCR amplification in this study. The amplified sequencing library was purified with Agencourt® AMPure XP beads (Beckman Coulter, Brea, CA, USA) and the quality of the library was checked using a 2100 Bio-analyzer (Agilent, Santa Clara, CA, USA). The library pool was sequenced with 250 bp paired-end reads on the MiSeq platform (Illumina, San Diego, CA, USA) using the MiSeq reagent kit V2 (Illumina).

Statistical analysis. Raw sequencing data were processed using the Quantitative Insight into Microbial Ecology software package 2 (QIIME 2, v 2019.10, http://qiime2.org). Denoising was performed using DADA2, and a taxonomy table was created using the Greengenes database (v13_8) normalized to a depth of 63,000, which was the minimum depth of the sample was used for alpha and beta diversity analysis. Data visualization was performed using the ggplot package of R (v4.0.3), and statistical analyses were performed through Wilcoxon signed rank test and PERMANOVA using the vegan package.

Declarations

Disclosure statement

The authors declare no competing interests

Author contributions

Study concept and design: Y.K., K.W.S., K.H.K., and J.H.K. Performed the experiments: D.H.S., S.L., Y.K., K.H.K., K.W.S., and J.H.K. Data analyzed: S.L., D.H.S., B.K.K., K.J., and S.J.P. Manuscripts drafting: Y.K and J.H.K. All authors reviewed and approved the manuscript prior to its submission.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

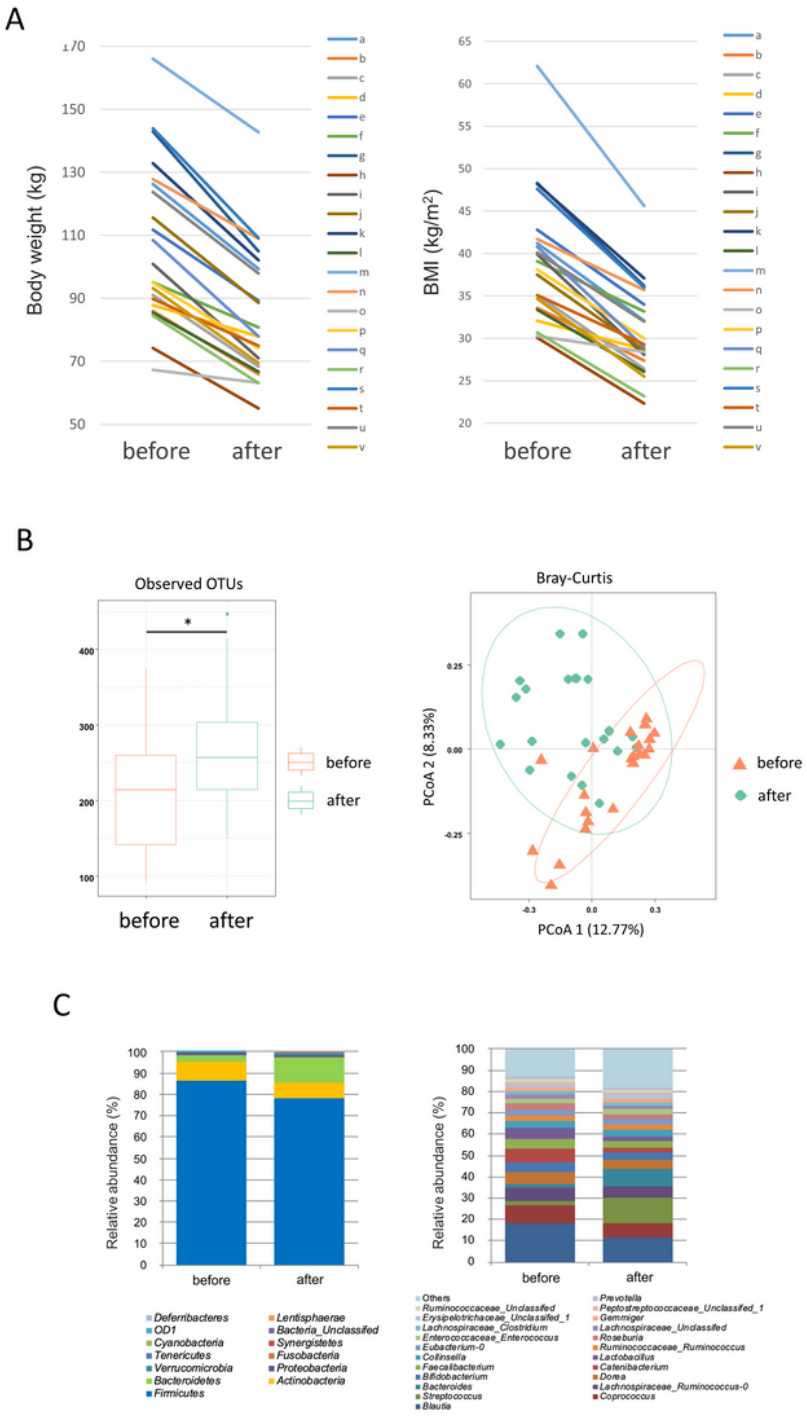

Figure 1

Changes of body profiles and gut microbiota after bariatric surgery. (**A**) Individual changes of body weight and (*left panel*) body mass index (*right panel*) after bariatric surgery. (**B**) Comparison of alpha diversity (*left panel*) and beta diversity (*right panel*) before and after bariatric surgery. (**C**) Alteration of taxonomy composition after bariatric surgery at the phylum level (*left panel*) and genus level (*right panel*). *BMI, body mass index.*

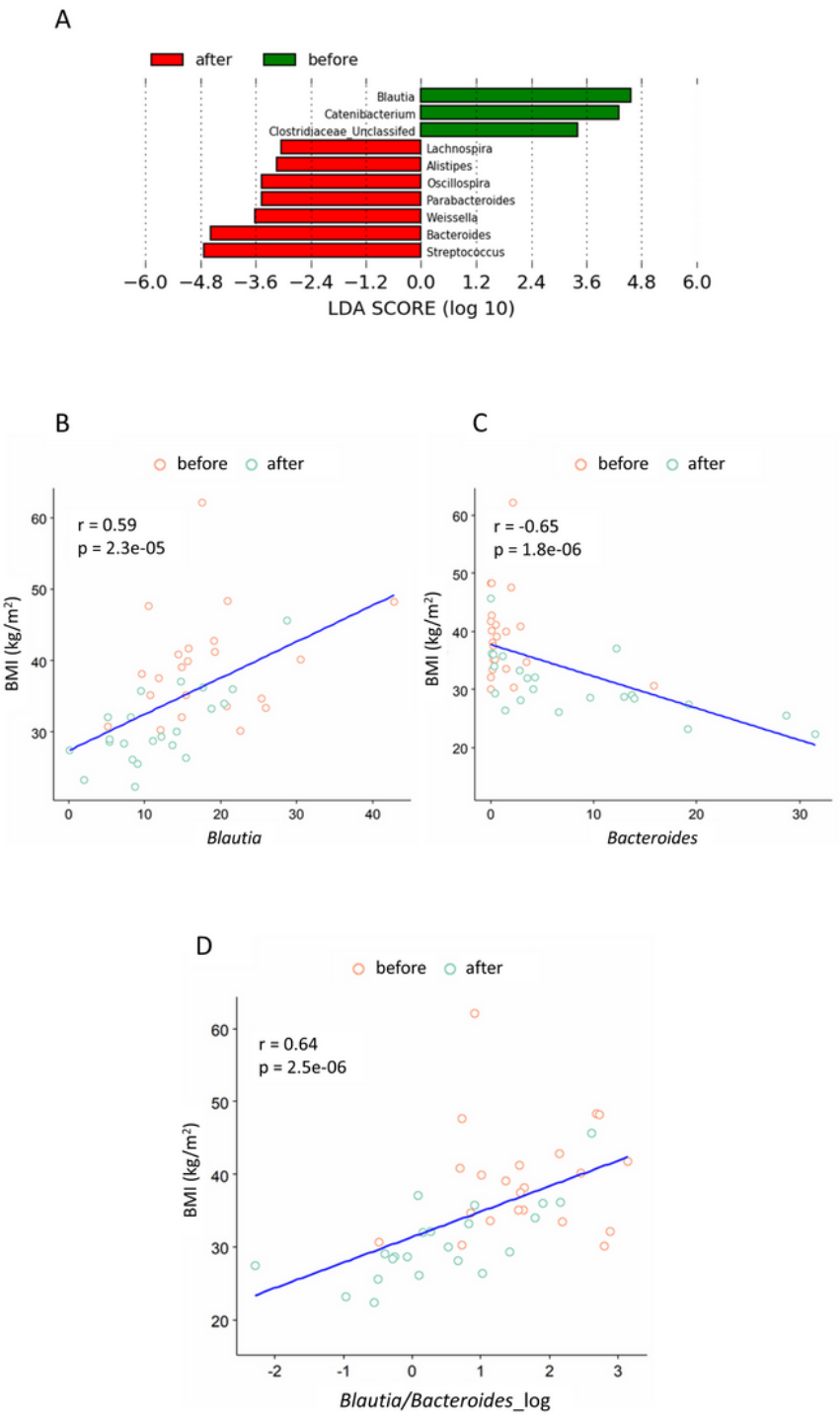

Figure 2

Prominent gut microbiota at the genus level before and after bariatric surgery and correlation with body mass index. (**A**) LDA effect size before and after bariatric surgery (threshold 2.4). (**B**) Correlation between *Blautia* and body mass index. (**C**) Correlation between *Bacteroides* and body mass index. (**D**) Correlation between the log value of *Blautia/Bacteroides* and body mass index. *BMI, body mass index; LDA, linear discriminant analysis.*

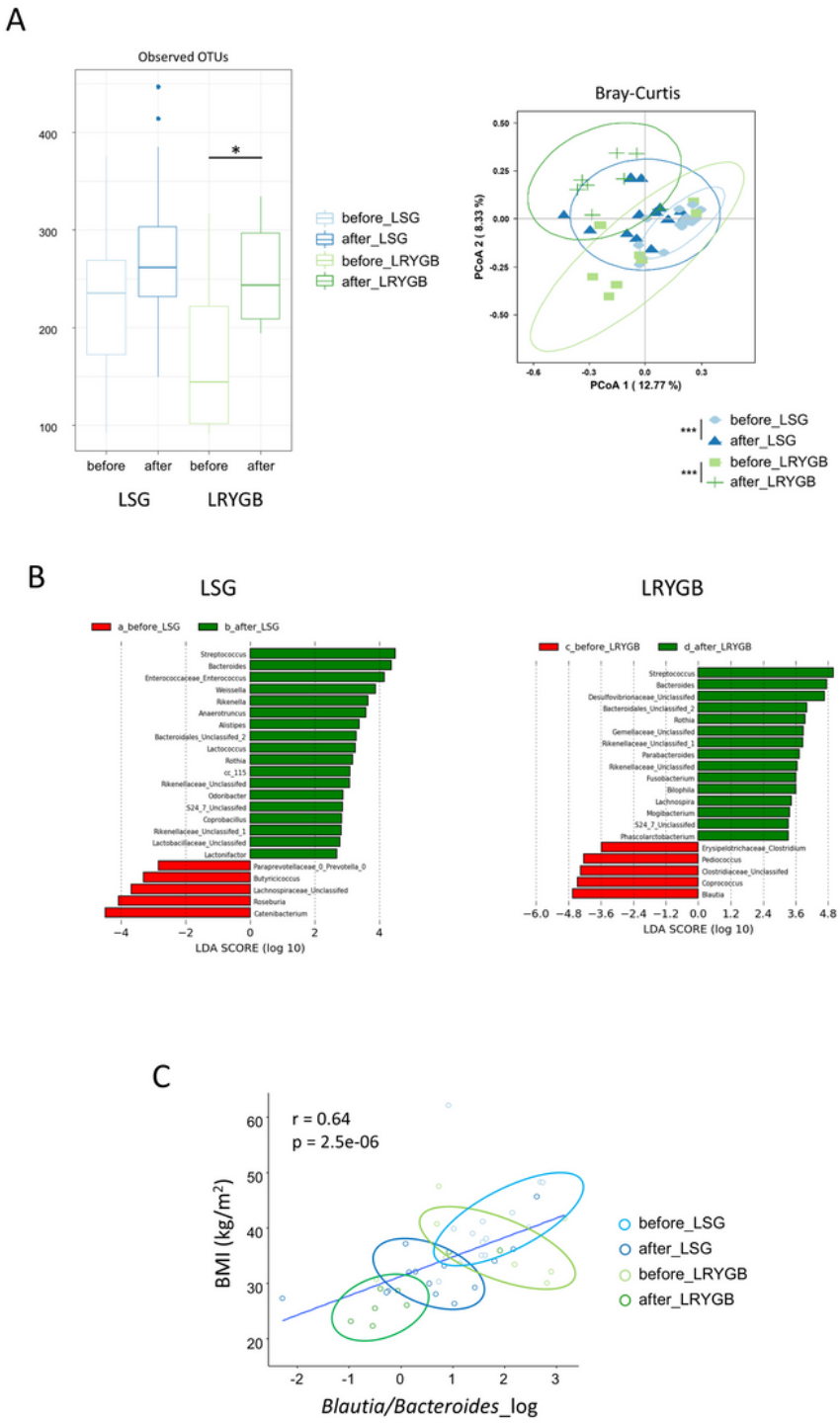

Figure 3

Comparison of altered gut microbiota after bariatric surgery according to the surgery type. (**A**) Comparison of alpha diversity (*left panel*) and beta diversity (*right panel*) according to surgery type before and after bariatric surgery. (**B**) LDA effect size before and after laparoscopic sleeve gastrectomy (*left panel*). LDA effect size before and after laparoscopic Roux-en-Y gastric bypass (*right panel*). (**C**) Correlation between the log value of *Blautia/Bacteroides* and body mass index in both two surgery types.

LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass; BMI, body mass index; LDA, linear discriminant analysis.

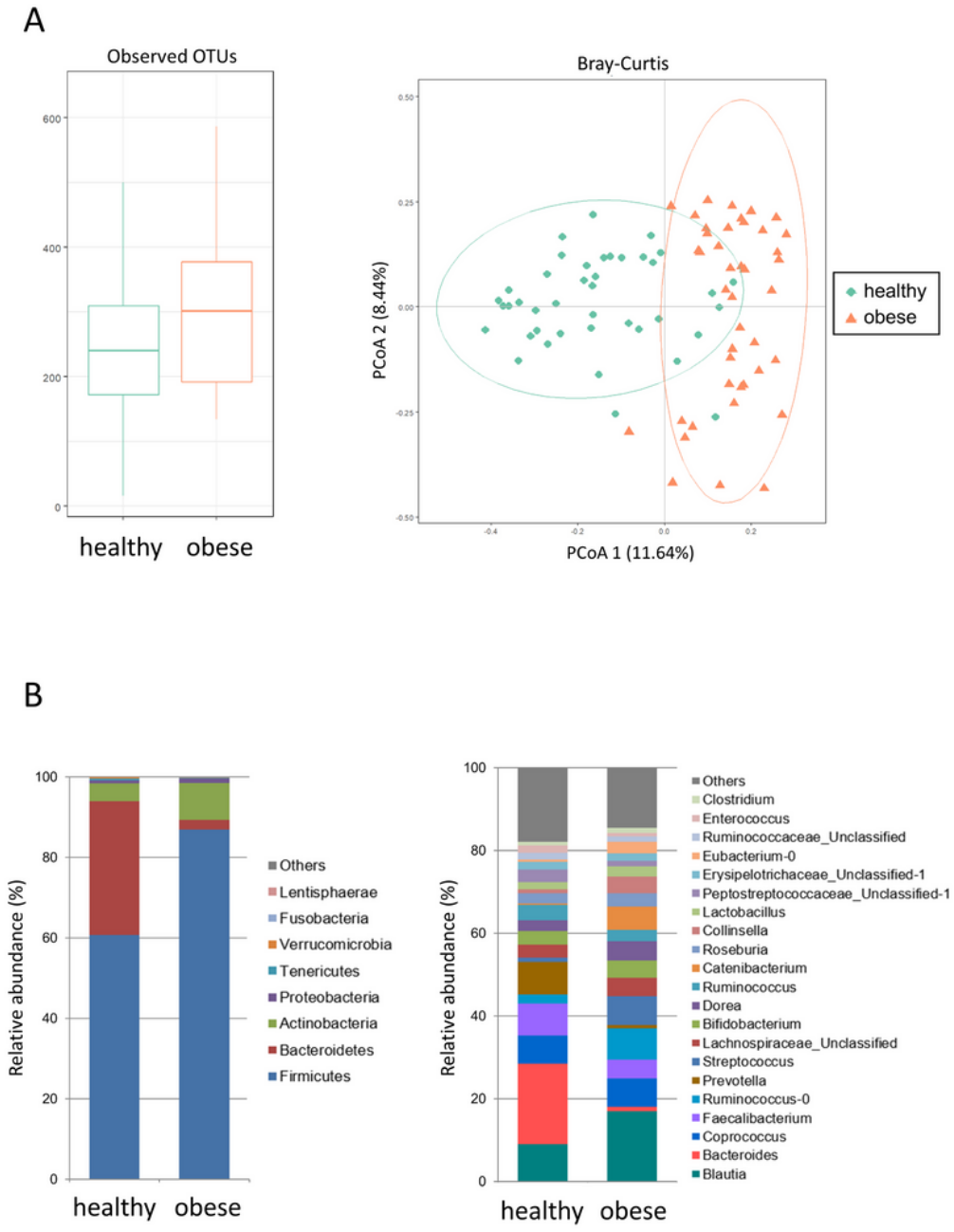

Figure 4

Comparison of gut microbiota between severely obese patients and healthy controls. (**A**) Comparison of alpha diversity (*left panel*) and beta diversity (*right panel*) between severely obese patients and healthy

controls. (**B**) Comparison of taxonomy composition at the phylum level (*left panel*) and genus level (*right panel*) between severely obese patients and healthy controls.

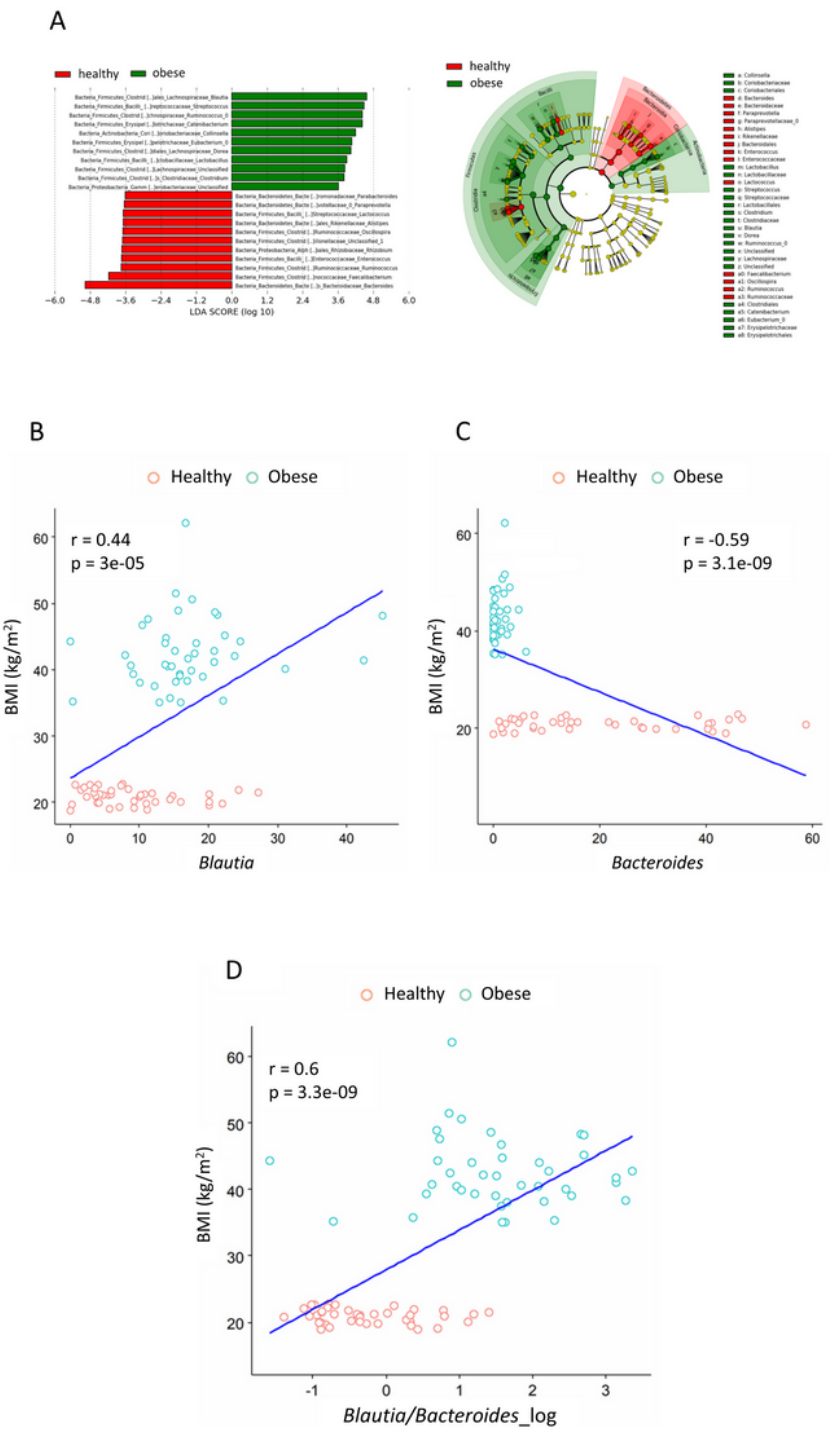

Figure 5

Prominent gut microbiota between severe obese patients and healthy controls and correlation with body mass index. (**A**) LDA effect size between severely obese patients and healthy controls (*left panel*).

Cladogram analysis between severely obese patients and healthy controls (*right panel*). (**B**) Correlation between *Blautia* and body mass index. (**C**) Correlation between *Bacteroides* and body mass index. (**D**) Correlation between the log value of *Blautia/Bacteroides* and body mass index. *BMI, body mass index; LDA, linear discriminant analysis.*

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryFig1.tif
- supplementaryFig2.tif
- supplementaryFig3.tif
- SupplementaryTable.docx