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The Intestinal Microbiome in Bariatric Surgery Patients

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Abstract

With nearly 39% of the worldwide adult population classified as obese, much of the globe is facing a serious public health challenge. Increasing rates of obesity, coupled with the failure of many behavioral and pharmacological interventions, have contributed to a rise in popularity of bariatric surgery as a treatment for obesity. Surgery-mediated weight loss was initially thought to be a direct result of mechanical alterations causing restriction and calorie malabsorption. However, the mounting evidence suggests that indirect factors influence the accumulation and storage of fat in patients that have undergone this procedure. Given the established impact the intestinal microbiota has on adiposity, it is likely that this complex enteric microbial community contributes to surgery-mediated weight loss and maintenance of weight loss post-surgery. In this review, we discuss the physiological and psychological traits exhibited by bariatric surgery candidates that can be influenced by the intestinal microbiota. Additionally, we detail the studies that investigated the impact of bariatric surgery on the intestinal microbiota in humans and mouse models of this procedure.

INTRODUCTION

The relationship between the enteric microorganisms that colonize the gastrointestinal (GI) tract, the intestinal microbiota, and human health has been the focus of intensive research over the past decade (Sekirov, Russell, Antunes, & Finlay, 2010). These investigations stem from early gnotobiotic (animals with a defined enteric microbiota) work where animals that are free from microbial colonization (germ-free, GF) exhibit abnormal intestinal physiology and immune responses (Gordon & Pesti, 1971). Subsequent investigations have demonstrated associations between this complex microbial community and myriad diseases (de Vos & de Vos, 2012). Interestingly, the concept that gut microorganisms are intimately linked to human health was developed over a century ago by Ilya Ilyich Mechnikov (Mechnikov, 1988), a Nobel Laureate in Physiology or Medicine (1908) for work on

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phagocytosis. Dr. Mechnikov postulated that certain bacteria could improve the intestinal health of the host in “Prolongation of Life: Optimistic Studies” (Metchnikoff 1908).

The intestinal microbiota is a complex community of bacteria, archaea, viruses and eukarya, with bacterial concentrations reaching as high as 10^{12} cells/mL of luminal contents in the colon. This complex microbial community harbors a gene repertoire over 100 times than that of the human host (Ley, Peterson, & Gordon, 2006; Whitman, Coleman, & Wiebe, 1998). Most species of bacteria that inhabit the mammalian GI tract cannot be cultured by traditional microbiological means (Eckburg et al., 2005; Hayashi, Sakamoto, & Benno, 2002); thus, molecular techniques have been utilized to determine the taxonomic composition and richness (degree of diversity) of enteric microbial communities. Typically, the 16S rRNA gene is used for these purposes, as this genetic locus is shared by all bacteria and exhibits blocks of sequence variation, permitting taxonomic identification of microbes within a complex community. Sequence data encompassing the intestinal microbiota’s entire gene catalogue, often referred to as the metagenome, is also used to extend analyses to predictive functional genomics.

Although host genetics contribute to the accumulation and storage of fat (adiposity), the role of the intestinal microbiota has been investigated in this process (Ley, Turnbaugh, Klein, & Gordon, 2006). Indeed, the composition and diversity of the intestinal microbiota differs between obese individuals and lean controls (Turnbaugh et al., 2009). Additionally, an obese phenotype can be transmitted to GF animals via introduction of enteric microbial communities (Ridaura et al., 2013). Thus, given the established impact of the intestinal microbiota on adiposity, the role of this complex microbial community in surgery-mediated weight loss warrants exploration. Extant studies have primarily documented that the intestinal microbiota is significantly altered after bariatric surgery (particularly with respect to the Bacteroidetes and Firmicutes phyla) and that the adaptation of these microbial communities have both local and global effects on human metabolism. A significant gap remains, however, in our knowledge regarding the specific contribution of enteric microbes to weight loss following gastric bypass surgery.

BARIATRIC SURGERY PARAMETERS IMPACTED BY THE INTESTINAL MICROBIOTA

Individuals who have undergone bariatric surgery to combat morbid obesity exhibit many physiological and behavioral abnormalities before and after surgery-mediated weight loss. Accumulating evidence highlights the impact of the intestinal microbiota on these traits, suggesting a role for this complex microbial community in weight loss and maintenance of weight loss in bariatric surgery patients. Specifically, we will discuss the role of obesity, nutrition, eating disorders, exercise, mood and affect, hormones, and bile acids on the human gut microbiota.

Obesity

The intestinal microbiota plays an important role in weight regulation in both humans and animals, and consistent evidence implicates this enteric microbial community in obesity—

though the degree of that contribution is controversial. Early work reported differences in weight were associated with compositional alterations in the intestinal microbiota, with the enteric microbiota in genetically obese (*ob/ob*) mice having a 50% reduction in abundance of the Bacteroidetes phylum and a similar increase in Firmicutes phylum (Ley *et al.*, 2005). Similarly, studies of humans revealed that the intestinal microbiota in obese people has relatively fewer Bacteroidetes and more Firmicutes than lean controls (Ley, Turnbaugh, et al., 2006), but following a one-year low-calorie diet (either low-fat or low-carbohydrate) raised the relative level of Bacteroidetes and lowered the relative level of Firmicutes in the obese group. Subsequent research both confirmed (Armougom, Henry, Vialettes, Raccach, & Raoult, 2009; Turnbaugh *et al.*, 2009; Zuo *et al.*, 2011) and refuted (Collado, Isolauri, Laitinen, & Salminen, 2008; Fernandes, Su, Rahat-Rozenbloom, Wolever, & Comelli, 2014; Mai, McCrory, Sinha, & Glei, 2009; Schwartz *et al.*, 2010) the association between obesity and an increase in Firmicutes and decrease in Bacteroidetes phyla.

Subsequently, studies moved from observational to experimental, introducing mouse:mouse, human:mouse, and human:human fecal transplants, and showed that the intestinal microbiota in *ob/ob* mice is more effective at extracting calories from food than that of lean mice—a trait that can be passed to germ-free (GF) mice via microbial transplant and cause increased adiposity (Turnbaugh *et al.*, 2006). Transferring fecal samples from obese adult females into GF mice has also shown that increased body fat, fat mass, and obesity-associated metabolic phenotypes can be transferred via the intestinal microbiota. Cohousing mice harboring an obese twin's microbiota (Ob) with mice containing the lean co-twin's microbiota (Ln) prevented the development of increased body mass and obesity-associated metabolic phenotypes in Ob cage-mates (Ridaura *et al.*, 2013). In humans, metabolic improvements have also been demonstrated via microbial transfer, as transplanting stool samples from healthy male donors (BMI <23) to obese males with metabolic syndrome improved insulin sensitivity after six weeks when compared to those randomized to receive transplants created from their own stool samples (Vrieze *et al.*, 2012).

Nutrition

Gastric bypass surgery significantly reduces the amount of nutrients consumed by a patient and can contribute to nutrient malabsorption. Nutrients consumed by a host are considered one of the major external modulators of the human intestinal microbiota. Thus, it is likely that the intestinal microbiota is altered by this surgical procedure. As gastric bypass surgery directly affects the availability of dietary components in the intestine, the enteric microbiota are potentially pivotal in mediating nutrient metabolism in this population and thus affect weight maintenance.

Long-term dietary patterns have a profound influence on the composition and diversity of the intestinal microbiota (De Filippo *et al.*, 2010; Muegge *et al.*, 2011; Walker *et al.*, 2011; Wu *et al.*, 2011). In children, significant differences in the composition of the intestinal microbiota were reported in different geographical regions (Italy versus Burkina Faso). It was concluded that differences were a result of regional (Western versus African) approaches to nutrition (De Filippo *et al.*, 2010). Subsequently, it was revealed that the intestinal microbiota in adults clustered into two primary dietary enterotypes (Wu *et al.*,

2011), which were distinguished by greater abundance of the genera *Prevotella* and *Bacteroides*, respectively. The *Prevotella* enterotype was associated with a carbohydrate-based diet, high in both complex carbohydrates and simple sugars, while the *Bacteroides* enterotype was associated with a more typical “Western diet” high in animal protein and saturated fat. Recently, it was reported that short-term dietary changes can also bring about rapid shifts in the composition of the intestinal microbiota, often evident within days (Fava *et al.*, 2013). Specifically, low-fat, high-carbohydrate diets and high-carbohydrate, low-glycemic index diets differentially affected the abundances of specific genera within the intestinal microbiota. Moreover, short-term diet effects of a plant-based diet (high in grains, legumes, fruits, and vegetables) versus an animal-based diet (high in meat, egg, and cheese) demonstrated rapid changes in the intestinal microbiota, which are believed to reflect functional adaptation to the digestion of drastically different foods (David *et al.*, 2014). Overall, it is evident that nutrition significantly impacts the composition and diversity of the intestinal microbiota both in the short- and long-term. Given the association of enteric microbes with adiposity, profound nutrient-mediated changes to the intestinal microbiota via gastric bypass surgery may functionally impact weight loss.

Eating disorders

The lifetime prevalence of any eating disorder diagnosis in bariatric candidates has been estimated between 13 and 50% (see (Muhlhans, Horbach, & de Zwaan, 2009) for a review). Although the composition of the intestinal microbiota differs between obese and lean individuals, and obese (versus lean) individuals may extract more energy from a given diet, very little is known about the intestinal microbiota in individuals with eating disorders—and the scant research in this area has focused on anorexia nervosa (AN). A study using traditional microbial culturing techniques of a single stool sample from a patient with acute AN identified 11 completely new bacterial species in the phyla Firmicutes (n=7), Bacteroidetes (n=2), and Actinobacteria (n=2), suggesting distinct characteristics of the intestinal microbiota in AN, which truly represents a unique nutrient-impooverished state (Pfleiderer *et al.*, 2013). Further research is needed to investigate whether these new species are specifically associated with AN. In addition, a cross-sectional study analyzing the intestinal microbiota of 9 patients with AN found increased levels of the archaeon *Methanobrevibacter smithii*, which plays an important role in efficiency of microbial fermentation (and associated energy yield from one’s diet). This difference could reflect an adaptive response in those individuals with AN to a very low-calorie diet (Armougom *et al.*, 2009). Because this study analyzed a limited number of microbial groups, further studies are needed to more comprehensively characterize the composition of the intestinal microbiota in individuals with AN and any changes as they undergo therapeutic renourishment. Early mechanistic research in animal models also suggests that the intestinal microbiota plays a role in satiety via interaction with peptide signaling (Tennoune *et al.*, 2014), which may be sex-specific. Research into the role of the intestinal microbiota in the development, maintenance, and recovery from eating disorders is expected to increase in the coming years and expand beyond studies of patients with AN to include other disorders, such as bulimia nervosa and binge eating disorder.

Exercise

Exercise is a significant factor that can influence the success of bariatric surgery outcomes, particularly in maintaining weight loss. Study of the impact of exercise on the intestinal microbiota is still in its infancy, and the majority of the available studies are limited to animal (e.g., mouse and rat) models. Collectively, this growing body of literature suggests that exercise has a significant impact on the diversity of the intestinal microbiota and that these effects are particularly pronounced with respect to the Bacteroidetes and Firmicutes phyla (Choi *et al.*, 2013; Evans *et al.*, 2014; Lambert *et al.*, 2015; Petriz *et al.*, 2014). Given that a higher Firmicutes to Bacteroidetes ratio has been associated with higher BMI and obesity in both human and animal models (Geurts *et al.*, 2011; Turnbaugh *et al.*, 2009), it was thought that a reduction in this ratio would have a beneficial impact on health. However, the effect of exercise in reducing this ratio is unclear. In fact, several animal models have shown increases in Firmicutes and decreases in Bacteroidetes levels following exercise (Choi *et al.*, 2013; Lambert *et al.*, 2015; Petriz *et al.*, 2014), while others reported findings in the more expected direction (Evans *et al.*, 2014). The inconsistencies in results across these studies suggest that further research is necessary to more fully elucidate the complex relationship between obesity and the intestinal microbiota, and to identify the specific effects that exercise might have on moderating this relationship.

In an effort to explore the relationship between exercise and the intestinal microbiota in humans, one study compared 40 elite rugby athletes with two control groups: a high BMI group (BMI > 28) and a low BMI group (BMI ≤ 25) (Clarke *et al.*, 2014). Participants were asked to complete a food frequency questionnaire as well as a questionnaire assessing the participants' normal amount of physical activity. In comparison with both control groups, athletes demonstrated: a) significantly greater levels of creatine kinase (a marker of extreme exercise); b) significantly greater diversity of gut microbes (particularly compared with the high BMI group); and c) lower inflammatory and improved metabolic markers (e.g., higher proportions of Akkermansiaceae). Furthermore, both protein intake (which was highest in athletes) and creatine kinase markers were significantly positively correlated with the diversity of the intestinal microbiota, suggesting that both might drive the observed biodiversity of the gut. Importantly, athletes had higher levels of Bacteroidetes and lower levels of Firmicutes as compared with controls; however, study authors point to the positive association between exercise and butyrate levels (possibly from members of the Firmicutes phylum) as one explanation for this potentially advantageous finding.

Mood and Affect

Dysregulated affective states (i.e. increased stress and anxiety) are prevalent in patients prior to gastric bypass surgery, and existing literature suggests that negative affective states such as anxiety can negatively influence the maintenance of weight loss (Sheets *et al.*, 2015). A growing body of evidence indicates a strong connection between the intestinal microbiota and the brain (see (Forsythe, Bienenstock, & Kunze, 2014; Foster & McVey Neufeld, 2013), for reviews). Although studies of a direct association between intestinal microbiota and stress-like and/or depressive behaviors are still forthcoming and largely investigated in animal models (Foster & McVey Neufeld, 2013), the collective body of evidence suggests bidirectional communication between the microbiome and brain function both in times of

homeostasis and disease (Mayer, 2011). This communication seems to occur primarily through complex interactional effects in the hypothalamic-pituitary-adrenal (HPA) axis and structures in the central nervous system (CNS) that can affect cognition, mood, and emotion. For example, Sudo and colleagues (Sudo *et al.*, 2004) investigated the potential role of the intestinal microbiota in HPA axis function, a factor thought to be involved in depression. These investigators found that inducing stress (also implicated in the pathogenesis of depression and composition changes in the gut microbiome) in GF mice caused an exaggerated response in the HPA axis that was reversed by *Bifidobacterium infantis*, a predominant bacterium in the gut microbiome. Similarly, a series of studies by Lyte *et al.* (Lyte, Varcoe, & Bailey, 1998) have demonstrated that oral administration of *Campylobacter jejuni* (a bacterium commonly associated with gastroenteritis) caused behaviors suggestive of anxiety in mice. A more recent study found that diversifying the intestinal microbiota through alteration of the diet resulted in improvements in working memory and reduced anxiety-like behavior in mice (W. Li, Dowd, Scurlock, Acosta-Martinez, & Lyte, 2009). Although further studies are needed to elucidate the complex interactions between the intestinal microbiota and mood/behavior, the extant literature would suggest this field is particularly rich for exploration into the causes and potential treatment of mood disorders and cognition.

Intestinal Hormones

As gut hormone balance is significantly affected by gastric bypass surgery and intestinal bacteria are associated with hormone levels, it is possible that enteric microbes may influence hormonal balance and impact weight loss. There is now evidence to suggest that the effects of body weight changes on the intestinal microbiota may be at least partially mediated by hormonal changes. Studies to date have primarily targeted two important gastrointestinal hormones: ghrelin and leptin (Cani & Delzenne, 2009; Cani *et al.*, 2009; Queipo-Ortuno *et al.*, 2013; Ravussin *et al.*, 2012). Although the relationship between the intestinal microbiota and ghrelin is not yet fully understood, several studies suggest that prebiotics (non-digestible food substances that promote the growth of gut microbes) modulate the intestinal microbiota such that these compounds decrease circulating levels of ghrelin (see (Cani & Delzenne, 2009), for a review). One recent study found that even a single dose of the prebiotic inulin significantly decreased postprandial ghrelin (Tarini & Wolever, 2010), which stands in contradiction to the previous notion that persistent and prolonged changes in the intestinal microbiota would be necessary to establish an effect on endocrine function. Two recent studies have also highlighted the potential mediating role of circulating leptin concentrations in the relationship between body weight changes and changes in the intestinal microbiota (Queipo-Ortuno *et al.*, 2013; Ravussin *et al.*, 2012). The first study examined leptin levels and the intestinal microbiota in four groups of mice: diet-induced obese mice (weight reduced and ad libitum) and control mice (weight reduced and ad libitum). These authors found that circulating levels of serum leptin were positively correlated with an abundance of *Mucispirillum*, *Lactococcus*, and unclassified *Lachnospiraceae*, and that some of these bacterial populations (e.g., *Mucispirillum*) have been shown to interact with intestinal mucin, which helps certain bacterial populations thrive in the gut. Furthermore, results indicated that leptin concentrations were reduced by 80% in weight-reduced diet-induced obese mice (compared with baseline) and by only 12% in

weight-reduced control mice (Ravussin *et al.*, 2012). These findings are particularly compelling given that *Muscipirillum* was seen in higher proportions in obese mice. Thus, taken collectively, results suggest that leptin concentrations may affect composition of the intestinal microbiota by regulating mucin in the intestine, and that a decline in obese mice may be more impactful than a small decrease in control mice given the relative abundance of certain bacterial populations at baseline. The second study (Queipo-Ortuno *et al.*, 2013) reported similar results in a rat model, which revealed that rats who were food restricted demonstrated increases in certain gut bacteria (e.g., *Bacteroides*, *Clostridium*, *Prevotella*) and decreases in others (e.g., *Bifidobacterium*, *Lactobacillus*, Firmicutes), with respect to unrestricted eater groups. Furthermore, leptin was found to be negatively correlated with *Bacteroides*, *Clostridium*, *Prevotella* and positively correlated with *Bifidobacterium* and *Lactobacillus*. Thus, decreases in body weight (in food restricted rats) in combination with lower leptin levels could explain changes in intestinal microbiota. Further research is still needed to more comprehensively understand the role of leptin and ghrelin in weight-related changes in the intestinal microbiota; however, these preliminary studies point to a potential mediating role of these gut hormones.

Bile acids

As alterations in bile flow appear to be a major component of gastric bypass surgery, the impact this alteration has on the intestinal microbiota may potentially influence the long-term outcome of surgery. Bile acids (BA) are sterol compounds that are manufactured from cholesterol in the liver and secreted into the duodenum as the main component of bile. The abundance of certain members of the intestinal microbiota can be impacted by BA via direct and indirect antimicrobial effects (Islam *et al.*, 2011). Thus, BA exert a strong selection pressure on the intestinal microbiota and impact the composition of this complex microbial community. Specific enteric microbes can modify BA in the colon, generating secondary bile acids (Ridlon, Kang, & Hylemon, 2006). Conversion of BA to secondary BA is typically mediated by a 7 α -dehydroxylation reaction catalyzed by specific members of *Clostridium* and *Ruminococcus* species (Akao, Akao, Hattori, Namba, & Kobashi, 1987; Edenharder & Pflutzner, 1989; Edenharder, Pflutzner, & Hammann, 1989). In addition to BA shaping the intestinal microbiota, enteric microbes profoundly affect the production of BA. Specifically, mice with a normal intestinal microbiota have a significantly reduced BA pool size (~70%) when compared to GF mice. Interestingly, mice with a normal enteric microbiota have higher levels of BA than GF mice in the cecum (Sayin *et al.*, 2013). Thus, the composition of BA and the enteric microbiota are dependent on each other. The majority of studies have reported an increase in serum BA following RYGB (Sweeney, Fan, & Jordan, 2014). However, it is currently unknown whether intestinal microbiota impacts BA production, or vice versa, in RYGB and whether these factors influence adiposity and weight maintenance in patients post-surgery.

THE INTESTINAL MICROBIOTA AND BARIATRIC SURGERY

Given the established relationship between the intestinal microbiota and adiposity in humans and mice (Turnbaugh & Gordon, 2009), this complex microbial community is a novel factor that may contribute to the success of surgery-mediated weight loss. To address the role of

enteric microbes in this process, investigators have characterized the intestinal microbiota in humans who have undergone bariatric surgery and murine (mouse and rat) models of this procedure.

Human studies

The data related to characterization of the intestinal microbiota in patients who have undergone bariatric surgery is relatively limited. However, some notable studies have set the stage for future investigations of the impact of enteric microbes on surgically-mediated weight loss. The first study to apply molecular microbiology techniques to investigate the impact of bariatric surgery on the intestinal microbiota came from Zhang *et al.*, (Zhang *et al.*, 2009) who investigated the microbiotas in fecal samples obtained from 3 normal weight individuals, 3 morbidly obese individuals, and 3 individuals post-bariatric surgery. This group used high throughput sequencing (454 pyrosequencing on the Roche platform) of the 16S rRNA gene to characterize the diversity and composition of the microbiotas in all samples. The bariatric group had a mean BMI of the 40.7 pre-surgery with a mean weight loss of 40 kg. This study found that obesity and gastric bypass clearly affected the composition of the intestinal microbiota. When microbiota compositions were summarized on the taxonomic class level, the post-bariatric surgery group had increased *Gammaproteobacteria* and decreases in *Clostridia*. Additionally, Verrucomicrobia were abundant in obese and normal weight subjects but rarely found in post-surgery subjects. On the family taxonomic level, post-surgery subjects were enriched for Enterobacteriaceae, Fusobacteriaceae, and *Akkermansia*. Interestingly, using a targeted PCR approach, this study also investigated the abundances of all microbes from the domain Archaea and a specific member of Archaea (*Methanobacteriales*) in all groups. Higher numbers of Archaea were found in obese individuals compared to normal weight and post-surgery participants. The hydrogen-consuming methanogen group Methanobacteriales matched the abundance of total Archaea in all groups implying that this group was the dominant archaeon in all samples investigated. Ultimately, this study demonstrated that intestinal microbiotas (represented by fecal samples) were distinct between normal weight, obese, and post-surgery groups and identified microbial taxa that may be responsible for these differences. Although this study concluded that bariatric surgery alters the intestinal microbiota in a unique way, limitations included the low numbers of participants tested and the fact that pre-surgery samples were not available from the post-surgery participants. This study used obese subjects as a surrogate for pre-bariatric surgery samples, which although relevant, does not fully represent patients prior to this operative procedure.

A subsequent study characterized the intestinal microbiota of 13 lean controls and 30 obese individuals (7 with type 2 diabetes) at baseline and 3 and 6 months post-bariatric surgery (Furet *et al.*, 2010). This study used targeted PCR to assess the levels of 7 bacterial groups within the intestinal microbiota. The average BMIs of surgery participants were 47.6, 40.6, and 37.3 at baseline, 3 months post-surgery, and 6 months post-surgery, respectively. At baseline (pre-surgery) the *Bacteroides/Prevotella* group was significantly lower in the obese subjects compared to lean controls. Additionally, *Faecalibacterium prausnitzii* was significantly lower in obese individuals with diabetes compared to lean controls and obese individuals without diabetes. Following bariatric surgery, the *Bacteroides/Prevotella*

population increased to a level close to that seen in lean controls in all individual at 3 months, and remained stable at 6 months post-surgery. *Escherichia coli* levels were significantly elevated at 3 and 6 months post-surgery when compared to baseline samples and lean controls. As *E. coli* is a member of the Gammaproteobacteria class, this result is consistent with the observations of Zhang *et al.*, (Zhang *et al.*, 2009). Conversely, the levels of *Bifidobacterium* and *Lactobacillus/Leuconostoc/Pediococcus* significantly decreased in abundance 3 and 6 months post-surgery when compared to baseline. The levels of *F. prausnitzii* in obese individuals with diabetes increased in abundance 3 and 6 months post-surgery when compared to baseline samples from this subset of individuals. Moreover, *F. prausnitzii* was negatively correlated with serum concentrations of inflammatory markers (i.e., high-sensitivity C-reactive protein and interleukin-6). This observation is consistent with the anti-inflammatory role *F. prausnitzii* is believed to play in inflammatory bowel diseases (Hansen *et al.*, 2012; Sokol *et al.*, 2009) and mouse models of intestinal inflammation (Sokol *et al.*, 2008). The strength of this study lies in the large number of patients investigated; however, the molecular characterization relied on a targeted approach, investigating only 7 bacterial groups in an ecosystem that can contain anywhere between 500 to 1000 bacterial species.

To further investigate the host-microbe relationship in patients who completed bariatric surgery, the same research group collected white adipose tissue (WAT) from the same individuals recruited for the Furet *et al.* (Furet *et al.*, 2010) study and performed a deeper analysis of the microbiota of fecal samples using next generation high throughput sequencing (a platform that provides deeper sequence reads compared to traditional Sanger sequencing) of the 16S rRNA gene (Kong *et al.*, 2013). This extensive study compared host-gene expression in WAT with the composition and diversity of the intestinal microbiota to uncover host-microbe associations. The authors found 58 more bacterial genera were detected in samples post-surgery than baseline, the majority of which belonged to the *Proteobacteria* phylum. This increase in novel bacterial groups was paralleled by an increase in diversity of the microbiota. Before surgery, a limited number of WAT expressed genes correlated with bacterial groups (8 WAT genes and 28 bacterial groups), whereas a significantly larger number of WAT expressed genes correlated with bacterial groups (562 WAT genes and 102 bacterial groups) post-surgery. Additionally, the correlations between WAT genes expression and enteric bacterial groups were stronger post-surgery. The overall structures of the intestinal microbiotas from individuals pre-surgery were distinct to the microbiotas from the same patients 3 and 6 months post-surgery. Further analyses revealed that 21 bacterial taxa on the genus level could distinguish the intestinal microbiotas between individuals at baseline, 3 months post-surgery, and 6 months post-surgery. Seven of these genera were considered dominant members of the intestinal microbiota (increased post-surgery: *Bacteroides*, *Escherichia*, and *Alistipes*; decreased post-surgery: *Bifidobacterium*, *Blautia*, *Dorea*, and *Lactobacillus*). Consistent with previous reports, the *Escherichia* genus was more abundant post-surgery. Numerous correlations were found between WAT gene expression, and these dominant groups post-surgery were found to be independent of reduced calorie intake. Most up-regulated genes post-surgery belonged to the transforming growth factor- β signaling pathway, whereas most down-regulated genes post-surgery belonged to metabolic pathways such as 24-dehydrocholesterol reductase. The WAT genes

there were associated with enteric microbe abundance post-surgery related to transport and binding, signaling, enzymatic activity, and cell structural components. Although this study did not control for factors (other than WAT gene expression) associated with bariatric surgery, it provides a stepping-stone for future in-depth analyses to understand the links between the intestinal microbiota and WAT function.

To investigate the microbial gene content (metagenome) associated with surgery-mediated weight loss Graessler *et al.* (Graessler *et al.*, 2013) applied metagenomic sequencing to fecal samples from 6 patients before and 3 months after bariatric surgery. The 6 subjects had a BMI range from 40.9–52.1 at baseline, which dropped by 15–32% post-surgery. Postoperatively, the abundances of 22 species, 11 genera, and 1 phylum were significantly impacted by bariatric surgery. Consistent with previous studies, the Proteobacteria phylum increased in abundance post-surgery. In contrast to a previous report (Furet *et al.*, 2010), the levels of *Faecalibacterium* species decreased post-surgery. Interestingly, this study identified 9 bacterial species that were positively and negatively impacted by bariatric surgery independent of BMI. In addition to taxonomic characterization, this study also yielded data provided the ability to perform functional genomic analysis. Carbohydrate analysis of the abundance of Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologues (KOs) revealed thirteen KOs assigned to phosphotransferase system were significantly increased post-surgery. This finding lead to the speculation that reduced dietary intake may trigger an increased ability to assimilate substrate in order to compensate for host nutritional energetic requirements. Altogether, this study demonstrated the taxonomic and functional genomic consequences of bariatric surgery on the intestinal microbiota.

Murine models of bariatric surgery

Given the numerous factors that could potentially influence surgery-mediated weight loss and the limited amount of biological samples available from human patients, it not surprising that investigators have turned to murine models to study the mechanisms involved in this procedure. Initially, Li *et al.* (J. V. Li, Ashrafian, et al., 2011) used a parallel metagenomic and metabolic profiling strategy to explore the impact of gastric bypass surgery on the intestinal microbiota in non-obese Wistar rats. This controlled approach provided the opportunity to investigate the role of the intestinal microbiota and metabolism in bariatric surgery while eliminating the impact of a pre-existing metabolic dysfunction on these factors. Rats received a RYGB or sham procedure. In the RYGB procedure, the proximal jejunum was divided distal to the pylorus to create a biliopancreatic limb, then a side-to-side jejuno-jejunostomy between the biliopancreatic limb the ileum was constructed. The gastric pouch and the alimentary limb were then anastomosed end-to-side and the gastric remnant was closed. The sham surgery consisted of gastrotomy on the anterior wall of the stomach and a jejunotomy with subsequent closures. Gastric bypass surgery in this model resulted in weight loss and decreased food consumption, thus mimicking the outcome in human patients. Gastric bypass surgery significantly impacted the taxonomic composition of the intestinal microbiota, with an increase in Gammaproteobacteria, an alteration consistent with that of human patients post-surgery (Furet *et al.*, 2010; Graessler *et al.*, 2013; Kong *et al.*, 2013; Zhang *et al.*, 2009). Additionally, increased activity of oligosaccharide fermentation, biogenesis of p-cresol, and the generation of amines were detected post-

surgery. In a parallel study (J. V. Li, Reshat, et al., 2011) the same group demonstrated that the resulting shift in the composition of the intestinal microbiota post gastric bypass surgery in rats correlated with increased cytotoxic environment in the gut. Specifically, urinary phenylacetyl glycine and indoxyl sulfate and fecal gamma-aminobutyric acid, putrescine, tyramine, and uracil were found to be inversely correlated with the survival of rodent cells. This additional study highlighted the potential for long-term cancer risk in gastric bypass surgery patients.

A more recent mouse model of RYGB sought to further delineate host-microbe interactions following surgery (Liou *et al.*, 2013). The experimental approach included RYGB, sham surgery, and sham surgery coupled to caloric restriction groups. Previous human and rat studies reported descriptive changes in the intestinal microbiota that correlated with changes in intestinal metabolite profiles. However, these studies did not demonstrate that the altered composition of the intestinal microbiota post-surgery had a functional impact on adiposity and metabolic outcomes. In this mouse model of RYGB, a significant increase in Gammaproteobacteria and Verrucomicrobia post-surgery paralleled weight loss, which is consistent with previous findings in humans and rats. Additionally, the impact of surgery on the intestinal microbiota was consistent irrespective of a normal or high fat diet, suggesting that this procedure can overwhelm the established dietary influence on this complex microbial community. Moreover, when intestinal microbiotas were transplanted from all experimental mouse groups into GF mice, RYGB mice significantly decreased in body weight compared to the sham surgery controls. This finding demonstrates that the composition of the intestinal microbiota that results from bariatric surgery has a functional impact on adiposity and is potentially a contributor to surgery-mediated weight loss. Furthermore, this study highlights the potential mechanistic role of the intestinal microbiota in gastric bypass-mediated weight loss. These human and animal studies consistently report an increase in the *Proteobacteria* phylum following bariatric surgery. This is likely due to the microbes within this phylum adapting to the drastic changes in the environment (e.g., increases in pH and oxygen tension). However, it is important to note that increases in this bacterial taxonomic group have also been identified in inflammatory bowel diseases (Sartor, 2008) and animal models of intestinal inflammation (Maharshak *et al.*, 2013). Additionally, given the finding that RYGB in rats results in increased cytotoxicity in the lumen of the gut, it is currently unknown whether changes in the intestinal microbiota provide a long term advantage to the host irrespective of the clear beneficial impact this surgery-influenced microbial community has on adiposity. Moreover, it has yet to be determined whether an altered intestinal microbiota following bariatric surgery has a functional consequence on adiposity.

CONCLUSIONS

In this review, we addressed the potential contribution of the intestinal microbiota to surgery-mediated weight loss. The most convincing evidence that this complex microbial community impacts surgery-mediated weight loss comes from a study that demonstrates that in a mouse model a bariatric surgery-altered intestinal microbiota has a reduced ability to accumulate fat and potentially a reduced capacity for energy harvest from nutrients from the gut. It yet remains to be determined whether human intestinal microbiotas from patients

post-gastric bypass surgery have the same impact on adiposity in GF mice. Additionally, the molecular mechanisms in which post gastric bypass surgery enteric microbiotas contribute to adiposity have yet to be delineated and whether they share a common pathway with obesogenic gut microbial communities.

The characterization of the intestinal microbiota in patients pre- and post-surgery raises many questions. For example, can the pre-surgical composition of the intestinal microbiota predict whether an individual is likely to lose a substantial amount of weight? Additionally, can the composition of the intestinal microbiota in a candidate pre- or post-surgery predict whether they are likely to maintain their post-surgical weight loss? The future challenge is to identify which commensal bacteria within this complex community can positively or negatively influence weight loss from this procedure. This endeavor is particularly important given that substantial numbers of patients experience weight recidivism after surgery (Karmali et al., 2013), thus novel approaches are needed to increase the efficacy of this procedure, particularly with respect to maintenance of weight loss. As the intestinal microbiota likely contributes to the mechanism of surgery-mediated weight loss, enteric microbes pose a novel and safe target to augment current therapies.

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