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REVIEW ARTICLE

The Importance of the Microbiome in Bariatric Surgery: a Systematic Review

Josianne C. H. B. M. Luijten[1] · Guusje Vugts[2] · Grard A. P. Nieuwenhuijzen[2] · Misha D. P. Luyer[2]

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Abstract

Bariatric surgery results in sustained weight loss, improvement of metabolic and hormonal changes, and reduction of comorbidities in obese patients. However, beneficial effects of bariatric surgery are not solely explained by restriction and malabsorption induced by surgery itself. Changes in the microbiome might play a role in this mechanism. A systematic review was performed in which 21 studies were included. The microbiome was affected by surgery and profound changes occurred in the first year of follow-up. An increase in *Bacteroides* and *Proteobacteria* and a decrease in Firmicutes were observed postoperatively in most studies. These changes were associated with weight loss. Bariatric surgery induces profound changes in the microbiome. This may be related to the beneficial effect of bariatric surgery on comorbidities associated with obesity.

Keywords Gut microbiome · Bariatric surgery · Comorbidities · Type 2 diabetes · Weight loss · Roux-en-Y gastric bypass (RYGB) · Sleeve gastrectomy (SG)

Introduction

Obesity and its related comorbidities are a growing epidemic with a profound impact on healthcare, especially in the "westernized countries" [1, 2]. In 2015, approximately 600 million obese adults worldwide have been reported [3, 4]. Bariatric surgery is the most effective treatment for prolonged weight loss resulting in changes in glucose metabolism and metabolic and hormonal changes, thereby improving comorbidities as diabetes and hypertension [5, 6]. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most frequently performed bariatric procedures and an increase in the number of bariatric procedures has been reported worldwide [4, 7, 8].

Recent studies have suggested that the effects of bariatric surgery are not solely explained by restriction and malabsorption induced by the procedure itself [9–11]. Resolution of obesity-related comorbidities such as type 2 diabetes and hypertension is independent of weight loss following bariatric surgery [12]. Emerging evidence suggests that bariatric surgery induces changes in gut microbiome which may provide an alternative explanation for the beneficial effects of bariatric surgery [9]. Changes in the gut microbiome have been shown to be associated with the resolution of insulin resistance and a low-grade inflammatory response observed in obesity and type 2 diabetes [13, 14]. Also, several experimental studies have shown that fecal microbial transplantation of non-obese animals is associated with a decrease in fat mass, weight loss, and insulin sensitivity [15].

The gut microbiome is a microbial ecosystem, mainly consisting of *Firmicutes* and *Bacteroidetes* followed by *Actinobacteria* and *Proteobacteria*. The symbiosis in this ecosystem is fragile and can be easily disturbed (dysbiosis). It has been recognized that a dysbiotic microbiome may have critical effects on morbidity and mortality in the general population [16]. For example, decreased bacterial richness is associated

Core Tip Bariatric surgery is associated with rapid and sustained alterations in the gut microbiome, with more pronounced changes in patients undergoing Roux-en-Y gastric bypass compared with sleeve gastrectomy. Furthermore, an increase of diversity and microbial richness of the human microbiome was observed following bariatric surgery. This may be related to the beneficial effect of bariatric surgery on comorbidities associated with obesity, such as type 2 diabetes. Unraveling the exact correlations between alterations in microbiome and bariatric surgery is challenging and may provide new therapeutic opportunities to reduce morbid obesity.

✉ Misha D. P. Luyer
misha.luyer@catharinaziekenhuis.nl

[1] Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands

[2] Department of Surgery, Catharina Hospital, Michelangelolaan 2, 5623 RJ Eindhoven, The Netherlands

with insulin resistance, dyslipidemia, and obesity [17, 18]. Furthermore, in obese subjects, a dysbiotic microbiome characterized by an increased ratio of *Firmicutes* to *Bacteroidetes* is observed [17]. Given the increasing incidence of obesity and its related need for bariatric surgery, it is important to get more insight in the changes of gut microbiome induced by briatric surgery, to optimize treatment strategies.

Evidence regarding this topic is scarce and scattered; therefore, the aim of this review is to identify the current evidence on changes in gut microbiome related to bariatric surgery and its influence on patient outcomes.

Materials and Methods

Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed while conducting the review [19]. The PubMed database (including MEDLINE) and OVID Embase were searched until 31 December 2018 using the following free and Mesh terms: gastrointestinal microbiome, microbiome, microbioma, obesity surgery, bariatric surgery, Roux-en-Y gastric bypass (RYGB), bilio-intestinal bypass (BIB), duodenal-jejunal bypass (DJB), biliopancreatic diversion, gastrojejunostomies, gastrojejunostomy, sleeve gastrectomy, gastric band, upper gastrointestinal surgery, gastrectomy, and gastric surgery. The full search strategy is presented in Appendix 1.

Selection

The selection process of the articles for this review is summarized in Fig. 1. The retrieved abstracts were screened independently by two authors (JL and GV) for eligibility, based on predefined inclusion and exclusion criteria. Articles were eligible if they met the following criteria: inclusion of adult patients who underwent any type of bariatric surgery (i.e., Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion, gastric banding), description of any details on the microbiome of these patients after surgery, with or without comparison to the preoperative status, and articles describing original research that were available in full-text. Review articles, editorials, conference reports, comments on other studies, and animal studies were excluded. Furthermore, studies investigating the effect of the use of proton-pump inhibitors, antibiotics, or probiotics in combination with bariatric surgery on microbiome were excluded. Of the selected articles, the full-text as well as the reference list was reviewed independently by two authors (JL and GV). If the reference list contained possible eligible articles, these were included. Any disagreement was solved by discussion.

Data Extraction, Quality Assessment, and Statistical Analysis

The following characteristics were extracted from included publications: study design, number of included patients, type of bariatric surgery, species present in the postoperative microbiome, whether a decrease or increase in these species was observed, and associations with clinical effect (i.e., weight loss, insulin resistance). The available data were collected and described. In this systematic review, the effects of procedures with a restrictive as well as a malabsorptive component (RYGB and bilio-intestinal bypasses) are described separately from the effects of purely restrictive procedures (sleeve gastrectomy, gastric banding).

To assess the methodological quality of the included studies, we used the tools of the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) for quality assessment of observational cohort and cross-sectional studies, case control studies, and controlled intervention studies. The NIH included an evaluation of participant selection, confounding variables, measurements of exposures, blinding of outcomes, and loss to follow-up. Due to the limited availability of high-quality trials, no meta-analyses were conducted.

No protocol was registered for this review.

Results

Studies Included and Methodological Quality

A total of 492 studies were identified and ultimately 39 articles were included for full-text screening. After application of inclusion and exclusion criteria, 21 studies were included in this review (Fig. 1). The details of these studies regarding the number of included patients, presence of a control group, type of surgical intervention, and follow-up period are presented in Table 1. Most studies included in this review were case control studies or observational cohort studies comparing microbiome pre- and post-surgery. Microbial richness (alpha diversity) and microbial diversity were frequently investigated. Microbial richness represents the number of species in a sample and is best detected by the rRNA approach [39]. Microbial diversity is defined as the variability of micro-organisms in the microbiome. A proportion of these studies described clinical effects of different species on weight loss and reduction of comorbidities.

Among the included studies, 9 involved an evaluation with the quality assessment tool for observational cohort and cross-sectional studies, 10 were assessed using the quality assessment tool of case control studies, and two studies were assessed using the assessment tool of controlled intervention studies. The overall quality of the included studies was average. The majority of the studies presented adequate participant

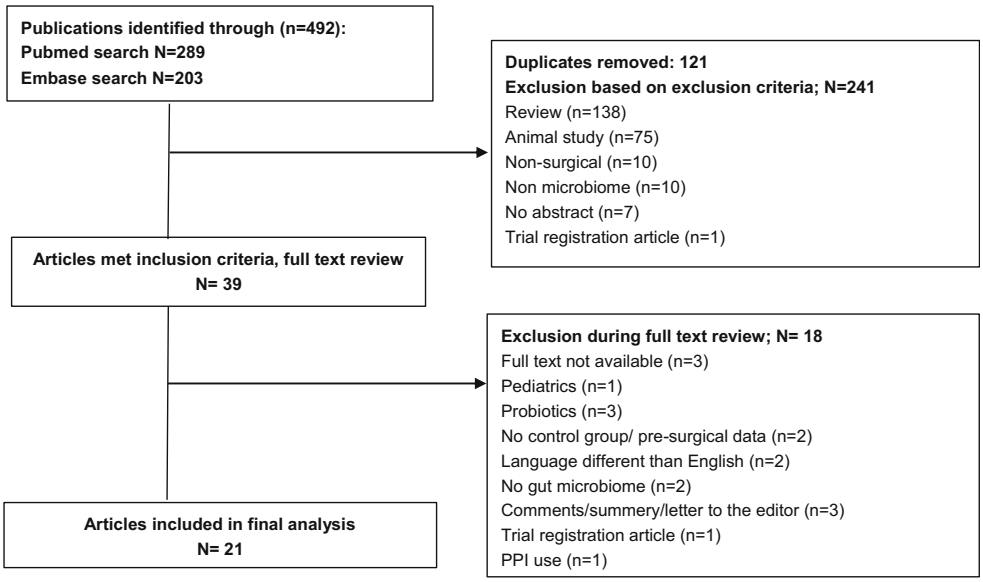

Fig. 1 Flow chart data selection

selection and measurements of exposures. Blinding of outcomes and loss to follow-up was not conducted or not reported in the majority of the included studies. The results of the quality assessment are presented in Appendix 2, Tables 6, 7, and 8.

Bariatric Surgery and Microbial Composition

In general, microbial richness increased from baseline to 3 months post-surgery and reached a statistically significant difference at 12 months after RYGB [35]. Microbiome changes were more profound in patients that underwent RYGB compared with patients with gastric banding (GB) [28]. Most changes in microbiome occurred within the first year postoperatively and this effect persisted until 9 years of follow-up in one smaller study ($N = 21$ patients) [24, 35].

Some species correlated with the resolution of comorbidities post-bariatric surgery. The abundance of the *F. prausnitzii* species had a direct association with reduction of low-grade inflammation observed in obesity and type 2 diabetes. Levels of *F. prausnitzii* were low in patients with type 2 diabetes before RYGB. An increase in *F. prausnitzii* was observed after bariatric surgery, leading to a reduction in low-grade inflammation [13, 14, 40]. Furthermore, a negative relationship between blood glucose levels and the abundance of *Lactobacillus* was observed. After correcting for caloric intake, associations between blood glucoses and *Lactobacillus* remained significant [25]. High levels of *Gammaproteobacteria* were associated with weight loss after RYGB [13]. Secondly, host metabolism was possibly affected by *Roseburia*, because *Roseburia* can ferment a large variety of carbohydrates [6]. Finally, an increase of *Escherichia coli* was associated with a higher efficiency to harvest energy in the post-RYGB starvation-like condition [22].

Alterations in Human Microbiome after Combined Restrictive and Malabsorptive Bariatric Procedures

A total of 15 studies investigated the specific effects of RYGB on the human microbiome. Microbial richness increased significantly within 3 months and was maintained after 1 to 2 years [26, 28, 37, 41]. However, no statistically significant changes in species richness were exhibited between 3 months and 1 year [26]. Ilhan et al. observed that greater alterations in the microbiome occurred after RYGB, then after purely restrictive bariatric procedures. Furthermore, the increase in microbial gene richness and thus the bacterial diversity was more pronounced in patients that underwent RYGB, compared to other types of bariatric surgery [28, 35].

A significant increase of *Bacteroides* and *Proteobacteria* and a decrease of *Firmicutes* were observed in patients after RYGB compared to the same patients at baseline or obese controls who did not undergo surgery [20–24, 26, 32, 38]. Furthermore, alterations in *Escherichia* (which belongs to the *Proteobacteria* phylum) were described frequently [13, 22, 24, 26, 28, 32]. Microbial diversity and its clinical effect after RYGB are displayed in Table 2. For many changes in gut microbiota, it remains unclear whether these changes are causally related to patient outcome parameters.

Only two small studies ($N = 11$ and $N = 19$ patients who underwent BIB) described changes in microbiome after this procedure. Results on the microbial changes after BIB were highly heterogeneous between patients. It appeared that the *Bacteroidetes* to Firmicutes ratio did not alter after BIB.

Table 1 Included studies in this review ($N = 21$)

Author	Year	RCT	*N*	Population	Surgery (Sx)	Case control	Microbiome prior to Sx	Duration of follow-up	Microbiome characterization
Zhang [20]	2009	No	9	Obese	Obese/lean/GB	Yes	No	6 months	16s rRNA
Furet [13]	2010	No	43	Obese/ normal weight	RYGB	Yes	Yes	3, 6 months	
Graessler [21]	2013	No	6	Obese	RYGB	No	Yes	3 months	16s rRNA
Kong [22]	2013	No	30	Obese	RYGB	No	Yes	3, 6 months	16s rRNA
Damms-Machado [23]	2014	No	10	Obese	LSG	Yes	Yes	6 months	800 bp
Tremaroli [24]	2015	No	21	Obese	RYGB/obese/VBG	Yes	No	9.4 year	Repeated bead beating
Patrone [25]	2015	No	11	Obese	BIB	No	Yes	6 months	16s rRNA
Federico [6]	2016	No	47	Obese (± Sx)/normal weight	BIB	Yes	Yes	6 months	PCR DGGE analyses
Palleja [26]	2016	No	13	Obese/T2D	RYGB	No	Yes	3, 12 months	IHMS
Murphy [27]	2016	Yes	14	Obese/T2D	RYGB/SG	Yes	Yes	12 months	
Ilhan [28]	2017	No	63	Obese	RYGB/LAGB/lean/obese	Yes	No	9 months	16s rRNA
Sanmiguel [29]	2017	No	8	Obese	LSG	No	Yes	1 months	16s rRNA
Medina [30]	2017	No	19	Obese	Medical/RYGB/SG	Yes	Yes	6, 12 months	16s rRNA
Liu [31]	2017	No	110	Obese	Obese/lean/SG	Yes	Yes	1, 3 months	16s rRNA
Chen [32]	2017	No	24	Obese/T2D	RYGB	No	Ye	6 months	16s rRNA
Campisciano [33]	2018	No	40	Obese/normal weight	LGB/SG	Yes	Yes	3 months	16s rRNA
Campisciano [34]	2018	No	40	Obese/normal weight	LGB/SG	Yes	Yes	3 months	16s rRNA
Aron-Wisnewsky [35]	2018	No	24	Obese	AGB/RYGB	No	Yes	12 months	182 MB
Kikuchi [36]	2018	No	44	Obese	LSG/LAG-DJB/LAGB	No	Yes	3 months	PCR
Kumar [37]	2018	No	34	Obese	RYGB/SG	No	Yes	2 years	150 bases
Cortez [38]	2018	Yes	21	Obese/T2D	DJBm/diet	Yes	Yes	6, 12 months	16s rRNA

GB gastric band, *RYGB* Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *VBG* vertical banded gastroplasty, *BIB* bilio-intestinal bypass, *T2D* type 2 diabetes, *DJB* duodenal-jejunal bypass, *DJBm* duodenal-jejunal bypass with minimal gastric resection

Table 2 Postoperative microbiome in patients after Roux-en-Y gastric bypass (total of 15 articles; describing 231 patients)

Species	Effect	Amount of articles (N = total amount of included patients)	Clinical parameters	Duration of effect
Proteobacteria	↑	7 (N = 78)	+ Correlation weight loss and bilirubin	9 years
Firmicutes	↑	3 (N = 27)	Remission of T2D	12 months
	↓	4 (N = 72)		9 years
Bacteroidetes	↑	4 (N = 70)	Remission of DM2	12 months
	↓	3 (N = 27)	Decrease monocytes	12 months
			Decreased liver markers	
Bifidobacterium	↑	1 (N = 24)	Monocytes	6 months
	↓	4 (N = 80)		9 years
Escherichia	↑	3 (N = 61)	+ correlation with TNF alfa	9 years
	↓	3 (N = 67)	levels, inverse relation with fat mass	1 year
Fusobacteria	↑	3 (N = 40)		12 months
Lactobacillus	=	1 (N = 24)	Relation with blood glucoses	6 months
	↓	2 (N = 60)		6 months
F. prausnitzii	↑	2 (N = 36)	Glucoses, inflammation markers	6 months
	↓	1 (N = 13)		1 year
Gammaproteobacteria	↑	3 (N = 34)		9 years
Veillonella	↑	3 (N = 43)	Invers correlation with plasma total and LDL cholesterol, triglycerides	9 months
Actinobacteria	↑	2 (N = 33)	Diabetes remission, − association with liver markers	12 months
	↓	1 (N = 30)		6 months
Roseburia	↑	2 (N = 48)	Remission of DM2	12 months
Akkermansia muciniphila	↑	3 (N = 33)	Reduction adiposity, body fat mass, inflammation, and glucose intolerance	12 months
Enterococcus	=	1 (N = 24)		6 months
	↑	1 (N = 13)		12 months
Enterobacteriaceae	↑	2 (N = 9)		6 months
Clostridium	=	1 (N = 30)		6 months
	↓	1 (N = 3)		6 months
Bacteroides/*Prevotella*	↑	1 (N = 30)		6 months
Leuconostoc	↓	1 (N = 30)		6 months
Pediococcus	↓	1 (N = 30)		6 months
Butyricimonas	↑	1 (N = 41)		12 months
Klebsiella pneumoniae	↑	1 (N = 13)		12 months
E. cancerogenus	↑	1 (N = 6)	Invers correlation plasma total and LDL cholesterol, triglycerides	3 months
Shigella	↑	1 (N = 6)		3 months
Salmonella	↑	1 (N = 6)		3 months
Mycobacterium	↓	1 (N = 6)		3 months
Treponema	↓	1 (N = 6)		3 months
C. comes	↓	1 (N = 6)		3 months
F. nucleatum	↑	1 (N = 13)		12 months
B uniformis	↓	1 (N = 10)		3 months
Dialister	↑	1 (N = 11)		12 months

Table 3 Postoperative microbiome in patients after bilio-ileo bypass (total of 2 articles; describing 31 patients)

Species	Effect	Amount of articles (total amount of included patients)	Clinical parameters	Duration of effect
Lactobacillus	↑	2 ($N = 20$)	− Relation with blood glucoses	6 months
Enterobacteriaceae	↑	1 ($N = 11$)		6 months

Post-surgery-enriched bacterial groups were *Selemonadales*, *Enterobacteriaceae*, and *Lactobacillus* [6, 25] (Table 3).

Alterations in Human Microbiome after Restrictive Bariatric Procedures

Nine studies investigated the influence of sleeve gastrectomy (SG) on the gut microbiome. In a large study including $N = 110$ patients who underwent SG, microbial richness and gene count substantially increased 3 months after SG, approaching that of lean controls [31]. In contrast, Murphy et al. did not find a statistically significant difference in diversity of gut microbiome post-SG in their cohort of $N = 14$ patients, but observed an increase in *Roseburia intestinalis* after SG induced type 2 diabetes remission [41]. Most studies investigating SG described a decrease in *Firmicutes* and increases in *Proteobacteria*, *Bacteroidetes*, and the *Bacteroidetes/Firmicutes* ratio (a surrogate marker for the microbiome of lean controls) [23, 27, 29, 30, 33, 34, 36]. Microbial diversity post-SG is described in Table 4. Alterations in gut microbiome related to clinical parameters and patient outcomes post-SG are observed in *B. thetaiotaomicron* and *Atopobium*. *B. thetaiotaomicron* were associated with a decrease in BMI and decreased circulating glutamate levels [31]. Furthermore, changes in *Atopobium* were associated with changes in BMI and body fat mass [29].

Three studies described the effect of gastric banding (GB) on microbiome. Comparable with other types of bariatric surgery, microbial richness increased within 3 months post-surgery and reached statistical significance at 12 months. However, alterations in microbiome of the GB patients were not as profound when compared to the changes observed after RYGB and were comparable to the alterations observed in obese patients in general [28, 35]. Alterations in gut microbiome are presented in Table 5.

Discussion

This review describes the association of bariatric surgery with gut microbiome composition. Changes were most profound in patients undergoing Roux-en-Y gastric bypass (RYGB), but also present in patients that underwent SG. Changes in gut microbiome were associated with maintained weight loss and type 2 diabetes remission. However, for many microbial changes, no clear causal relationship with patient outcome parameters was shown.

Bacteroidetes and *Firmicutes* were found to be the dominant bacteria related to obesity. The abundance of *Bacteroidetes* was less, while the abundance of *Firmicutes* was more in obese individuals [10, 17, 42]. It has been hypothesized that the obese microbiome is more efficient in absorbing energy from digested food compared to the lean microbiome [10]. Decreased levels of *Firmicutes* could result in a more sustained weight loss and maintenance due to a reduction of energy harvest [23]. Increases in proportions of *Bacteroides* correlate with the reduction in body fat mass and plasma leptin, also contributing to weight loss by the same mechanism [13]. An increase in *Bacteroidetes* and *Proteobacteria* and a decrease in Firmicutes post-bariatric surgery are observed in most of the included studies. These changes induce an increase of the *Bacteroides/Firmicutes* ratio after bariatric procedures. This ratio may act as a surrogate marker for the observed changes in the obese microbiome compared to the lean microbiome. Therefore, alterations in the *Bacteroides/Firmicutes* ratio are positively associated with weight loss post-bariatric surgery.

Hence, bariatric surgery leads to major alterations in the gut microbiome. However, the changes in microbiome were not consistent between the described studies. This might be related to differences in methods used for microbial analyses, different time points after surgery, the presence of type 2 diabetes, medication, and nutritional status in the cohorts examined. As a result, the clinical relevance of at least some of these changes is still subject to debate.

In the last decades, it has been recognized that gut microbiome dysbiosis is a condition which leads to the pathogenesis of several intestinal and extra-intestinal diseases. In a dysbiotic ecosystem, potentially pathogenic microbes take over at the expense of potentially beneficial microbes [43]. Administration of probiotics, prebiotics, and symbiotics as well as fecal microbial transplantation has been described as potential treatment strategies in patients with obesity, metabolic syndromes, and type 2 diabetes, as well as inflammatory bowel disease [43]. Although the mechanisms of these gut microbiome interventions in obesity are not clear, the potential benefits could be substantial with a great impact.

Fecal microbial transplantation (FMT) is aimed to restore the gut microbiota by transferring gut microbiome of healthy donors [44] and might have a role in the treatment of inflammatory bowel disease (IBD) [45–47]. Several experimental studies have investigated the effects of FMT on remission of obesity [11, 15]. Turnbaugh et al. transplanted fecal microbiota of obese and lean mice into germ-free mice and observed that

mice colonized with an obese microbiome exhibited a significant increase in total body fat compared with mice colonized with lean microbiome. Another study transplanted the microbiota of RYGB-treated mice and sham surgery mice to non-operated mice. In the non-operated mice, FMT of RYGB-treated mice resulted in weight loss and decreased fat mass compared to sham surgery FMT [11]. These data indicate a potential role for investigating FMT for treatment of obesity in a clinical setting.

While gut microbiome dysbiosis leading to several pathological intestinal diseases and contributing to weight loss post-bariatric surgery, it is hypothesized that changes in gut microbiome might also be related to the occurrence of post-operative complications in different types of gastrointestinal surgery. In colorectal surgery, for example, several studies suggest an association between specific alterations in the post-operative microbiome and anastomotic leakage [48, 49]. A recent study observed that anastomotic leakage corresponded with low microbial richness and an increased abundance of *Lachnospiraceae* and *Bacteroidaceae* [49]. Another study investigated oral and gastric microbiota in patients with esophageal cancer after esophagectomy. The variation in bacterial richness between the preoperative oral microbiome compared with the intraoperative gastric microbiome was significantly different in patients who had an anastomotic leakage [50]. These findings indicate that alterations or differences in microbiome could be associated with the occurrence of complications. After bariatric surgery, changes in the postoperative microbiome appear to affect energy harvesting as well as the inflammatory state in the bariatric population [6, 13, 14, 26, 40]. It could be hypothesized that the influence of microbial changes might induce multiple physiological pathways leading to a higher risk of postoperative complications such as anastomotic leakage. Research on these associations is limited and, therefore, an important focus for future research could involve clarifying whether surgical complications could be associated with a dysbiotic microbiome.

Table 4 Postoperative microbiome in patients after sleeve gastrectomy (total of 8 articles; describing 73 patients)

Species	Effect	Amount of articles (total amount of included patients)	Clinical parameters	Duration of effect
Bacteroides/Firmicutes	↑	3 ($N = 50$)	Surrogate marker normal weight/morbid obese	12 months
	↓	1 ($N = 8$)		1 month
Bacteroidetes	↑	3 ($N = 52$)	− Correlation with body weight	12 months
	↓	1 ($N = 5$)		12 months
Firmicutes	↑	1 ($N = 19$)	+ Correlation with body weight, reduction of energy harvest, + metabolic effects	12 months
	↓	2 ($N = 13$)		6 months
Proteobacteria	↑	2 ($N = 20$)		3 months
	↓	1 ($N = 5$)		12 months
Bifidobacterium	↓	2 ($N = 48$)		9 years
Enterobacteriales	↑	2 ($N = 45$)		12 months
B. uniformis	↑	2 ($N = 20$)		3 months
F. prausnitzii	↑	1 ($N = 5$)	Glucose, inflammation markers	6 months
Akkermansia muciniphila	↑	1 ($N = 22$)		3 months
Fusobacteria	↑	1 ($N = 8$)		1 month
Lactobacillus	=	1 ($N = 22$)		3 months
B. thetaiotaomicron	↑	1 ($N = 6$)	Decrease circulating glutamate levels and decrease in BMI	3 months
E. rectale	↓	1 ($N = 5$)	+ Correlation obesity related comorbidities	6 months
Streptococcus	↑	1 ($N = 22$)		3 months
Enterococcus	=	1 ($N = 22$)	Correlates with BMI, reduction body fat mass, and hunger levels	3 months
Atopobium	↑	1 ($N = 8$)	Changes in BMI and body fat mass	1 month
Bulleidia	↑	1 ($N = 8$)	Decreased desire to eat sweets	1 month

Table 5 Postoperative microbiome in patients after gastric band (total of 3 articles; describing 28 patients)

Species	Effect	Amount of articles (total amount of included patients)	Clinical parameters	Duration of effect
Butyricimonas virosa	↑	1 ($N = 10$)		12 months
Flavobacteriia	↑	1 ($N = 14$)	− Correlation with nucleic acid degradation products	9 months
Porphyromonadaceae	↑	1 ($N = 14$)		9 months
Akkermansia muciniphila	↑	1 ($N = 4$)		6 months

There are some limitations associated with this review that should be considered while interpreting the results. The most important limitation of this study is the lack of included randomized controlled trials and the limited number of included studies. However, there are solely two randomized controlled trials published that met inclusion criteria. Hence, no meta-analysis was conducted.

Due to the different methodologies and techniques applied in studies on microbiota following bariatric surgery, inconsistent findings were inevitable and, moreover, quality of the described studies was relatively average. Furthermore, the majority of the studies did not control for confounders such as antibiotic or probiotic use prior to fecal sample collection.

Several other reviews about the effects of bariatric surgery on gut microbiome have been published. The majority of those reviews are not conducted systematically and use solely on one database [51, 52]. With a growing interest in the effects of bariatric surgery on microbiome, half of the articles that are now included in this systematic review were published after 2017 [53, 54]. Moreover, differences in microbiome are now presented stratified for several types of bariatric surgery.

In conclusion, bariatric surgery plays a crucial role in treatment of obesity and resolution of related comorbidities. Bariatric surgery and the resolution of metabolic disorders such as type 2 diabetes are associated with changes in the gut microbiome. However, it has not yet been elucidated whether or not these changes in gut microbiome are relevant and causally related to patient outcome measures. Unraveling the exact correlations between alterations in microbiome and bariatric surgery is challenging and may provide new therapeutic opportunities in addition to bariatric surgery to effectively reduce morbid obesity.

Author Contributions All authors equally contributed to this paper. Conception and design of the study: ML and GN; literature review and analysis: JL and GV; drafting and critical revision and editing, and final approval of the final version: JL, GV, ML, and GN.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Statements Regarding Ethics and Consent This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix 1. Full search strategy

PubMed

("gastrointestinal microbiome" OR microbiome OR microbioom OR microbioma) AND ("gastric band" OR "obesity surgery" OR RYGB OR "Roux-en-Y gastric bypass" OR "biliopancreatic diversion" OR DJB OR "duodenal-jejunal bypass" OR gastrojejunostomies OR gastrojejunostomy OR "sleeve gastrectomy" OR "bariatric surgery" OR "upper gastrointestinal surgery" OR "gastric surgery")

Embase

("gastric band" or "bariatric surgery" or "upper gastrointestinal surgery" or "gastric surgery" or "sleeve gastrectomy" or gastrojejunostomy or gastrojejunostomies or "duodenal-jejunal bypass" or "biliopancreatic diversion" or "Roux-en-Y gastric bypass" or DJB or RYGB or "obesity surgery").af. AND ("gastrointestinal microbiome" or microbiome or microbioom or microbioma).af.

Appendix 2 Quality Assessment

Table 6 Quality assessment tool for observational cohort and cross-sectional studies

	Graessler et al.	Kong et al.	Patrone et al.	Palleja et al.	Sanmiguel et al.	Chen et al.	Aron-Wisnewsky et al.	Kikuchi et al.	Kumar et al.
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✗
2. Was the study population clearly specified and defined?	✗	✗	✗	✗	✓	✓	✗	✗	✓
3. Was the participation rate of eligible persons at least 50%?	N.R.	N.R.	✓	N.R.	N.R.	N.R.	N.R.	N.R.	✓
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the	✗	✗	✗	✗	✓	✓	✗	✗	✗

Table 6 (continued)

	Graessler et al.	Kong et al.	Patrone et al.	Palleja et al.	Sanmiguel et al.	Chen et al.	Aron-Wisnewsky et al.	Kikuchi et al.	Kumar et al.
study prespecified and applied uniformly to all participants?									
5. Was a sample size justification, power description, or variance and effect estimates provided?	✗	✗	✗	✓	✗	✗	✗	✗	✗
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	✓
10. Was the exposure(s) assessed more than once over time?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓
12. Were the outcome assessors blinded to the exposure status of participants?	✗	✗	✗	✗	✗	✗	✗	✗	N.R.
13. Was loss to follow-up after baseline 20% or less?	N.R.	N.R.	N.R.	✗	✓	N.R.	N.R.	N.R.	✓
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	✗	✗	✗	✗	✓	✗	✗	✗	✗

Yes ✓, *No* ✗, *N.A.* not applicable, *N.R.* not reported

Table 7 Quality assessment tool for case control studies

	Zhang et al.	Furet et al.	Damms-Machado et al.	Tremaroli et al.	Federico et al.	Ilhan et al.	Medina et al.	Liu et al.	Campisciano (30) et al.	Campisciano (31) et al.
1. Was the study question or objective clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	✗	✓	✓	✗	✓	✓	✗	✓	✓	✓
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4. Were all eligible participants that met the prespecified entry criteria enrolled?	N.R.	N.R.	N.R.	N.R.	✓	N.R.	N.R.	N.R.	N.R.	N.R.
5. Was the sample size sufficiently large to provide confidence in the findings?	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
	✓	N.R.	✓	✓	✓	N.A.	N.R.	N.R.	N.R.	N.R.

Table 7 (continued)

	Zhang et al.	Furet et al.	Damms-Machado et al.	Tremaroli et al.	Federico et al.	Ilhan et al.	Medina et al.	Liu et al.	Campisciano (30) et al.	Campisciano (31) et al.
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	✗	✗	✓	N.A.	✓	✗	✓	✓	✗	✗
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *p* values for the pre-to-post changes?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

Yes ✓, *No* ✗, *N.A.* not applicable, *N.R.* not reported

Table 8 Quality assessment tool for controlled intervention studies

	Murphy et al.	Cortez et al.
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	✓	✓
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	✓	✗
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	✓	N.R.
4. Were study participants and providers blinded to treatment group assignment	✓	N.R.
5. Were the people assessing the outcomes blinded to the participants' group assignments?	✓	N.R.
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, comorbid conditions)?	✓	✗
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	✓	✗
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	✓	✗
9. Was there high adherence to the intervention protocols for each treatment group?	N.A.	N.A.
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	✗	✗
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	✗	✓
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	✗	✗
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	✓	✓
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	✓	✓

Yes ✓, *No* ✗, *N.A.* not applicable, *N.R.* not reported

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