Modulation of the gut microbiome: a systematic review of the effect of bariatric surgery

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Abstract

Objective: Bariatric surgery is recommended for patients with obesity and type 2 diabetes. Recent evidence suggested a strong connection between gut microbiota and bariatric surgery.

Design: Systematic review.

Methods: The PubMed and OVID EMBASE were used, and articles concerning bariatric surgery and gut microbiota were screened. The main outcome measures were alterations of gut microbiota after bariatric surgery and correlations between gut microbiota and host metabolism. We applied the system of evidence level to evaluate the alteration of microbiota. Modulation of short-chain fatty acid and gut genetic content was also investigated.

Results: Totally 12 animal experiments and 9 clinical studies were included. Based on strong evidence, 4 phyla (Bacteroidetes, Fusobacteria, Verrucomicrobia and Proteobacteria) increased after surgery; within the phylum Firmicutes, Lactobacillales and Enterococcus increased; and within the phylum Proteobacteria, Gammaproteobacteria, Enterobacteriales Enterobacteriaceae and several genera and species increased. Decreased microbial groups were Firmicutes, Clostridiales, Clostridiaceae, Blautia and Dorea. However, the change in microbial diversity is still under debate. Faecalibacterium prausnitzii, Lactobacillus and Coprococcus comes are implicated in many of the outcomes, including body composition and glucose homeostasis.

Conclusions: There is strong evidence to support a considerable alteration of the gut microbiome after bariatric surgery. Deeper investigations are required to confirm the mechanisms that link the gut microbiome and metabolic alterations in human metabolism.

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Introduction

Obesity, combined with its related comorbidities, such as type 2 diabetes (T2D), cardiovascular disease and psychological disorders, is attracting increasing attention and becoming a worldwide health problem. Although additional studies are needed to further demonstrate mechanistic basis of these benefits, there is clinical evidence that show the long-term benefit of bariatric

surgery (1), supporting the inclusion of bariatric surgery among the anti-diabetes interventions for people with type 2 diabetes and obesity (2). The gut microbiome has been recognized as a potential contributor for regulating host metabolism in patients undergoing bariatric surgery (3, 4). Furthermore, recent research found a great similarity between the genetic content of the human and rat gut

(5), suggesting that more investigations on gut microbiota from both human and rodents are needed.

Bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), induces important changes in the digestive tract, including decreased acid production and anatomical gut rearrangement, which may affect the modification of the gut microbiota. Given the impact that the gut microbiota has on host metabolism through several mechanisms (6), it is probably that this complex enteric microbial community contributes to surgery-mediated weight loss and the maintenance of the benefit for host metabolism post-surgery.

Magouliotis *et al.* composed a meta-analysis to report the impact of bariatric surgery on metabolic and gut microbiota profiles recently (7); however, the alteration of gut microbiota and the host-microbiota crosstalk on patients undergoing bariatric surgery still warrants investigation due to the lack of a quantitative summary. So we composed this systematic review to further identify the alteration of gut microbial composition after bariatric surgery and gain a better understanding of the interaction between the host metabolism and the microbiome (2, 8).

Subjects and methods

Data sources

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines were used to guide the search (9). We retrieved studies from PubMed and OVID Embase. The date of the last search was December 2016. In addition, we searched the reference list of the studies we retrieved. The main search terms were 'Bariatric Surgery', 'Sleeve gastrectomy', 'Gastrojejunostomy', 'Gastrojejunostomies', 'duodenal-jejunal bypass', 'DJB', 'RYGB', 'Gastrointestinal Microbiome', 'flora' and 'microbial'.

Study selection

The inclusion criteria were as follows:

- clinical trials or observational experiments reporting primary data of bariatric surgery;
- alteration of the gut microbiota profile after bariatric surgery was used as an outcome measure;
- composed in English.

We applied the exclusion criteria as follows:

- letters to the editor, conference proceedings, abstracts or review;
- the study included the patients combined with certain diseases, such as Crohn's disease, ulcerative colitis, gastric tumors or lower gastrointestinal tumors.

Data extraction and quality assessment

Two investigators independently reviewed the selected studies and extracted data from them. To assess the quality of the human trials, we used the guideline called 'The Newcastle-Ottawa Scale (NOS) for cohort studies' (10, 11), which contains 8 items based on 3 sections of the article regarding selection, comparability and outcome. We also evaluated the included animal reports with The Animal Research: Reporting of the *In Vivo* Experiments (ARRIVE) guideline, which refers to several parts of the manuscript: title, abstract, introduction, method, results and discussion (12).

Importantly, we considered an animal research to be of good quality if the score was more than 14 and a clinical study to be of good quality if the score was more than 7. Otherwise, the study was labeled 'poor quality'. The third assessor was needed if there was disagreement between the two investigators.

Data synthesis and level of evidence

Considering the heterogeneity of the study methodology, a quantitative analysis of the system of evidence level was performed (Table 1) (13, 14, 15, 16). We evaluated the evidence of the alteration of each specific taxon of microbiota by strictly considering the number, the methodological quality and the consistency of studies manifesting this alteration. Findings were considered consistent when more than 75% of the studies that reported the specific microbiota showed the same trend of alteration (Table 1).

Results

Studies included and methodological quality

Initially, 477 reports were recovered during the retrieval and a total of 22 papers reporting 21 studies, including 9 human studies and 12 animal experiments, were included

Table 1 Levels of evidence.

Strong	Consistent findings ($\geq 75\%$) in at least 2 high-quality studies
Moderate	Consistent findings ($\geq 75\%$) in one high-quality study and at least one low-quality study
Weak	Findings of one high-quality study or consistent findings ($\geq 75\%$) in at least 3 or more low-quality studies
Inconclusive	Inconsistent findings, or less than 3 low-quality studies available

in this review (Fig. 1). In total, 6 types of bariatric surgeries were applied: RYGB, vertical banded gastroplasty (VBG), sleeve gastroplasty (SG), duodenal-jejunal bypass (DJB), bilio-intestinal bypass (BIB) and ileal interposition (IT). Using the above-described criteria to define the quality, of the 21 overall studies, we found that 6 animal studies and 5 clinical studies were of good quality (Tables 2, 3 and 4).

Altered microbial composition

The results of the population of the microbiota represent new findings based on the level of evidence (Table 5 and Supplementary Table 1, see section on supplementary data given at the end of this article), and microbial species analyzed in only one study were omitted.

Microbial richness and diversity

The change in the richness and diversity of microbiota after surgery was still controversial. The gut microbiota richness, as estimated by Chao1 (17) and abundance-

based coverage estimators, increased after RYGB in a human study (18) but showed no difference in an animal model (19). For patients undergoing BIB, there was a significant decrease in the mean microbial richness estimated by Chao1 in post-surgery subjects (20). Murphy *et al.* demonstrated that the mean number of species increased 1 year after surgery (21). Another study showed that species richness was higher 3 months after RYGB and that this higher richness was maintained at 1 year (22). However, the gut microbiota diversity, as estimated by the Shannon index, was reported to be higher after surgery both in animal studies (19, 23) and in people with obesity undergoing RYGB (22) and BIB (20). However, a human study in 2014 (24) showed a similar Shannon diversity index before and after RYGB. In 2016, it was shown that the Shannon diversity index of the gut microbiota of the RYGB group remained significantly depressed 3 weeks postoperatively (25).

Microbiota altered on strong evidence

The population of 21 microbial taxa was altered on a strong level of evidence (Table 5 and Supplementary Table 1). Metagenomic sequencing of the human gut microbiome before and after RYGB in diabetic patients exhibited an increased population of Proteobacteria (22, 26), resembling the results observed in a study focusing on patients undergoing BIB surgery (20). An increased population of Proteobacteria was observed in diet-induced mice with obesity after RYGB (27). Experimental results on rats showed an increase of Proteobacteria after DJB (28) and RYGB (19, 25). In addition, Li *et al.* found substantial shifts of the main gut phyla toward higher concentrations of Proteobacteria, specifically *Enterobacter hormaechei* (*E. hormaechei*), from a non-obese rat model characterizing the effect of RYGB (29). An increase in *E. hormaechei* was also observed in patients undergoing either RYGB or VBG (30). An upregulation of the abundance of Bacteroidetes was observed on animal experiences after RYGB (19, 27) and SG (31). However, contrary results were provided on rats after DJB (28). Two studies reported the increase of the phylum Fusobacteria in 2016 (19, 22). The abundance of phylum Verrucomicrobia was found to be increased in patients after RYGB (24) and mice after RYGB (27) and DJB (32).

Figure 1

Flow chart of study selection.

Clinical Study	Y Guo, Z-P Hunag, C-Q Liu and others	Microbiota and bariatric surgery	178:1	46
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Table 2 Methodological assessment for animal experiments.

Study	Number of items of ARRIVE* checklist																				Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
(63)	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0	16
(25)	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	0	16
(19)	1	1	1	1	0	1	1	0	1	0	1	1	1	0	1	1	1	1	1	1	16
(27)	1	1	1	1	0	0	1	1	0	0	1	1	1	0	1	1	1	1	1	1	15
(29)	1	1	1	1	1	1	1	0	1	0	0	1	0	0	1	1	1	1	1	1	15
(32)	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	0	1	0	15
(23)	1	1	0	1	1	1	1	0	1	0	1	1	1	0	1	0	0	1	1	1	14
(28)	1	1	0	1	0	0	1	1	1	0	0	1	1	1	1	1	1	1	0	1	14
(31)	1	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0	1	1	0	14
(37)	1	1	0	1	1	1	1	0	0	1	0	1	1	0	1	0	1	1	0	1	13
(33)	1	1	1	0	0	1	0	0	0	1	1	1	1	0	1	1	1	1	1	0	13
(34)	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	0	1	1	1	10

*ARRIVE, reporting of the *in vivo* experiments.

The population of Gammaproteobacteria increased in rats after RYGB (19, 25, 29), DJB (33), SG (23) and IT surgery (34). The fecal samples from patients undergoing RYGB or BIB also implies a significant increase of Gammaproteobacteria (20, 35). Lactobacillales was found to increase after bariatric surgeries (20, 25). The results from an experiment using rat models undergoing RYGB and a clinic cohort investigating BIB demonstrated an increase in the population of Enterobacteriales (20, 27). The family of Enterobacteriaceae showed an increase in quantity according to the pyrosequencing analysis of fecal sample from a non-obese rat model (35), three people with obesity after gastric bypass (29) and eleven people with obesity undergoing BIB (20). Both animal and human studies indicated an upregulation of the concentration of Alistipes after gastric bypass (18, 19, 27). Postoperative increases in the population of Escherichia were found in diabetic IT-operated rats and mice after RYGB (27, 34), and further clinical investigations focusing on RYGB revealed the same trend of the alteration of *Escherichia* (18, 30). The increase of Enterococcus was observed on humans and rats (19, 30). Additionally, the population of

Enterococcus faecalis (*E. faecalis*), *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*) and *Streptococcus gordonii* (*S. gordonii*) ascended in 2 clinical studies (22, 30).

The decrease of the phylum Firmicutes was observed after RYGB (21, 24, 29), as verified in 2 studies after SG (19, 31). The abundance of Clostridiales were found decreased in 4 studies (20, 25, 32, 36). The reduced concentration of Clostridiaceae was found in non-obese Wistar rats after RYGB operation (29). Fecal sample of 11 severely obese people who experienced BIB also revealed a reduction of Clostridiaceae (20). An examination of the impact of RYGB on the modifications of gut microbiota in 2013 demonstrated a marked decrease in Blautia (18), and the same result was stated in 2016 by Patrone *et al.* (20). RYGB (18), SG (36) and BIB (20) could cause a significant reduction in Dorea.

Microbiota altered on moderate evidence

There is moderate evidence that the population of 20 specific microbial taxa changed after surgery (Table 5 and Supplementary Table 1). The increase of Erysipelotrichales was observed in 2 animal studies (23, 25). Three studies found an increase in abundance of *Akkermansia* (24, 27, 35). In 2015, Tremaroli *et al.* analyzed the population of the genus *Citrobacter* and *Salmonella* and the species *Enterobacter cancerogenus* (*E. cancerogenus*), *Salmonella enterica* (*S. enterica*) and *Shigella boydii* (*S. boydii*) (30), and they found an increase after surgery, which was in agreement with a study conducted in 9 individuals in 2013 (26). Two studies showed the increase of Enterobacter after bariatric surgery (26, 30). The increased abundance of Parabacteroides was verified by 2 studies on rats (19, 31). The abundance of Veillonella was found to

Table 3 Methodological assessment for human studies.

Study	Newcastle–Ottawa scale for cohort studies		
	Selection	Comparability	Outcome
(30)	★★★★★	★★	★★★
(20)	★★★★	★☆	★★★
(22)	★★★★	★☆	★★★
(21)	★★★★	★☆	★★★
(18), (38)	★★★★	★☆	★★★
(26)	★★★★	★☆	★★★
(36)	★★★★☆	★☆	★★★
(24)	★★★★☆	★☆	★★★
(35)	★★★☆☆	★☆	★★★

Table 4 Study characteristics of included studies.

Reference	Country	Objects	BMI (kg/m ²)	Comorbidities	Surgery	Sample size	Microbiota analysis technique	Microbiome samples	Fecal samples extraction
(35)	China	Human	27.7 ± 4.1	Not stated	RYGB	9	Sanger sequencing and high-throughput pyrosequencing	Distal colon	8 and 15 months after operation
(38)	France	Human	≥40	Hypertension, T2D, dyslipidemia, obstructive sleep apnea syndrome	RYGB	43	Real-time polymerase chain reaction	Distal colon	Before, 3 months after and 6 months after operation
(18)	France	Human	≥40	Not stated	RYGB	30	High-throughput pyrosequencing	Distal colon	Before, 3 months after and 6 months after operation
(26)	Germany	Human	≥40	T2D	RYGB	6	Metagenomic sequencing	Distal colon	Before and 3 months after operation
(24)	USA	Human	≥40	Not stated	RYGB	14	High-throughput DNA sequencing	Distal colon	Before and 6 months after operation
(36)	Germany	Human	45.8 ± 0.9	Not stated	SG	10	Shotgun sequencing	Distal colon	One day before, 3 months after and 6 months after surgery
(30)	Sweden	Human y	RYGB: 42.2*VBG: 43.0*	Not stated	RYGB and VBG	14	Shotgun sequencing	Distal colon	9.4 years after operation
(20)	Italy	Human	>35	Hypertension, T2D	Bilio-intestinal bypass	11	Illumina high-throughput sequencing	Distal colon	6 months after operation
(22)	Denmark	Human	>35	T2D	RYGB	13	Shotgun metagenomic sequencing	Distal colon	Before and 3 months after RYGB
(21)	New Zealand	Human	RYGB: 38.4* SG: 36.9*	T2D	RYGB and SG	14	Illumina high-throughput sequencing	Distal colon	12 months after RYGB 1 year post operation
(29)	UK	Male Wistar rats (non-obese)		None	RYGB	12	High-throughput pyrosequencing	Distal colon	2 and 8 weeks after operation
(34)	USA	UCD-type 2 diabetes mellitus rats		T2D	Ileal interposition	48	High-throughput pyrosequencing	Cecum	4.5 months after operation, cecum
(27)	USA	Diet-induced obese C57BL/6J mice		None	RYGB	23	High-throughput pyrosequencing	Distal colon	Before and weekly for 3 months after operation
(63)	Switzerland	Male Wistar rats		None	RYGB	16	Metagenomic sequencing	Cecum and distal colon	Unknown
(31)	China	Male diabetic Goto-Kakizaki rats		T2D	SG	30	Sanger sequencing	Distal colon	1 month after operation
(28)	China	Male Wistar rats		None	DIB	20	16S ribosomal RNA gene sequencing	Distal colon	2 weeks and 12 weeks after operation

(Continued)

Clinical Study			Y Guo, Z-P Hunag, C-Q Liu and others		Microbiota and bariatric surgery		178:1		48	
Reference	Country	Objects	BMI (kg/m ²)	Comorbidities	Surgery	Sample size	Microbiota analysis technique	Microbiome samples	Fecal samples extraction	
(37)	Japan	Male Otsuka Long-Evans Tokushima fatty rats		None	DJB	18	Illumina high-throughput sequencing	Distal colon	12 weeks after operation	
(23)	Italy	Male Wistar rats		None	SG	60	High-throughput pyrosequencing	Distal colon	10 weeks after operation	
(33)	Japan	Male Otsuka Long-Evans Tokushima fatty rats		None	DJB	6	The PCR-clone library method targeting the 16S ribosomal RNA	Distal colon	8 weeks after operation	
(25)	China	Male Sprague-Dawley rats		None	RYGB and SG	18	Illumina high-throughput sequencing	Distal colon	Before and 1, 3, 6, and 9 weeks after operation	
(19)	China	Male Zucker diabetic fatty rats		None	RYGB and SG	40	Pyrosequencing	Distal colon	10 weeks post operation	
(32)	China	Timo mice		None	DJB	15	16S ribosomal RNA gene amplicon sequencing	Distal colon	9 weeks post operation	

* values are the mean BMI. BMI, body mass index; DJB, duodenal-jejunal bypass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; T2D, type 2 diabetes; VBG, vertical banded gastroplasty.

increase after RYGB for both humans and rats (19, 26). Two studies on RYGB demonstrated the increase of *Veillonella dispar* (*V. dispar*) and *Veillonella parvula* (*V. parvula*) after surgery (22, 26).

Four studies demonstrated the decrease of clostridia after bariatric surgery (23, 29, 35, 36). The population of Ruminococcaceae was shown to reduce after surgical weight loss intervention, which was observed 3 months after SG in a cohort study (36), and additional evidence was found in people with obesity undergoing BIB (20). A reduction in the population of Anaerostipes was shown in metagenomic sequencing of the human gut microbiome in patients (20, 26). Rat models of diabetes undergoing bariatric surgery exhibited a decrease in the population of Clostridium (31, 37) and further exploration of patients after BIB confirmed this phenomenon (20). A decrease in the population of Coprococcus was found in patients undergoing 3 different bariatric surgeries (20, 26, 36). The reduction of Faecalibacterium was confirmed in patients undergoing bariatric surgery (20, 26). Ruminococcus were found to decrease in 4 studies (20, 23, 31, 36). The decreased abundance of Turicibacter was observed in two studies (18, 37).

Microbiota altered on weak and inconclusive evidence

The population of 51 microbial taxa changed based on a weak level of evidence: the phylum Archaea and Cyanobacteria, class Betaproteobacteria, order Selenomonadales and Verrucomicrobiales, family Bacteroidaceae, Carnobacteriaceae, Coriobacteriaceae, Eubacteriaceae, Lachnospiraceae, Lactobacillaceae, Peptostreptococcaceae and Veillonellaceae and genus Acidaminococcus, Acinetobacter, Aeromonas, Aggregatibacter, Anaerofilum, Campylobacter, Cronobacter, Dermacoccus, Desulfurispirillum, Dickeya, Edwardsiella, Elusimicrobium, Erwinia, Eubacterium, Filifactor, Fusobacterium, Gemmiger, Granulicatella, Klebsiella, Lactococcus, Megasphaera, Neisseria, Oscillibacter, Pantoea, Parasutterella, Pectobacterium, Peptostreptococcus, Phenyllobacterium, Proteus, Providencia, Pseudomonas, Rahnella, Serratia, Shewanella, Shigella, Treponema, Vibrio and Yersinia (Table 5 and Supplementary Table 1).

Associations between bacterial population and host metabolic parameters

The following analysis was mainly based on 9 reports, of which 6 were of good quality (18, 19, 20, 21, 25, 38)

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Table 5 Level of evidence for alterations of microbiome.

		Levels of evidence		
		Strong	Moderate	Weak
Decrease after surgery				
Phylum	Firmicutes			
Class			Clostridia	
Order	Clostridiales			
Family	Clostridiaceae		Ruminococcaceae	Peptostreptococcaceae, Carnobacteriaceae, Coriobacteriaceae, Eubacteriaceae, Lachnospiraceae
Genus	Blautia, Dorea		Anaerostipes, Coprococcus, Faecalibacterium, Turicibacter, Clostridium, Ruminococcus	Eubacterium, Gemmiger, Granulicatella, Lactococcus, Oscillibacter
Species				
Increase after surgery				
Phylum	Bacteroidetes, Fusobacteria, Proteobacteria, Verrucomicrobia			Cyanobacteria, Betaproteobacteria, Selenomonadales, Archaea
Class	Gammaproteobacteria			
Order	Enterobacteriales, Lactobacillales		Erysipelotrichales	Verrucomicrobiales
Family	Enterobacteriaceae			Bacteroidaceae, Lactobacillaceae, Veillonellaceae
Genus	Alistipes, Enterococcus, Escherichia		Akkermansia, Citrobacter, Enterobacter, Parabacteroides, Salmonella, Veillonella	Acidaminococcus, Acinetobacter, Aeromonas, Aggregatibacter, Anaerofilum, Campylobacter, Cronobacter, Dermacoccus, Desulfurispirillum, Dickeya, Edwardsiella, Elusimicrobium, Erwinia, Filifactor, Fusobacterium, Klebsiella, Megasphaera, Neisseria, Pantoea, Parasutterella, Pectobacterium, Peptostreptococcus, Phenyllobacterium, Proteus, Providencia, Pseudomonas, Rahnella, Serratia, Shewanella, Shigella, Treponema, Vibrio, Yersinia
Species	<i>Enterobacter hormaechei</i> , <i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Streptococcus gordonii</i>		<i>Enterobacter cancerogenus</i> , <i>Salmonella enterica</i> , <i>Shigella boydii</i> , <i>Veillonella dispar</i> , <i>Veillonella parvula</i>	

and 3 were of poor quality (26, 28, 36). Statistical methods, such as Spearman's correlation tests, principal component analysis and univariate linear mixed models were frequently used in relevant studies. Only statistically significant results ($P \leq 0.05$) were extracted.

Corpulence parameters

The abundance of *Bifidobacterium* was positively correlated to body mass index (BMI), body weight, calorie intake and leptin concentration; however, a negative correlation was found with the same parameters for *E. coli*, observed in patients undergoing RYGB (38). In 2013, the same researchers extended the results by using a pyrosequencing method and found 5 bacterial genera (*Bifidobacterium*, *Blautia*, *Dorea*, *Lactobacillus* and

Turicibacter) showed positive correlations with most corpulence parameters, and another 8 genera (*Bacteroides*, *Escherichia*, *Alistipes*, *Campylobacter*, *Neisseria*, *Filifactor*, *Peptostreptococcus* and *Gemella*) were negatively correlated with most corpulence parameters (18). In the same year, Graessler *et al.* found that BMI of patients undergoing RYGB correlated to 10 bacterial species, of which *Acinetobacter johnsonii* (*A. johnsonii*), *Coprococcus comes* (*C. comes*), *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Fibrobacter succinogenes*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Thermomicrobium roseum* (*T. roseum*) and *Treponema pallidum* (*T. pallidum*) were directly associated with BMI (26). Furthermore, *E. cancerogenus* and *V. dispar* were inversely associated with BMI (26). Moreover, the body weight was found to be negatively correlated with the abundance of *Bacteroidetes* after SG (36), *Treponema* after

Table 6 Taxonomy of microbiota altered on strong/moderate level of evidence. This table is to illustrate the commonalities of taxonomic distribution of microbiota altered on strong/moderate level of evidence, specifically, classes Bacteroidia, Bacilli and Gammaproteobacteria cover most groups of microbiota in this table, and this table is organized according to the detailed taxonomy to make these commonalities more obvious.

Name	Taxonomic level	Trend	Levels of evidence	Phylum	Class	Order	Family	Genus
Parabacteroides	Genus	Increase	Moderate	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	
Alistipes	Genus	Increase	Strong	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	
Bacteroidetes	Phylum	Increase	Strong					
Enterococcus	Genus	Increase	Strong	Firmicutes	Bacilli	Lactobacillales	Enterococcaceae	Enterococcus
Enterococcus faecalis	Species	Increase	Strong	Firmicutes	Bacilli	Lactobacillales	Enterococcaceae	Enterococcus
Streptococcus gordonii	Species	Increase	Strong	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	Streptococcus
Lactobacillales	Order	Increase	Strong	Firmicutes	Bacilli			
Turicibacter	Genus	Decrease	Moderate	Firmicutes	Bacilli	Bacillales	Turicibacteraceae	
Anaerostipes	Genus	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	
Clostridium	Genus	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	
Faecalibacterium	Genus	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	
Clostridiaceae	Family	Decrease	Strong	Firmicutes	Clostridia	Clostridiales		
Blautia	Genus	Decrease	Strong	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	
Coproccoccus	Genus	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	
Dorea	Genus	Decrease	Strong	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	
Ruminococcus	Genus	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	
Ruminococcaceae	Family	Decrease	Moderate	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	
Clostridiales	Order	Decrease	Strong	Firmicutes	Clostridia	Clostridiales		
Clostridia	Class	Decrease	Moderate	Firmicutes	Clostridia			
Firmicutes	Phylum	Decrease	Strong					
Erysipelotrichales	Order	Increase	Moderate	Firmicutes	Erysipelotrichia			
Veillonella dispar	Species	Increase	Moderate	Firmicutes	Negativicutes	Selenomonadales	Veillonellaceae	Veillonella
Veillonella parvula	Species	Increase	Moderate	Firmicutes	Negativicutes	Selenomonadales	Veillonellaceae	Veillonella
Veillonella	Genus	Increase	Moderate	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	
Fusobacteria	Phylum	Increase	Strong					
Citrobacter	Genus	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	
Enterobacter	Genus	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	
Enterobacter cancerogenus	Species	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Enterobacter
Enterobacter hormaechei	Species	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Enterobacter
Escherichia	Genus	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	
Escherichia coli	Species	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Escherichia
Klebsiella pneumoniae	Species	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Klebsiella
Salmonella	Genus	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	
Salmonella enterica	Species	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Salmonella
Shigella boydii	Species	Increase	Moderate	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	Shigella
Enterobacteriaceae	Family	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales		
Enterobacteriales	Order	Increase	Strong	Proteobacteria	Gammaproteobacteria	Enterobacteriales		
Gammaproteobacteria	Class	Increase	Strong					
Proteobacteria	Phylum	Increase	Moderate					
Akkermansia	Genus	Increase	Strong	Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobiaceae	
Verrucomicrobia	Phylum	Increase	Strong					

RYGB and SG (19) and Gammaproteobacteria after RYGB and SG (25) and positively correlated with the abundance of the phylum Firmicutes after SG (36).

Glucose homeostasis

Ling-Chun Kong *et al.* found that after RYGB, 10 of the 14 discriminating gut microbiota genera were correlated with one or more of the 4 glucose metabolism-related parameters (fasting glycemia, glycated hemoglobin, homeostasis model assessment of insulin resistance (HOMA-IR) and insulinemia) (18). However, a study by Graessler *et al.* indicated correlations for *F. prausnitzii*, *T. roseum* and *V. parvula* with glucose homeostasis in patients after RYGB (26). A positive connection between the variation of Clostridium and blood insulin was also exhibited in patients undergoing BIB (20). Study on patients receiving RYGB or SG showed a negative correlation for Dialister and Megamonas with HOMA-IR (21). Guo *et al.* found that the serum insulin in patients undergoing SG and RYGB negatively correlated with the abundance of Alistipes, Anaerofilum, Clostridium, Dorea, Enterococcus, Fusobacterium, Parabacteroides and Veillonella (19).

Lipid profile

Overall, 6 discriminating gut microbiota genera, Alistipes, Bacteroides, Blautia, Dorea, Escherichia and Phenyllobacterium, were associated with cholesterol metabolism, observed in patients undergoing RYGB (18). Furthermore, *F. succinogenes*, *A. johnsonii*, *T. pallidum*, *T. roseum*, *C. spiroforme* and *Anaerostipes caccae* (*A. caccae*) were significantly positively correlated with several lipid parameters in another study applying RYGB (26); moreover, *E. cancerogenus*, *V. parvula*, *V. dispar*, and *S. enterica* were negatively correlated with plasma total cholesterol and low-density lipoprotein cholesterol in patients undergoing RYGB (26). A connection between triglyceride and 5 bacterial species (*A. johnsonii*, *A. caccae*, *E. cancerogenus*, *T. pallidum* and *V. parvula*) was also found (26). In addition, an animal study applying RYGB and SG in 2016 showed a negative correlation between total cholesterol and Parasutterella, Treponema and Veillonella (19).

Bile acid

As for patients receiving SG, a significant direct correlation with lithocholic acid (LCA) was found for *F. prausnitzii*,

whereas plasma deoxycholic acid (DCA) was positively correlated with the abundance of Clostridium sp. L2-50, *C. comes* and *Lachnospiraceae bacterium* (36). As for rats undergoing DJB, significant connections have been found that colonic total bile acid was positively correlated with the abundance of Proteobacteria and negatively correlated with the abundance of Bacteroidetes (28).

Highlighted microbiota

Some specific microbiota showed connections with several different parameters according to more than one study. First, the species *F. prausnitzii* had a positive correlation with BMI and glucose level in patients undergoing RYGB (26), LCA in patients undergoing SG (36) and inflammatory factors such as C-reactive protein (CRP), interleukin-6 and orosomucoid levels in patients receiving RYGB (38). Second, the Lactobacillus and its species *Lactobacillus reuteri* were found to be positively correlated with BMI in patients undergoing RYGB (18, 26). Third, the variation of *C. comes* was found to be positively correlated with BMI and CRP in patients undergoing RYGB (26) and DCA in patients undergoing SG (36).

Further investigation of the functions of microbiota

Change of short-chain fatty acids (SCFAs)

By measuring the levels of fecal SCFAs and branched chain fatty acids (BCFAs), it was found that the SCFAs levels were consistent between animals with and without RYGB (27); this was also demonstrated for patients after BIB (20). However, patients undergoing RYGB showed a decrease in the SCFAs/BCFAs ratio (30).

Change of genetic content

By applying the Kyoto Encyclopedia of Genes and Genomes (KEGG) biological categories, a total of 6 clinical studies assigned the extracted gut genes to different KEGG Othologues (KOs) and annotated the function of the genes and analyzed the metabolic capacity of the gut microbiota through related KEGG modules and KEGG pathways (18, 21, 22, 26, 30, 36). The phosphotransferase system (PTS) was upregulated after RYGB (26), further proved by 2 human studies (22, 30). ABC transporters were enriched after VBG (30) and downregulated after RYGB (18). Nitrogen metabolism, fatty acid metabolism and the two-component system were also upregulated after bariatric surgery (30). Moreover, three KOs related

to butanoate metabolism, K00074, K00929 and K00626, were significantly higher after SG (36). A total of 53 microbial KEGG modules increased after RYGB, which implied an increased oxygen tolerance and the utilization of macronutrients and micronutrients (22). The increased use of sulfur relay and phosphotransferase systems, purine metabolism and an increase in several nutrient transport systems were observed after RYGB (21).

Transplantation of gut microbiota

Transplantation of the gut microbiota from bariatric surgery donors to germ-free mice was applied in 2 studies, and the donors were mice and patients, respectively (27, 30). The results showed significant weight loss, a lower adiposity index, a lower leptin level and more SCFAs in mice colonized with RYGB microbiota than those in mice colonized with a sham group microbiota (27). Further, a gain of less fat mass was found in mice colonized with RYGB and VGB microbiota than in mice colonized with people with obesity' microbiota (30).

Discussion

To the best of our knowledge, this is the first systematic review to quantitatively compare the current literature on the gut microbiome of patients or rodents after bariatric surgery. Our study is unique in that it systematically compiles the interaction between the host metabolism and the microbiome. Only with a standardized and strict statistical methodology can the particular correlation of bariatric surgery and the gut microbiome be unbiasedly summarized. The result of this systematic review furthers our understanding of the gut microbiome, which may contribute a great deal to regulating obesity-related conditions after bariatric surgery.

Many previous studies observed an overall lower bacterial diversity and a lower relative abundance of Bacteroidetes in individuals with obesity (39, 40). Although controversial results were found regarding the change of richness and diversity of microbiota related to the bariatric surgery procedures, four studies had reached an agreement on the higher gut microbiota diversity, as estimated by the Shannon index after surgery (19, 20, 22, 23). This fact revealed that the surgery itself or the metabolic benefit conferred by surgery allowed the modulation of the gut microbiota. Kong *et al.* (18) suggested that the change in eating habits might account for this change in microbiota diversity, such as reducing

the amount of fat and increasing the consumption of polysaccharides (41). However, in our previous study (19), the pair-fed group served as the RYGB diet-matched control group. Thus, the increased microbiota diversity induced by RYGB may be food independent.

Based on strong evidence, the population of Proteobacteria and its class Gammaproteobacteria, order Enterobacteriales, family Enterobacteriaceae and genus *Escherichia* increases after bariatric surgery. Several genera (*Citrobacter*, *Enterobacter*, *Escherichia* and *Salmonella*) and species (*E. cancerogenus*, *E. hormaechei*, *E. coli*, *K. pneumoniae* and *S. enterica*) belong to the family Enterobacteriaceae also increase on strong or moderate evidence (Table 6). Mice with obesity and insulin resistance induced by a high-fat diet had improved insulin sensitivity concomitant with a significant overrepresentation of the phylum Proteobacteria when given the antibiotics ampicillin, neomycin, and metronidazole by mouth, which showed that the abundance of the phylum Proteobacteria and insulin sensitivity may be linked (42).

Within the order Clostridiales (an abundant order of the phylum Firmicutes), there are 7 genera (*Anaerostipes*, *Clostridium*, *Faecalibacterium*, *Blautia*, *Coprococcus*, *Dorea* and *Ruminococcus*) and 2 families (Clostridiaceae and Ruminococcaceae) that decreased after surgery on strong or moderate evidence (Table 6). This is to be expected because several reports found the decline of *Clostridium* in the fecal samples from the gut of people with obesity (20, 31, 37). Because the production of butyrate appears to be a underlying feature of a few bacterial taxa within the order Clostridiales, a significant change of the population of such bacteria furthers the high interest on the crosstalk between them and host metabolism (43, 44, 45, 46). Additionally, the anaerobic gram-positive bacterium *Clostridium difficile* causes intestinal infections responsible for symptoms ranging from mild diarrhea to fulminant colitis (47).

F. prausnitzii, the sole known species of the genus *Faecalibacterium*, seemed to be of great importance in the inflammatory process and glucose homeostasis, as demonstrated by 3 studies (26, 36, 38). *F. prausnitzii* is an anti-inflammatory commensal bacterium that was identified by gut microbiota analysis (48), which is also found at lower abundance in those with Crohn's disease (49).

Lactobacillus contributed more to body composition, and two studies indicated correlations for the abundance of *Lactobacillus* and BMI (18, 26). *Lactobacillus* can play a role by producing lactic acid and extracting energy

from the fermentation of different sugars, which helps regulate the corpulence metabolism in people with obesity (50). Because bariatric surgery delays glucose and amino absorption in the host tract, the increase in simple sugars and amino acids in the large intestine may activate the colonic bacteria to derive energy from malabsorbed nutrients (51, 52, 53).

Although *C. comes* has been found to be correlated with the inflammation procedure and bile acid homeostasis, the mechanism that affects the host metabolism remains unclear, which suggests more investigations (54, 55, 56). Previous studies showed that agglutinating antibodies to *C. comes* are more frequently found in the sera of Crohn's patients than that in ulcerative colitis patients and healthy subjects, which suggests its important role in patients with Crohn's disease (54, 56, 57).

Approximately 5–10% of bile acids are biotransformed and degraded by intestinal bacteria during the enterohepatic circulation (58). The alteration in bile flow after RYGB may have considerable effects on the composition of the gut microbiota. Changes to the gut microbiome are also seen following SG, this is supported from studies interfering with BA homeostasis and the gut microbiome in a bidirectional way (59). Therefore, it is likely the gut microbiota mediates the phenotype and its metabolic complications in part through bile acid co-metabolism. More studies are needed to discover the relationship between bile acid and gut microbiota (60).

Previous studies have shown the difference between obese microbiota and lean microbiota. Obese microbiota may produce more SCFAs, which impede glucose incorporation in adipocytes and modulates energy expenditure through the sympathetic neuronal network. Thus, more energy can be extracted from a certain diet (61, 62). However, the results of our study failed to converge to a common conclusion regarding the change of SCFAs after bariatric surgery.

Due to the limited number of included studies and the different methodologies and technique applied in studies on microbiota following bariatric surgery, inconsistent findings were inevitable. Although in this review, we used the evidence level system to analyze and summarize the existing literature, there is still a justified need in the field to elucidate useful information that could move this line of research forward. This review could serve as an incentive for the field to harmonize techniques and improve the study design to generate complementary findings. More advanced sequencing technology and metagenomic and bioinformatic methods are needed to investigate the

microorganisms inhabiting the human gut. As for the type of design, a non-surgical weight loss treatment group for control in the human study and a pair-fed and weight-limited control group in the animal study are needed for further research. However, randomized and double-blind studies are currently extremely scarce in this field.

Limitation

Our study has some limitations. First, the low cohort numbers may influence the results. Second, the different diet and comorbidities may influence the gut microbiome. Third, the time point to extract the fecal sample are inconsistent among studies, however, the diet after bariatric surgery may change a lot with time going, so the gut microbiome may be affected. Fourth, the difference on varying types of surgery remains unclear according to our results.

Conclusion

Bariatric surgery is included in the treatment of T2D and obesity, and gut microbiota were implicated in the crosstalk of host metabolic change and bariatric surgery. In this review, we found that microbial composition is greatly altered after bariatric surgery. Based on strong evidence, 4 phyla (Bacteroidetes, Fusobacteria, Verrucomicrobia and Proteobacteria) increased after surgery; within the phylum Firmicutes, Lactobacillales, Enterococcus, *E. faecalis* and *S. gordonii* increased; and within the phylum Proteobacteria, Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae, Escherichia, Alistipes, *E. coli*, *E. hormaechei* and *K. pneumoniae* increased. The decreased microbial groups were Firmicutes, Clostridiales, Clostridiaceae, Blautia and Dorea. Lactobacillus, *F. prausnitzii* and *C. comes* are more related to the metabolic alteration of patients after bariatric surgery. The results of gut genetic content, microbiome transplantation and SCFAs production imply the potential of microbiota in modulating host metabolic regulation. More long-term prospective studies are warranted to investigate the mechanism of gut microbiota on modulating host metabolism after bariatric surgery.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0403>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Author contribution statement

Yuan Sheng and Da-Jin Zou designed the research study; Yan Guo, Zhi-Ping Huang and Chao-Qian Liu performed the research; Yan Guo, Zhi-Ping Huang and Chao-Qian Liu analyzed the data; Yan Guo, Zhi-Ping Huang wrote the paper; Yuan Sheng, Da-Jin Zou and Lin Qi revised the paper.

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