The importance of the gut microbiota after bariatric surgery

Judith Aron-Wisnewsky, Joel Doré and Karine Clement

Abstract | The gut microbiota is recognized to have an important role in energy storage and the subsequent development of obesity. To date, bariatric surgery (indicated for severe obesity) represents the only treatment that enables substantial and sustained weight loss. Bariatric surgery is also a good model to study not only the pathophysiology of obesity and its related diseases but also the mechanisms involved in their improvement after weight reduction. Scarce data from humans and animal models have demonstrated that gut microbiota composition is modified after Roux-en-Y gastric bypass (RYGB), suggesting that weight reduction could affect gut microbiota composition. However, weight loss might not be the only factor responsible for those modifications. Indeed, bariatric surgery not only improves hormonal and inflammatory status, but also induces numerous changes in the digestive tract that might account for the observed modifications of microbiota ecology. In future bariatric surgery studies in humans or mice, these major surgery-induced modifications will need to be taken into account when analyzing the link between gut microbiota composition, obesity, its complications and their improvement after bariatric surgery. This Review outlines the potential mechanisms by which the major changes in the digestive tract after bariatric surgery can affect the gut microbiota.

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Introduction

Bacteria colonize the gut soon after birth. Although the initial composition of the gut microbiota varies,[1,2] it becomes relatively stable after the age of 2 years and onward into adult life.[3] Understanding the composition and role of the gut microbiota was initially limited by an inability to cultivate most of the microorganisms colonizing the digestive tract. The field has progressed rapidly with the availability of new culture-independent tools, such as 16S rRNA gene sequencing.[4] Metabolomic and metagenomic sequencing enable even broader insights into the composition of the gut microbiota.[5–7] The various methodologies used to characterize the gut microbiota might give rise to some of the different results that have been reported in the literature. International studies, such as the Human Microbiome Project and the MetaHIT consortium are currently ongoing to improve understanding of the role of the microbiota in health and disease.[8] Of interest, a study in healthy individuals using analysis of 16S rRNA to determine gut microbiota composition suggests the existence of a core microbiome (that is, the presence of identical bacterial sequences in unrelated individuals).[9]

Obesity has become an epidemic worldwide (particularly in countries that have adopted a Western diet and sedentary mode of living[10]), resulting in an increased prevalence of associated disorders such as metabolic syndrome, type 2 diabetes mellitus and NASH.[11] The causes responsible for the development and progression of obesity are complex and involve diverse factors such as lifestyle habits, genetics, neural mechanisms and endocrine hormones. Interesting data from mouse models have suggested a new pathophysiological component, with the contribution of the gut microbiota not only in the development of obesity,[12–14] but also in its related complications.[15–17] These important discoveries in the past 8 years or so have led to a major expansion in the number of scientific studies investigating the role of dysbiosis (that is, imbalanced microbiota composition compared with healthy individuals) in the complex facets of obesity. Although convincing in mouse models, it remains difficult to conclude whether dysbiosis is the cause or consequence of obesity in humans, particularly given that major environmental confounding factors, including dietary changes, are known to have a role both in the modulation of the microbiota[18,19] and the development of obesity.[20]

Bariatric surgery has emerged as a research model to understand the pathophysiological mechanisms underlying both obesity and its associated complications. It is reserved for the treatment of the most severe forms of the disease (that is, BMI >40 kg/m² or BMI >35 kg/m² with comorbidities), and is more effective than dietary interventions[21] for the treatment of morbid obesity and associated cardiometabolic risks. As well as inducing marked and rapid weight loss and numerous hormonal modifications, bariatric surgery enables researchers to evaluate microbiota kinetic changes and to address the question of whether these changes in the microbiota after weight reduction contribute to the improvement

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of obesity-related diseases. The comparison of well-characterized patients undergoing different types of bariatric surgery could help decipher potential interactions with confounding factors.

This Review summarizes current knowledge on microbiota composition during obesity and after bariatric surgery. The potential mechanisms by which the major modifications in the digestive tract after bariatric surgery can affect the composition of the gut microbiota are discussed. Although current data are scarce, there is no doubt that more studies will be forthcoming.

Key points

- Obesity is associated with dysbiosis of the gut microbiota, in particular with decreased bacterial diversity
- Bariatric surgery represents a successful treatment option for severe obesity, and is also a good model to study the mechanisms involved in weight reduction and obesity-related disease improvement
- Bariatric surgery is associated with major modifications in microbiota composition and function; to date, however, only limited data are available concerning gut microbiota composition after bariatric surgery
- In particular, RYGB induces important changes in the digestive tract, namely gastric-pouch narrowing, decreased acid production and anatomical gut rearrangement, which might have an affect on the gut microbiota

Microbiota composition in health

The gastrointestinal tract harbours >10^{14} microorganisms, many of which have not been identified.[8] 90% of the mammalian gut microbiota belongs to two phyla: Bacteroidetes and Firmicutes.[22] Different species and quantities of bacteria are found at different points along the digestive tract according to major variations in the environmental niche (Figure 1)—the largest number of bacteria reside in the large intestine.[23] The high level of acid production in the stomach is deadly for most microbes; therefore, two acid-resistant microorganisms are predominant in this organ, *Lactobacillus* and *Streptococcus*.[24] Although the bile and pancreatic secretions produced within the duodenum and upper part of the jejunum are also very toxic to most microorganisms, the number of bacteria rises steadily up to 10^7 cells/ml in the distal ileum.[25] Finally, the large intestine harbours a complex and dense microbial community mainly made up of anaerobic species. In this section of the gastrointestinal tract, there is a close interaction between bile acids and the resident microbiota. Primary conjugated bile acids secreted by the liver and stored in the gallbladder enter the entero–hepatic cycle in the duodenum and circulate in the ileum. These bile acids undergo major modifications (that is, deconjugation)[26] mediated by enzymes catalyzed by specific anaerobes from the large bowel.[27] Importantly, these secondary free bile acids exert concentration-dependent antimicrobial activity. In particular, they have been observed to induce membrane damage, leading to the leakage of H^+, ions and other cellular components out of the cell, eventually leading to cell death.[28] Thus, the concentration and proportion of different secondary bile acids might directly affect the composition of the microbiota, or at least the overall number of bacteria.

Microbiota composition in obesity

The first pioneering experiments demonstrating a role for the microbiota in weight regulation originally came from mouse studies. In comparison to control mice, germ-free mice had reduced levels of adiposity despite increased food consumption. After colonization with cecal content from control mice, the germ-free mice rapidly gained weight, in particular fat mass, despite a decrease in food intake, suggesting an important role for the microbiota in the regulation of fat and energy storage.[12,19,29] Further studies manipulating the gut microbiota in mice illustrate two mechanisms by which the gut microbiota might

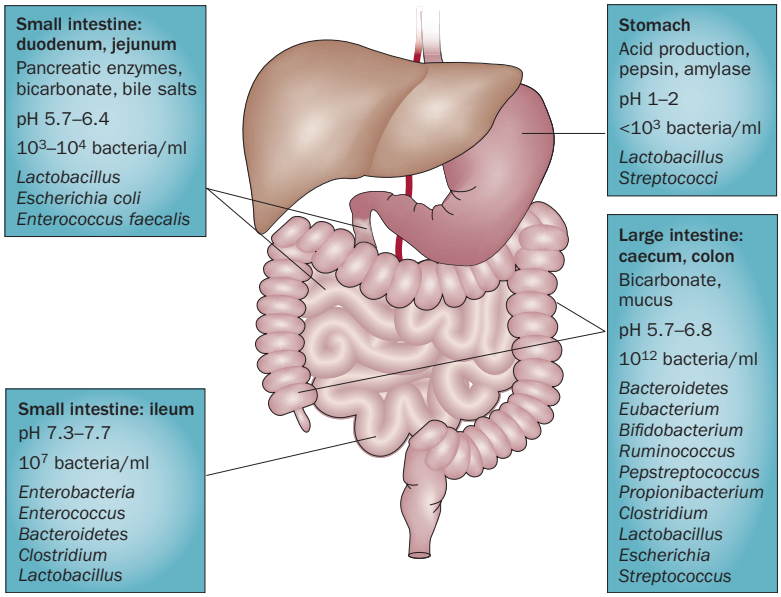

Figure 1 | Characteristics of the normal gastrointestinal tract. The various organs of the gastrointestinal tract differ according to digestive secretions and pH. Different species and quantities of bacteria are found at different points along the digestive tract according to these major variations in the environmental niche.

contribute to the development of obesity: first, via energy regulation and the capacity to process otherwise indigestible dietary polysaccharides,[29–31] leading to subsequent intestinal absorption of short-chain fatty acids;[32] second, via gene regulation promoting increased fat storage in adipose tissue.[12] Thus, the hypothesis is that the gut microbiota in obese animals is more efficient than that of lean individuals at extracting energy from dietary intake and subsequently promoting fat storage. Indeed, obese individuals have higher levels of short-chain fatty acids and reduced levels of residual calories from food in faeces than lean individuals.[32,33]

Various studies in mouse models[29,34] using 16S rRNA gene sequencing have demonstrated that obesity is associated with increased Firmicutes and decreased Bacteroidetes levels compared with lean counterparts, independent of food consumption (reviewed elsewhere[35]). This observation has been partially confirmed in human studies.[6,36,37] Indeed, comparing the microbiota composition of 12 obese individuals and three lean individuals revealed that those who were obese had significantly increased levels of Firmicutes ($P = 0.002$)

and decreased levels of Bacteroidetes ($P<0.001$) than their lean counterparts.[37] Although this study included a limited number of individuals, 18,348 bacterial 16S rRNA sequences were analyzed, giving the study sufficient statistical power. These results were confirmed in two larger cohorts of humans.[6,36] However, these data are controversial, as other well performed studies have found diverging results.[33,38,39] Indeed, Duncan *et al.*[39] failed to detect any difference in the proportion of Bacteroidetes in obese and nonobese individuals. These apparently conflicting results between the studies cannot derive either from different techniques (as they were validated with 16S rRNA inventory), nor by a lack of power (as the study by Duncan *et al.*[39] was a second study performed to confirm previous concordant results). Jumpertz *et al.*[40] also found no difference in the levels of the three dominant phyla (namely, Bacteroidetes, Firmicutes and Actinobacteria) between lean and obese individuals. The discrepancies observed between studies across the literature suggest that differences at the phylum level might not be universally true (reviewed elsewhere[41]). In any case, these studies have encouraged further analysis of the microbiota in pathological conditions in humans.

The human microbiome has been extensively studied in large-scale projects using metagenomic sequencing and uncovered interesting findings that might revise the conclusions of previous studies using 16S rRNA. Qin *et al.*[42] found that in a cohort of 124 individuals, 40% of the genes from each individual were shared with at least half of the individuals in the cohort, suggesting both the existence of large inter-individual variability in gut microbiota composition but also a 'core' microbiota shared by a large number of individuals. This finding has been confirmed in a large gut microbiome study including patients of three different nationalities.[43] Three clusters called 'enterotypes' have been identified, characterized by higher relative abundance of *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2) or *Ruminococcus* (enterotype 3), respectively. These enterotypes do not seem to be driven by body weight but rather by food habits. Each enterotype is characterized by a network of dominant bacterial species that has specific abilities in deriving energy from specific types of nutrients. Another study with more detailed information on long-term food habits demonstrated that enterotype 1 is highly associated with long-term consumption of animal proteins and saturated fat, whereas enterotype 2 is associated with a carbohydrate-based diet.[44] Furthermore, this study highlighted that acute diet modifications can induce rapid changes in the gut microbiome, but not a complete switch from one enterotype to the other. The latter results suggest that food habits and/or short-term feeding constraints must be considered as key parameters linking BMI to gut microbiota composition. In that respect, well-designed longitudinal studies with precisely characterized diet interventions could be extremely useful and informative.

Finally, bacterial diversity might be of greater relevance than the ratio between different types of phyla or taxa; in a study by Yatsunenko *et al.*[45] bacterial diversity differed greatly in humans originating from different countries. Indeed, in populations with a high prevalence of severe obesity and obesity-related disease, the overall diversity and number of gut microbiota was decreased. Moreover, previous data from mice[19] and humans[6] demonstrated that obesity is associated with reduced bacterial diversity. Similarly, our team, in collaboration with the European network MetaHit, has found that decreased microbiota diversity in human obesity is strongly associated with metabolic complications (Cotillard *et al.*, unpublished data). Most importantly, major weight loss after bariatric surgery is associated with increased bacterial diversity (Cotillard *et al.,* unpublished data).

Bariatric surgery

The different weight-loss solutions to treat morbid obesity—that is, dietary or physical activity interventions or a combination of both—have proven disappointing in the long term[46,47] with regard to insufficient weight reduction[20] and inadequate reduction in obesity-associated complications.[48] Moreover, not only do pharmacological solutions display very modest results,[49] but to date, few molecules remain approved by the FDA owing to adverse secondary effects, such as valvular heart disease for benfluorex and fenfluramine[50,51] or pulmonary hypertension for treatment with anorexigens.[52] In this context, the demand for bariatric surgery (which is only indicated for severe forms of obesity), has increased—it is considered the only efficient means to achieve major and sustainable weight reduction.[53,54] Furthermore, it yields a decrease in all-cause mortality and improves many of the obesity-related diseases via various mechanisms (reviewed elsewhere[55]).

The different bariatric procedures fall into two categories (Figure 2): purely restrictive, including laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy; or both restrictive and malabsorptive, such as Roux-en-Y gastric bypass (RYGB). Only the most frequently performed procedures[56] are addressed here.

Surgery induces changes in both environmental and systemic factors, as well as anatomical changes in the digestive tract (Table 1), all of which might have an effect on the composition of the gut microbiota.[57] During most abdominal surgery, it is highly recommended that patients undergo perioperative antibiotic prophylaxis to prevent infection of the surgical site. Whatever the type of prophylaxis, an acute but probably transient effect on microbiota composition cannot be excluded, which might differ from one patient to another according to the antibiotic protocol.[58,59] After any type of bariatric surgery, patients are advised to increase mastication[60] for improved food tolerance and comfort.[61] This approach facilitates the initial steps of digestion by enhancing gastric motion, saliva production and parasympathetic activity.

LAGB reduces the size of the gastric pouch, resulting in reduced food intake and sometimes a somewhat different food texture preference to preserve digestive comfort.[62] Food transit time through the stomach also increases. Sleeve gastrectomy involves surgical resection

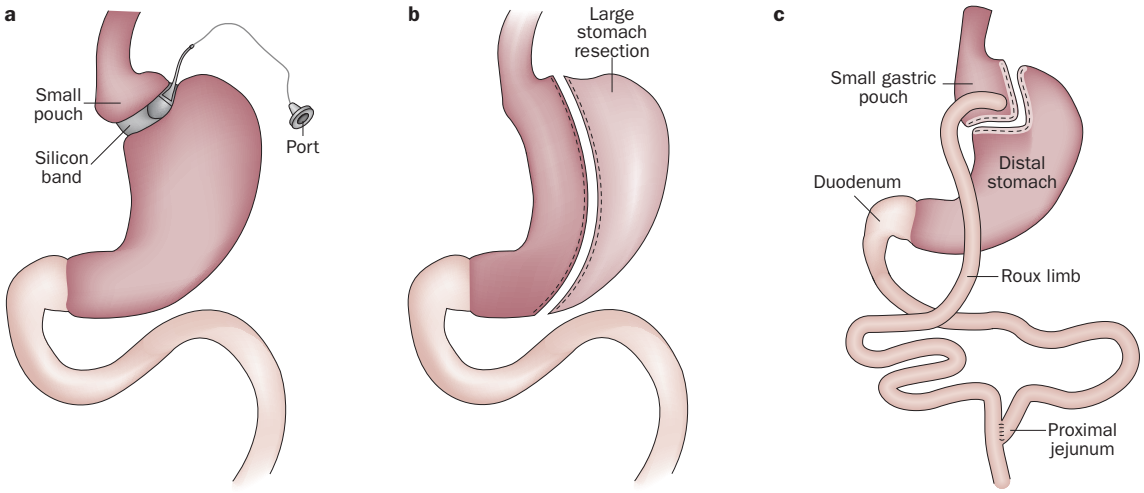

Figure 2 | The three main bariatric surgical interventions. **a** | Laparoscopic adjustable gastric banding. A small pouch is created in the upper part of the stomach. A silicon band is connected to a port placed in a subcutaneous position to enable adjustment of the band. **b** | Sleeve gastrectomy. A large stomach resection is carried out to create a tube of about 60 ml, leaving the pyloric sphincter intact. This surgery is irreversible. **c** | Roux-en-Y gastric bypass. This surgery creates a small gastric pouch (~30 ml) directly linked to the distal jejunum by the Roux limb. The distal stomach, duodenum and proximal part of the jejunum is subsequently anastomosed 1.5 m below the gastrojejunal anastomosis.

of the fundal part of the stomach, resulting in both a reduced gastric pouch and a marked reduction in acid production. Modification of gut hormone secretions after surgery has also been demonstrated, such as a reduction in the levels of the orexigenic hormone, ghrelin, and increased levels of incretins, such as glucagon-like peptide-1 (GLP1) and peptide YY (PYY).[57,63,64] RYGB induces decreased acid production and a faster transit time of food through the stomach.[65] Variations of the gastric bypass procedure exist. However, these surgeries do share some common modifications of the digestive tract and anatomical rearrangement, including: bile flow alteration; restriction of stomach size; altered flow of nutrients; vagal manipulation; and modulation of enteric and adipose hormones.[66–68] These changes are referred to in the literature as the Brave effect.[69–71]

Along with digestive tract modifications, the observed changes related to inflammation and the immune system could also affect microbiota composition. Importantly, weight loss and fat-mass reduction[72] induced by bariatric surgery are associated with decreased low-grade systemic inflammation[73] and modified adipose tissue inflammation. After surgery macrophage accumulation in adipose tissue decreases and inflammatory cells might switch their phenotype toward a less inflammatory profile.[74,75] For example, substantial weight loss after surgery leads to a major decrease in two subsets of circulating monocytes, namely $CD14^{dim}CD16^{+}$ and $CD14^{+}CD16^{+}$.[76] Finally, although this field is currently being explored further, a number of modifications in food choice have already been demonstrated after bariatric surgery. In particular, both in rat models and in humans, RYGB leads to a reduction in fat intake.[77,78]

Microbiota composition after bariatric surgery

To date, limited data are available concerning the changes in microbiota composition after bariatric surgery; two main studies (with very different methodologies) have been performed in humans. Zhang *et al.*[79] used a large scale pyrosequencing method but on a very small subset of patients (three in each group of normal weight, morbidly obese and post-RYGB). Patients in the post-RYGB

Table 1 | Dietary and digestive changes induced by different types of bariatric surgery

Changes	LAGB	Sleeve gastrectomy	RYGB
Time spent masticating	Increased	Increased	Increased
Levels of food intake	Decreased	Decreased	Decreased
Food transit time	Decelerated	No change	Accelerated
Food choices and preferences	Preference for puréed food and fewer fibre-containing foods	No change	Reduced preference for high-fat or high-sugar foods
Acid production	No change	Decreased	Decreased
Enterohepatic cycle	No change	No change	Disrupted
Grehlin levels	No change	Decreased	No change
GLP1 and PYY levels	No change	No change	Increased

Abbreviations: GLP1, glucagon-like peptide-1; LAGB, laparoscopic adjustable gastric band; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass.

group were not investigated at the same time points, and no presurgical data were available for these patients. Although Furet *et al.*[80] used a real-time quantitative PCR technique, this study investigated microbiota changes before, 3 months and 6 months after RYGB, on a precisely phenotyped cohort of 30 obese patients (for whom clinical data as well as dietary questionnaires were available) and compared the results with 12 lean individuals as controls. These two studies have given the first insights into changes in the microbiota after surgery.

Zhang *et al.*[79] found that Firmicutes were dominant in normal weight and obese individuals but were markedly reduced in post-RYGB patients. Most importantly, microbiota functional differences were observed in obese versus normal weight or postsurgery individuals. Indeed, hydrogen (H_2)-producing bacterial groups (such as *Prevotellaceae*) as well as H_2-using methanogenic Archea (which are both involved in energy extraction from indigestible polysaccharides) were present only in the obese individuals. No such bacteria were observed in lean individuals or those after surgery. Furthermore, levels of Gammaproteobacteria increased markedly after surgery. However, to date it is impossible to conclude whether these modifications are the cause or consequence of weight loss.

Interestingly, Furet *et al.*[80] found that the *Bacteroides*:*Prevotella* ratio was lower in obese than in control individuals and increased within 3 months after surgery to remain stable thereafter. Importantly, this ratio negatively correlated with corpulence traits (namely body weight, BMI, body fat mass and serum leptin concentrations), but the correlation was highly dependent on calorie intake. By contrast, in patients with obesity, increased levels of *Faecalibacterium prausnitzii* were directly associated with a reduction in the low-grade inflammation state independent of calorie intake; levels of *F. prausnitzii* were low in obese patients with type 2 diabetes at baseline and increased after surgery, highlighting the fact that microbiota changes after surgery could depend on presurgical characteristics (particularly metabolic traits).

In both studies, one cannot decipher whether bacterial modifications are due to changes in food ingestion and digestion, to specific surgical procedure modifications or to metabolic improvements. There is a need to address the specific role of either energy restriction or surgery-induced modification on gut microbiota changes after bariatric surgery. For that purpose, we are currently conducting a clinical trial with two groups of obese patients before and after either restrictive (LAGB) or restrictive and malabsorptive (RYGB) bariatric procedures (ClinicalTrials.gov Identifier NCT01454232).[81]

Animal models of bariatric surgery can also help to dissect some of these mechanisms. A study in a rat model used metagenomic analysis and metabolic profiling to explore the impact of RYGB on gut microbiota composition.[82] The researchers observed a major disruption in gut microbiota ecology with a 52-fold higher concentration of Proteobacteria and a decreased concentration of both Firmicutes and Bacteroidetes when comparing post-RYGB rats to sham-operated rats; notably, this last observation is different from previous results in humans (in whom an increase in Bacteroidetes was observed after surgery[80] and after diet-induced weight loss[37]). Functional studies in the same model have also been performed, using both pyrosequencing methods and faecal water cytotoxicity assessment. Faecal waters were found to be highly cytotoxic after surgery, mainly due to an increase in faecal metabolites such as putrescine and other monoamines (both of which derive from the microbial catabolism of digested nutrients).[83] This finding is consistent with the observed increase in levels of Gammaproteobacteria (particularly *Enterobacter*, which is responsible for the increased production of monoamines) following RYGB (in line with previous results[79]).

Bariatric surgery and changes in microbiota

pH

Evidence indicates that pH is modified after RYGB; both basal and peak-stimulated acid production in the small stomach pouch is virtually absent after RYGB[84] and pH increases markedly.[85] Furthermore, RYGB is effective in the treatment of obesity-associated GERD.[86,87] Although previous studies assessing bacterial activity indicated that pH <4 was deadly for most microorganisms, culture methods have since confirmed the presence of live bacterial species even at low pH[88] (that is, acid-resistant bacteria[89]). Interestingly, some studies have demonstrated that pH modification markedly affects genus and species relative proportions rather than the overall cell number. More specifically, the relative abundance of some species increases with a rise in pH.[88,90,91] By contrast, other *in vivo* studies demonstrated that pH >4 enabled bacterial overgrowth with a sustained and increased effect with time spent pH ≥4.[92,93] Interestingly, achlorhydria is associated with an increased number of Gram-positive bacteria. Clinical studies have also confirmed bacterial overgrowth in patients receiving acid inhibitory therapy,[91] and in the RYGB small pouch.[85] Finally, a study performed in patients undergoing RYGB revealed a reduction in the number of lactic acid bacteria after surgery.[80] Although the different techniques used in these studies to characterize the effect of pH on microbiota species or bacteria proportions might be responsible for some of the apparent discrepancies, these data confirm that RYGB-induced modifications of acid secretion and subsequent pH have an effect on microbiota ecology at least in the stomach but potentially also in the lower gastrointestinal tract. Indeed, pH modification in the colon also influences microbial community composition and short-chain fatty acid production and ratios (Figure 3).[94]

Entero–hepatic cycle diversion

Food transit time is accelerated after RYGB[65] and nutrients pass along the Roux limb while bile acids are secreted in the excluded digestive tract, thus creating asynergy between nutrients and flow of bile acids. RYGB also creates a blind intestinal segment, which is associated with bacterial overgrowth; some of these bacteria display deconjugation properties. To date, studies

linking microbiota composition and entero–hepatic cycle diversion after bariatric surgery have only been performed in animal models. In a rat model of RYGB, microorganisms able to produce secondary free bile acids were observed not only in the blind loop but also in the proximal intestine,[95] suggesting that RYGB induces transformation of primary bile acids higher up in the digestive tract after surgery compared to the normal digestive tract.[96] In line with this finding, a study in humans demonstrated that RYGB increases levels of systemic free bile acids,[97] whilst, by contrast, germ-free mice display increased levels of conjugated bile acids levels. Moreover, as described above, faecal water analysis in rats revealed increased cytotoxicity after RYGB,[83] further suggesting that bacterial overgrowth (including deconjugating bacteria) occurs in the blind loop. The effect of bile acid modification on the gut microbiota has been further investigated. In a rat model, the adjunction of free secondary bile acids to their food intake resulted in marked phylum alteration, with increased Firmicutes and decreased Bacteroidetes levels.[98] Finally, a study in humans observed that the concomitant increase in primary bile acids and decrease in secondary bile acids was associated with dysbiosis of the gut microbiota, specifically bacteria involved in bile-acid transformation. Although this study included patients with IBS, a very different disease to obesity, it highlights the link between bile-acid modification and microbiota composition. Overall, these data suggest that RYGB seems to be associated with an increase in both primary bile acids in the blind loop and secondary bile acids further down the gastrointestinal tract, which have antimicrobial properties.[28,99] This finding confirms that entero–hepatic diversion induces profound changes in microbiota ecology in the lower gastrointestinal tract after RYGB.

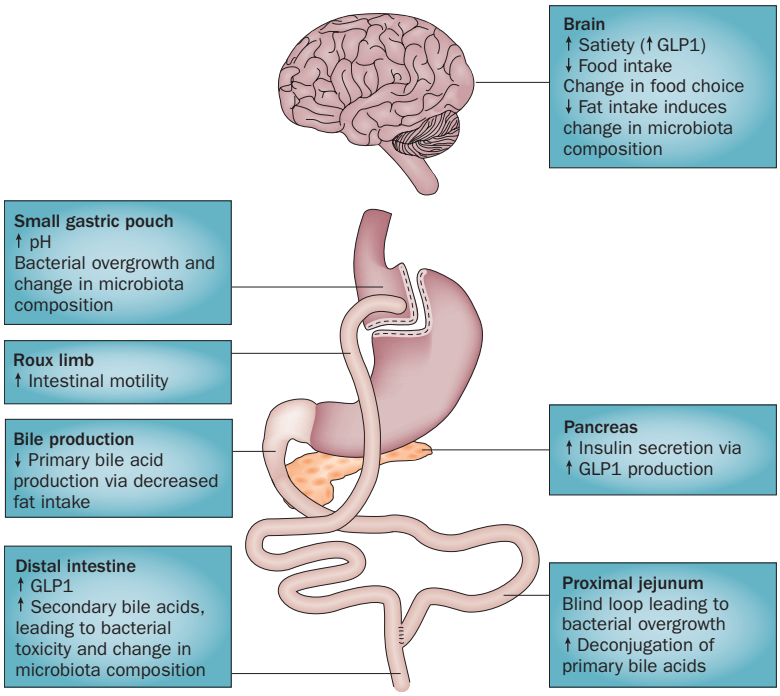

Figure 3 | Roux-en-Y gastric bypass induces various environmental, systemic and anatomical changes that might directly or indirectly affect the composition of the gut microbiota. Abbreviation: GLP1, glucagon-like peptide-1.

Antibiotic use

Bariatric surgery requires administration of antibiotic prophylaxis, the regimens of which differ according to each institution's practice.[58] Furthermore, infectious complications after surgery represent 11.5% of early hospital readmissions after RYGB, also requiring antibiotic therapy.[100] Studies in mouse models, controlling for potential confounding factors, have confirmed the major effect of antibiotics on the gut microbiota.[101] Indeed, antibiotics favour the growth of some taxonomic groups, but also decrease the overall diversity.[102] Interestingly, different antibiotics reduce the total number of bacteria in different parts of the digestive tract, thus possibly inducing regional intestinal microbiota dysbiosis.[103] Of note, each antibiotic induces reproducible and consistent microbiota modifications,[102] and the ability and time to recover baseline microbiota composition differ according to the antibiotic used (and occur long after its cessation—several weeks in most cases). Human studies using pyrosequencing methods have confirmed that antibiotics affect the relative abundance of 30% of dominant taxa.[104] Although some taxa recovered their baseline levels within the 4 weeks of the study, others did not.[104] Finally, a study in humans in which patients who received antibiotics were compared to individuals who did not revealed that the use of antibiotics induced an increase in levels of Bacteroidetes and a decrease in Firmicutes.[105] These observations confirm that antibiotics affect the whole microbiota in the short term, and potentially also the long term.[106]

Change in diet or change in weight

Bariatric surgery induces profound changes in dietary habits and decreases calorie intake.[73] RYGB is also responsible for taste modifications towards a reduced preference for high-fat or high-sugar containing foods.[78,107] Notably, numerous dietary interventions (either responsible for weight gain or reduction) have demonstrated a direct role of dietary habit on microbiota composition.[35,41] Indeed, an overall increase in dietary content is associated with a concomitant rapid increase in numbers of Firmicutes and decrease in Bacteroidetes in both lean and obese humans.[40] In both mice and humanized mouse models, the same pattern of changes was observed when subjected to a high-fat[18,108] or Western diet.[19,109] A study in weight-matched mice fed with a high-fat diet or conventional *ad libitum* diet demonstrated that it was the increase in the fat content, rather than weight modifications, that drove the increase in numbers of Firmicutes.[110] By contrast, and in line with a previous study in mice,[19] Ley *et al.*[37] observed that food restriction was associated with increased levels of Bacteroidetes and concomitant decreased levels of Firmicutes. Interestingly, other studies evaluating microbiota modifications after different types of dietary interventions have also found an

increase in Bacteroidetes levels.[21,111] Numerous shifts of other bacterial species are also observed, but these differ greatly across studies.[21,39,111,112] Overall, these results suggest that dietary content has an important influence on microbiota composition. This factor should be taken into account when analyzing the gut microbiota after bariatric surgery.

However, some researchers believe that weight modification—rather than changes in dietary content—drives microbiota changes. For example, in the mouse study performed by Ley *et al.*,[37] microbiota changes were mainly driven by weight modification rather than the nutrient content of the diet when two types of diet were compared (low-fat or low-carbohydrate). In addition, in human studies, postintervention shifts in gut microbiota were mainly observed in the individuals who successfully, and dramatically, responded to the weight-loss programme.[21,111] Studies in humans comparing RYGB or LAGB with comparable weight loss will help to distinguish the respective influence of weight reduction or dietary modifications. Preliminary investigations using both metagenomic and metatranscriptomic approaches have demonstrated that the microbiota is in fact highly responsive to dietary changes, not only on the level of microbiota composition but also on a transcriptional regulation level.[30,113] Overall, it seems that both surgery-induced food intake modifications and weight loss have an important role in microbiota composition after surgery.

Improvement of obesity-related diseases

Obesity-related metabolic diseases such as type 2 diabetes mellitus and NASH have also been found to improve after bariatric surgery.[114–116] Mouse studies have demonstrated a potential role of the gut microbiota in these improvements.[82,108,117–119] Indeed, modulation of the gut microbiota with prebiotics was associated with reduced fat mass development, improved glucose tolerance and increased levels of GLP1 in obese and diabetic mice.[117] Microbiota modification and its effects on bile acids is also important; secondary bile acids seem to decrease hepatic fatty acid uptake, thus potentially having an effect on hepatic triglyceride metabolism and leading to an improvement in NASH.[120] However, the hypothesis that bariatric surgery induces microbiota changes that can affect obesity-related diseases remains to be demonstrated in humans.

Enterohormones

RYGB leads to an increase in the level of GLP1,[68,121,122] which is known to signal satiety, reduce food intake, decrease stomach motility and increase β-cell insulin production.[123,124] As discussed above, these changes might have an effect on the gut microbiota. Although not yet proven, GLP1 might also exert some direct role on microbiota modulation; conversely, it cannot be excluded that microbiota signals might modulate PYY or GLP1.[125] Many other entero-hormones that could also affect gut microbiota composition are modified after bariatric surgery.[68,121]

Conclusion

A large body of evidence supports the role of the gut microbiota in the development of obesity and related diseases. Bariatric surgery leads to major and sustainable weight loss and the improvement of obesity-related comorbidities. Scarce data already suggest that the composition of the gut microbiota evolves after RYGB, but these observations remain to be confirmed in large cohorts and in the long term (particularly as some patients regain weight). As reviewed herein, bariatric surgery induces changes in the anatomy of the digestive tract, hormonal status, and quantity and choice of ingested nutrients, all of which might modify the microbiota composition. To date, scientists have not been able to decipher whether microbiota evolution is the cause or the consequence of weight loss and the improvement of obesity-related diseases (or whether the changes are more related to the specificities of the surgical procedure). Comparing the effects of different types of surgery will help to answer these questions. Finally, other issues still need to be tackled such as the potential association between the shift in microbiota composition after surgery and the changes in enterotypes. Large-scale studies using high-throughput pyrosequencing, and metabogenomic and metabolomic tools will enable further insight into the composition of the microbiota and its functional evolution after bariatric surgery.

Review criteria

This Review is based on an extensive literature search of PubMed. The PubMed search string contained the following terms: "gut microbiota" OR "microflora" OR "microbes" AND "obesity" OR "bariatric surgery" OR "bypass gastric" OR "sleeve" OR "digestive tract" AND "acidity" OR "pH" OR "bile acids" OR "entero-hepatic cycle" OR "gut hormones" OR "food choice" OR "diet". The search string was limited to "[Title/Abstract]" and language or publication date did not serve as a search criterion. All cited references were available in full-text.

1. Penders, J. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* **118**, 511–521 (2006).
2. Palmer, C., Bik, E. M., DiGiulio, D. B., Relman, D. A. & Brown, P. O. Development of the human infant intestinal microbiota. *PLoS Biol.* **5**, e177 (2007).
3. Marchesi, J. R. Human distal gut microbiome. *Environ. Microbiol*. **13**, 3088–3102 (2011).
4. Shendure, J. & Ji, H. Next-generation DNA sequencing. *Nat. Biotechnol*. **26**, 1135–1145 (2008).
5. DiBaise, J. K. *et al.* Gut microbiota and its possible relationship with obesity. *Mayo Clin. Proc.* **83**, 460–469 (2008).
6. Turnbaugh, P. J. *et al.* A core gut microbiome in obese and lean twins. *Nature* **457**, 480–484 (2009).
7. Clemente, J. C., Ursell, L. K., Parfrey, L. W. & Knight, R. The impact of the gut microbiota on human health: an integrative view. *Cell* **148**, 1258–1270 (2012).
8. Turnbaugh, P. J. *et al.* The human microbiome project. *Nature* **449**, 804–810 (2007).
9. Tap, J. *et al.* Towards the human intestinal microbiota phylogenetic core. *Environ. Microbiol*. **11**, 2574–2584 (2009).
10. Flegal, K. M., Carroll, M. D., Ogden, C. L. & Curtin, L. R. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* **303**, 235–241 (2010).
11. Kopelman, P. G. Obesity as a medical problem. *Nature* **404**, 635–643 (2000).
12. Backhed, F. *et al.* The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101**, 15718–15723 (2004).

13. Backhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A. & Gordon, J. I. Host-bacterial mutualism in the human intestine. *Science* **307**, 1915–1920 (2005).
14. Backhed, F., Manchester, J. K., Semenkovich, C. F. & Gordon, J. I. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl Acad. Sci. USA* **104**, 979–984 (2007).
15. Cani, P. D., Delzenne, N. M., Amar, J. & Burcelin, R. Role of gut microflora in the development of obesity and insulin resistance following high-fat diet feeding. *Pathol. Biol. (Paris)* **56**, 305–309 (2008).
16. Henao-Mejia, J. *et al.* Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* **482**, 179–185 (2012).
17. Serino, M. *et al.* Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. *Gut* **61**, 543–553 (2012).
18. Hildebrandt, M. A. *et al.* High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* **137**, 1716–1724 (2009).
19. Turnbaugh, P. J., Backhed, F., Fulton, L. & Gordon, J. I. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* **3**, 213–223 (2008).
20. Astrup, A., Dyerberg, J., Selleck, M. & Stender, S. Nutrition transition and its relationship to the development of obesity and related chronic diseases. *Obes. Rev.* **9** (Suppl. 1), 48–52 (2008).
21. Santacruz, A. *et al.* Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity (Silver Spring)* **17**, 1906–1915 (2009).
22. Tilg, H. & Kaser, A. Gut microbiome, obesity, and metabolic dysfunction. *J. Clin. Invest.* **121**, 2126–2132 (2011).
23. Prakash, S., Tomaro-Duchesneau, C., Saha, S. & Cantor, A. The gut microbiota and human health with an emphasis on the use of microencapsulated bacterial cells. *J. Biomed. Biotechnol.* 981214 (2011).
24. Dicksved, J. *et al.* Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. *J. Med. Microbiol.* **58** (Pt 4), 509–516 (2009).
25. Guarner, F. & Malagelada, J. R. Gut flora in health and disease. *Lancet* **361**, 512–519 (2003).
26. Midtvedt, T. Microbial bile acid transformation. *Am. J. Clin. Nutr.* **27**, 1341–1347 (1974).
27. Ridlon, J. M., Kang, D. J. & Hylemon, P. B. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **47**, 241–259 (2006).
28. Kurdi, P., Kawanishi, K., Mizutani, K. & Yokota, A. Mechanism of growth inhibition by free bile acids in lactobacilli and bifidobacteria. *J. Bacteriol.* **188**, 1979–1986 (2006).
29. Turnbaugh, P. J. *et al.* An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **444**, 1027–1031 (2006).
30. Sonnenburg, J. L. *et al.* Glycan foraging *in vivo* by an intestine-adapted bacterial symbiont. *Science* **307**, 1955–1959 (2005).
31. Gill, S. R. *et al.* Metagenomic analysis of the human distal gut microbiome. *Science* **312**, 1355–1359 (2006).
32. Topping, D. L. & Clifton, P. M. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiol. Rev.* **81**, 1031–1064 (2001).
33. Schwiertz, A. *et al.* Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)* **18**, 190–195 (2010).
34. Ley, R. E. *et al.* Obesity alters gut microbial ecology. *Proc. Natl Acad. Sci. USA* **102**, 11070–11075 (2005).
35. Clarke, S. *et al.* The gut microbiota and its relationship to diet and obesity: new insights. *Gut Microbes* **3** (2012).
36. Armougom, F., Henry, M., Vialettes, B., Raccah, D. & Raoult, D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. *PLoS ONE* **4**, e7125 (2009).
37. Ley, R. E., Turnbaugh, P. J., Klein, S. & Gordon, J. I. Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022–1023 (2006).
38. Duncan, S. H. *et al.* Human colonic microbiota associated with diet, obesity and weight loss. *Int. J. Obes. (Lond.)* **32**, 1720–1724 (2008).
39. Duncan, S. H. *et al.* Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl. Environ. Microbiol.* **73**, 1073–1078 (2007).
40. Jumpertz, R. *et al.* Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.* **94**, 58–65 (2011).
41. Harris, K., Kassis, A., Major, G. & Chou, C. J. Is the gut microbiota a new factor contributing to obesity and its metabolic disorders? *J. Obes.* 879151 (2012).
42. Qin, J. *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65 (2010).
43. Arumugam, M. *et al.* Enterotypes of the human gut microbiome. *Nature* **473**, 174–180 (2011).
44. Wu, G. D. *et al.* Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108 (2011).
45. Yatsunenko, T. *et al.* human gut microbiome viewed across age and geography. *Nature* **486**, 222–227 (2012).
46. Dyson, P. A. The therapeutics of lifestyle management on obesity. *Diabetes Obes. Metab.* **12**, 941–946 (2010).
47. Wing, R. R. & Phelan, S. Long-term weight loss maintenance. *Am. J. Clin. Nutr.* **82** (1 Suppl.), 222S–225S (2005).
48. Sjöström, L. *et al.* Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N. Engl. J. Med.* **351**, 2683–2693 (2004).
49. Ioannides-Demos, L. L., Piccenna, L. & McNeil, J. J. Pharmacotherapies for obesity: past, current, and future therapies. *J. Obes.* 179674 (2011).
50. Frachon, I. *et al.* Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS ONE* **5**, e10128 (2010).
51. Sachdev, M., Miller, W. C., Ryan, T. & Jollis, J. G. Effect of fenfluramine-derivative diet pills on cardiac valves: a meta-analysis of observational studies. *Am. Heart J.* **144**, 1065–1073 (2002).
52. Rich, S., Rubin, L., Walker, A. M., Schneeweiss, S. & Abenhaim, L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. *Chest* **117**, 870–874 (2000).
53. Sjostrom, L. *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* **307**, 56–65 (2012).
54. Buchwald, H. *et al.* Bariatric surgery: a systematic review and meta-analysis. *JAMA* **292**, 1724–1737 (2004).
55. Dixon, J. B., Straznicky, N. E., Lambert, E. A., Schlaich, M. P. & Lambert, G. W. Surgical approaches to the treatment of obesity. *Nat. Rev. Gastroenterol. Hepatol.* **8**, 429–437 (2011).
56. Buchwald, H., Consensus Conference Panel. Consensus conference statement bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. *Surg. Obes. Relat. Dis.* **1**, 371–381 (2005).
57. Sandoval, D. Bariatric surgeries: beyond restriction and malabsorption. *Int. J. Obes. (Lond.)* **35** (Suppl. 3), S45–S49 (2011).
58. Chopra, T., Zhao, J. J., Alangaden, G., Wood, M. H. & Kaye, K. S. Preventing surgical site infections after bariatric surgery: value of perioperative antibiotic regimens. *Expert Rev. Pharmacoecon. Outcomes Res.* **10**, 317–328 (2010).
59. No authors listed] ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. American Society of Health-System Pharmacists. *Am. J. Health Syst. Pharm.* **56**, 1839–1888 (1999).
60. Favretti, F., O'Brien, P. E. & Dixon, J. B. Patient management after LAP-BAND placement. *Am. J. Surg.* **184**, 38S–41S (2002).
61. Godlewski, A. E. *et al.* Effect of dental status on changes in mastication in patients with obesity following bariatric surgery. *PLoS ONE* **6**, e22324 (2011).
62. Brunault, P. *et al.* Observations regarding 'quality of life' and 'comfort with food' after bariatric surgery: comparison between laparoscopic adjustable gastric banding and sleeve gastrectomy. *Obes. Surg.* **21**, 1225–1231 (2011).
63. Peterli, R. *et al.* Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. *Obes. Surg.* **22**, 740–748 (2012).
64. Basso, N. *et al.* First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. *Surg. Endosc.* **25**, 3540–3550 (2011).
65. El Oufir, L. *et al.* Relations between transit time, fermentation products, and hydrogen consuming flora in healthy humans. *Gut* **38**, 870–877 (1996).
66. Laferrère, B. *et al.* Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **93**, 2479–2485 (2008).
67. Reed, M. A. *et al.* Roux-en-Y gastric bypass corrects hyperinsulinemia implications for the remission of type 2 diabetes. *J. Clin. Endocrinol. Metab.* **96**, 2525–2531 (2011).
68. Laferrère, B. *et al.* Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. *Diabetes Care* **30**, 1709–1716 (2007).
69. Beckman, L. M., Beckman, T. R. & Earthman, C. P. Changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass procedure: a review. *J. Am. Diet. Assoc.* **110**, 571–584 (2010).
70. Ashrafian, H. *et al.* Diabetes resolution and hyperinsulinaemia after metabolic Roux-en-Y gastric bypass. *Obes. Rev.* **12**, e257–272 (2011).
71. Ashrafian, H. *et al.* Metabolic surgery: an evolution through bariatric animal models. *Obes. Rev.* **11**, 907–920 (2010).
72. Ciangura, C. *et al.* Dynamics of change in total and regional body composition after gastric bypass in obese patients. *Obesity (Silver Spring)* **18**, 760–765 (2010).

73. Dalmas, E. *et al.* Variations in circulating inflammatory factors are related to changes in calorie and carbohydrate intakes early in the course of surgery-induced weight reduction. *Am. J. Clin. Nutr.* **94**, 450–458 (2011).
74. Aron-Wisnewsky, J. *et al.* Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss. *J. Clin. Endocrinol. Metab.* **94**, 4619–4623 (2009).
75. Cancello, R. *et al.* Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277–2286 (2005).
76. Poitou, C. *et al.* CD14dimCD16+ and CD14+CD16+ monocytes in obesity and during weight loss: relationships with fat mass and subclinical atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **31**, 2322–2330 (2011).
77. Shin, A. C., Zheng, H., Pistell, P. J. & Berthoud, H. R. Roux-en-Y gastric bypass surgery changes food reward in rats. *Int. J. Obes. (Lond.)* **35**, 642–651 (2011).
78. le Roux, C. W. *et al.* Gastric bypass reduces fat intake and preference. *Am. J. Physiol. Regul. Integr Comp. Physiol.* **301**, R1057–R1066 (2011).
79. Zhang, H. *et al.* Human gut microbiota in obesity and after gastric bypass. *Proc. Natl Acad. Sci. USA* **106**, 2365–2370 (2009).
80. Furet, J. P. *et al.* Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* **59**, 3049–3057 (2010).
81. US National Library of Medicine. Adaptation of Human Gut Microbiota to Energetic Restriction (microbaria). *ClinicalTrials.gov* [online], http://clinicaltrials.gov/ct2/show/NCT01454232 (2011).
82. Li, J. V. *et al.* Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut* **60**, 1214–1223 (2011).
83. Li, J. V. *et al.* Experimental bariatric surgery in rats generates a cytotoxic chemical environment in the gut contents. *Front. Microbiol.* **2**, 183 (2011).
84. Smith, C. D. *et al.* Gastric acid secretion and vitamin B12 absorption after vertical Roux-en-Y gastric bypass for morbid obesity. *Ann. Surg.* **218**, 91–96 (1993).
85. Ishida, R. K. *et al.* Microbial flora of the stomach after gastric bypass for morbid obesity. *Obes. Surg.* **17**, 752–758 (2007).
86. Prachand, V. N. & Alverdy, J. C. Gastroesophageal reflux disease and severe obesity: Fundoplication or bariatric surgery? *World J. Gastroenterol.* **16**, 3757–3761 (2010).
87. Frezza, E. E. *et al.* Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg. Endosc.* **16**, 1027–1031 (2002).
88. O'May, G. A., Reynolds, N. & Macfarlane, G. T. Effect of pH on an *in vitro* model of gastric microbiota in enteral nutrition patients. *Appl. Environ. Microbiol.* **71**, 4777–4783 (2005).
89. Giannella, R. A., Broitman, S. A. & Zamcheck, N. Gastric acid barrier to ingested microorganisms in man: studies *in vivo* and *in vitro*. *Gut* **13**, 251–256 (1972).
90. O'May, G. A., Reynolds, N., Smith, A. R., Kennedy, A. & Macfarlane, G. T. Effect of pH and antibiotics on microbial overgrowth in the stomachs and duodena of patients undergoing percutaneous endoscopic gastrostomy feeding. *J. Clin. Microbiol.* **43**, 3059–3065 (2005).
91. Williams, C. Occurrence and significance of gastric colonization during acid-inhibitory therapy. *Best Pract. Res. Clin. Gastroenterol.* **15**, 511–521 (2001).
92. Theisen, J. *et al.* Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. *J. Gastrointest. Surg.* **4**, 50–54 (2000).
93. Fried, M. *et al.* Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. *Gut* **35**, 23–26 (1994).
94. Walker, A. W. *et al.* pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. *Appl. Environ. Microbiol.* **71**, 3692–3700 (2005).
95. Midtvedt, T., Norman, A. & Nygaard, K. Bile acid transforming micro-organisms in rats with an intestinal blind segment. *Acta Pathol. Microbiol. Scand.* **77**, 162–166 (1969).
96. Swann, J. R. *et al.* Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc. Natl Acad. Sci. USA* **108** (Suppl. 1), 4523–4530 (2011).
97. Patti, M. E. *et al.* Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity (Silver Spring)* **17**, 1671–1677 (2009).
98. Islam, K. B. *et al.* Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology* **141**, 1773–1781 (2011).
99. Binder, H. J., Filburn, B. & Floch, M. Bile acid inhibition of intestinal anaerobic organisms. *Am. J. Clin. Nutr.* **28**, 119–125 (1975).
100. Dorman, R. B. *et al.* Risk for hospital readmission following bariatric surgery. *PLoS ONE* **7**, e32506 (2012).
101. Cotter, P. D., Stanton, C., Ross, R. P. & Hill, C. The impact of antibiotics on the gut microbiota as revealed by high throughput DNA sequencing. *Discov. Med.* **13**, 193–199 (2012).
102. Antonopoulos, D. A. *et al.* Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. *Infect. Immun.* **77**, 2367–2375 (2009).
103. Ubeda, C. *et al.* Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J. Clin. Invest.* **120**, 4332–4341 (2010).
104. Dethlefsen, L., Huse, S., Sogin, M. L. & Relman, D. A. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* **6**, e280 (2008).
105. Claesson, M. J. *et al.* Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proc. Natl Acad. Sci. USA* **108** (Suppl. 1), 4586–4591 (2011).
106. Dethlefsen, L. & Relman, D. A. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc. Natl Acad. Sci. USA* **108** (Suppl. 1), 4554–4561 (2011).
107. Miras, A. D. & le Roux, C. W. Bariatric surgery and taste: novel mechanisms of weight loss. *Curr. Opin. Gastroenterol.* **26**, 140–145 (2010).
108. Cani, P. D. *et al.* Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–1772 (2007).
109. Turnbaugh, P. J. *et al.* The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci. Transl. Med.* **1**, 6ra14 (2009).
110. Ravussin, Y. *et al.* Responses of gut microbiota to diet composition and weight loss in lean and obese mice. *Obesity (Silver Spring)* **20**, 738–747 (2012).
111. Nadal, I. *et al.* Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int. J. Obes. (Lond.)* **33**, 758–767 (2009).
112. Walker, A. W. *et al.* Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J.* **5**, 220–230 (2011).
113. Di Marzo, V., Bifulco, M. & De Petrocellis, L. The endocannabinoid system and its therapeutic exploitation. *Nat. Rev. Drug Discov.* **3**, 771–784 (2004).
114. Laferrère, B. Do we really know why diabetes remits after gastric bypass surgery? *Endocrine* **40**, 162–167 (2011).
115. Thaler, J. P. & Cummings, D. E. Minireview: Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology* **150**, 2518–2525 (2009).
116. Mathurin, P. *et al.* Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. *Gastroenterology* **137**, 532–540 (2009).
117. Everard, A. *et al.* Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* **60**, 2775–2786 (2011).
118. Shi, H. *et al.* TRL4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Invest.* **116**, 3015–3025 (2006).
119. Musso, G., Gambino, R. & Cassader, M. Obesity, diabetes and gut microbiota: the hygiene hypothesis expanded. *Diabetes Care* **33**, 2277–2284 (2010).
120. Nie, B. *et al.* Specific bile acids inhibit hepatic fatty acid uptake. *Hepatology* http://dx.doi.org/10.1002/hep.25797.
121. le Roux, C. W. *et al.* Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann. Surg.* **246**, 780–785 (2007).
122. le Roux, C. W. *et al.* Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann. Surg.* **243**, 108–114 (2006).
123. Asmar, M. New physiological effects of the incretin hormones GLP-1 and GIP. *Dan. Med. Bull.* **58**, B4248 (2011).
124. Vella, A. & Rizza, R. A. Extrapancreatic effects of GIP and GLP-1. *Horm. Metab. Res.* **36**, 830–836 (2004).
125. Flint, H. J. Obesity and the gut microbiota. *J. Clin. Gastroenterol.* **45** (Suppl.), S128–S132 (2011).

Author contributions

J. Aron-Wisnewsky contributed to the research, discussion of content and writing of this manuscript. J. Doré and K. Clement contributed to the discussion of content, writing and reviewing/editing the manuscript before submission.