HHS Public Access

Author manuscript

Best Pract Res Clin Gastroenterol. Author manuscript; available in PMC 2015 August 12.

Published in final edited form as:

Best Pract Res Clin Gastroenterol. 2014 August ; 28(4): 727–740. doi:10.1016/j.bpg.2014.07.016.

Metabolic surgery: action via hormonal milieu changes, changes in bile acids or gut microbiota? A summary of the literature

Timothy E. Sweeney, MD, PhD and **John M. Morton, MD, MPH***

Stanford University, Department of General Surgery, Section of Bariatric and Minimally Invasive (BMI) Surgery, 300 Pasteur Drive, H3680, Stanford CA 94025, USA

Abstract

Obesity and type 2 diabetes remain epidemic problems. Different bariatric surgical techniques causes weight loss and diabetes remission to varying degrees. The underlying mechanisms of the beneficial effects of bariatric surgery are complex, and include changes in diet and behavior, as well as changes in hormones, bile acid flow, and gut bacteria. We summarized the effects of multiple different bariatric procedures, and their resulting effects on several hormones (leptin, ghrelin, adiponectin, glucagon-like peptide 1 (GLP-1), peptide YY, and glucagon), bile acid changes in the gut and the serum, and resulting changes to the gut microbiome. As much as possible, we have tried to incorporate multiple studies to try to explain underlying mechanistic changes. What emerges from the data is a picture of clear differences between restrictive and metabolic procedures. The latter, in particular the roux-en-Y gastric bypass, induces large and distinctive changes in most measured fat and gut hormones, including early and sustained increase in GLP-1, possible through intestinal bile acid signaling. The changes in bile flow and the gut microbiome are causally inseparable so far, but new studies show that each contributes to the effects of weight loss and diabetes resolution.

Keywords

Bariatric surgery; RYGB; hormone; bile acid; microbiome

Introduction

Obesity and type 2 diabetes are a worldwide epidemic. Medical weight loss through proper diet and exercise are essential to good health, but some patients require bariatric surgery in addition. Bariatric surgery has proven to be safe and effective in inducing weight loss and improving or even curing type 2 diabetes. Although all bariatric surgery procedures end up changing the patient's diet, the alteration to patient anatomy and/or nutrient flow has effects that are independent of the restriction on diet.

Corresponding author. Morton@stanford.edu.

Conflict of interest statement: None

Weight loss surgery can generally be divided into three classes: restrictive, metabolic, or both. The restrictive procedures discussed here are: the adjustable gastric band (AGB), which simply encircles the cardia of the stomach with an inflatable silicone ring; and the sleeve gastrectomy (SG), in which most of the greater curvature of the stomach is removed. After these procedures, nutrients follow their pre-surgical course, but the patient is limited in the rate of food intake. There are many metabolic procedures, some of which also include a restrictive component. Here we review several procedures, as their similarities and differences in anatomical rearrangement and downstream effect can be compared to draw insight into the underlying physiology. The duodenal-jejunal bypass (DJB) involves separating the duodenum from the stomach outlet, and connecting a jejunal limb in its place.. This procedure has a restrictive component; nutrients bypass the duodenum, which as a result is exposed to undiluted bile, and the bile and nutrients mix in the jejunum. Similar is the biliary-pancreatic diversion (BPD), which involves a much longer intestinal bypass, wherein the alimentary limb is anastomosed to the ileum. The BPD also usually involves a gastrectomy of varying types. BPD can lead to severe nutrient deficiencies, and is falling out of favor as RYGB and SG become more common (1, 2). Finally, the roux-en-Y gastric bypass (RYGB) involves separating the stomach into a small upper pouch, which is anastomosed to a roux jejunal limb, while leaving the remnant stomach attached to the biliary limb, into which the bile still drains. It is thus both restrictive and metabolic. The RYGB has been proven to induce greater weight loss and resolution of diabetes than the restrictive procedures, with a good safety record (3). Each weight loss intervention has its pros and cons; their various differences also induce different changes in patient physiology, leading to direct effects on weight loss and diabetes resolution.

The last 10–15 years has seen a great increase in research in the hormone environments of the gut and the adipose tissue as they relate to weight loss. The stomach and intestine are now known to be crucial in the production of hormones such as ghrelin and glucagon-like peptide (GLP)-1. Further, adipose tissue is under homeostatic control by leptin and adiponectin. Weight loss procedures all have differing effects on these and other hormones;RYGB, in particular, is known to have an incretin effect, through both the ‘foregut’ mechanism, whereby bypass of the proximal small intestine leads to decreased anti-incretin effects, and the ‘hindgut’ mechanism, whereby direct flow nutrients to the distalsmall bowel cause a direct increase in incretin hormones. Disentangling the surgical changes from the changes induced by weight loss and diet are keys to understanding both the underlying physiology of obesity as well as the success of bariatric surgery.

Metabolic bariatric surgery has long been known to exert at least some of its effects through altered bile flow, including decreased absorption of fatty acids and increased bile production by the liver. Bile acids are now understood as signaling molecules in their own right; mechanistic studies of oral bile acid sequestrants have shown a significant incretin effect from altered bile flow (4). Mechanistic studies of bile flow after surgery are difficult, and only few have been accomplished. Still, new evidence points to a causal link between the altered bile flow in malabsorptive procedures and the subsequent incretin effect.

The alterations in diet and bile flow that accompany weight loss surgery lead to changes in the gut microbiome. The techniques that are now used to profile the gut microbiome are

relatively new, so mechanistic studies of bariatric surgery and changes in gut bacteria are only now beginning to come out (5). Studies of the microbiome after change in diet, weight loss, bariatric surgery, probiotics, and antibiotics have all given new insights into how changes in the gut bacteria lead to profound changes in host physiology.

Here, we report a review of the impact of known weight loss procedures on gut and adipose hormones, bile acids, and the gut microbiome. From the large body of research that has been amassed, we can begin to glean new insights into the mechanism of weight loss and diabetes resolution after weight loss surgery.

Methods

A review of the mechanisms of bariatric surgery and medical weight loss was undertaken. Pubmed was hand-searched for the following interventions: gastric band or gastric banding or AGB; sleeve gastrectomy or SG; duodenal bypass or duodenojejunal bypass or DJB; roux en Y gastric bypass or gastric bypass or RYGB; biliary pancreatic diversion or biliopancreatic diversion or BPD; and bile acid sequestrant or colestipol or cholestyramine or colesevelam. Each intervention was searched with the following terms: hormone; leptin; ghrelin; adiponectin; glucagon; GLP-1; peptide YY or PYY; or serum bile acid or bile acids; and microbiome or microbiota. Medical weight loss was searched with: medical weight loss or restrictive diet weight loss. As this review is intended to focus on bariatric surgical interventions, the medical weight loss review was not designed to be comprehensive.

This list generated several hundred articles. We excluded reviews or studies not done in humans, with the exception of some mechanistic studies of bile acid sequestrants and the gut microbiome, where human data are sparse. Studies that did not provide adequate statistical comparisons between groups (ie, studies that showed trends without tests) were not included. Also not included were studies that did not group patients according to a single intervention (ie, grouped several surgery types together). Trends that did not achieve statistical significance were listed as ‘no change’. For time-course measurements, achievement of a statistical difference at any time point was listed as a change (ie, measurements at 3,6, and 12 months that were significantly increased only at 12 months were listed as ‘increased’), unless there were significant changes in opposite directions during the time course. Due to the significant amount of literature present in this field, some studies may have been missed.

Results

Hormonal changes in weight loss and bariatric surgery

Energy homeostasis and fat metabolism in the body are heavily regulated by a complex network of hormones (6, 7). A relatively small subset of hormones has been thoroughly studied in the setting of bariatric surgery (leptin, ghrelin, adiponectin, glucagon-like peptide 1 (GLP-1), glucagon, and peptide YY (PYY)), and we will focus on this subset. This list is not comprehensive; however, each hormone included in this review has data available across most surgical interventions. Each hormone will be discussed in turn; Table 1 shows the literature findings of hormone changes across the various interventions.

Leptin is a hormone made in adipose tissue and increased by increased fat mass; its main function is to decrease hunger. When a person loses fat mass by any means, the level of circulating leptin falls, thereby triggering a hunger response at the hypothalamus. Thus, leptin normally acts to keep fat mass constant. Since all reviewed interventions lead to weight loss, it is perhaps not surprising that all have evidence of late decrease in leptin levels, perhaps in rough proportion to the amount of weight lost (i.e., leptin levels decrease less with AGB than RYGB, and total weight loss follows the same trend, (8)). Interestingly, AGB is the only procedure which has repeated measures of increases in leptin (which would thereby function to decrease hunger in such patients). Although 21 of 27 studies still report a decline in leptin in patients post-AGB (9–29), there are several papers which show either no change (30, 31), an immediate increase (32, 33), or a late increase (8, 34). Our literature review did not turn up any similar increases in leptin in other bariatric interventions. Why a small proportion of the literature would show an increase (as opposed to simply no change) in AGB is unclear, and an open question.

Ghrelin is a hormone that is a cleavage product of preproghrelin, along with obestatin (31). Ghrelin's best-known function is to stimulate hunger, somewhat opposite of leptin. Preproghrelin is made mainly in the stomach (31); thus it might be expected that removal of part of the stomach might decrease ghrelin, and indeed, we see such an effect with SG. A total of 14 out of 15 studies of ghrelin levels after SG show a significant decrease (35–49). In contrast, both medical weight loss and AGB show either no change or an increase in ghrelin, thereby stimulating hunger (8, 10, 11, 14, 16, 20–22, 26, 28, 46, 47, 50–58). Malabsorptive procedures all show mixed data, indicating that nutrient flow likely alters ghrelin production to some degree. BPD (44, 59) and DJB (36, 60) each show either a decrease in ghrelin or no change. Studies of ghrelin after RYGB exhibit the full range of responses: decreased, unchanged, and increased (8, 11, 21, 35, 37–39, 43, 49, 54, 56, 57, 61, 62). There can be considerable variation in ghrelin levels based on timing of blood draw with relation to surgery, operative technique, and remnant gastric pouch; these may partly explain the mixed nature of these results. These data suggest that ghrelin production is decreased at least in part by altered upper GI nutrient flow, though this mechanism may be indirect.

Adiponectin is a complex hormone that has a variety of actions. Briefly, although it is produced by adipose tissue, its circulating level has been found to negatively correlate to BMI (63). Adiponectin is involved in energy homeostasis and insulin sensitivity. A literature review shows that adiponectin is almost universally increased after bariatric surgery or medical weight loss (17, 19, 23, 29, 34, 41, 45, 47, 50, 55, 64–84). Moreover, no study showed an increase in adiponectin due to a given procedure not also possibly explained by weight loss. The only studies which did not show a change in adiponectin were one showing a decrease in adiponectin after medical weight loss (85) and a study of duodenal-jejunal bypass in which the surgical group did not show a significant change in fat mass or BMI (86). It thus seems most likely that adiponectin production is increased secondary to weight loss in all procedures, since it is increased by weight loss of any kind, including medical weight loss.

GLP-1 is a hormone that is made in the ileum. As an incretin, it is known to increase insulin production and decrease glucagon production. The GLP-1 analogues exenatide and liraglutide are used in the treatment of type 2 diabetes. Six studies have shown that GLP-1 is not increased after medical weight loss and may be decreased (54, 55, 71, 87–90). Only 1 of 10 studies in AGB showed an increase in GLP-1, and in that one study it was increased less than RYGB (30); the others showed no change (8, 21, 22, 56, 57, 68, 91–93). Every malabsorptive procedure exhibits an increase in GLP-1 (for a discussion of the impact of bile acids on GLP-1, see the section below). RYGB has been especially well-studied with 19 of 20 studies showing an increase in GLP-1 after RYGB (8, 21, 37–39, 42, 49, 50, 56, 57, 68, 71, 84, 87, 90, 91, 94–96), and only 1 study showing a decrease (92). The increase in GLP-1 has been shown to occur prior to weight loss, and may contribute to the early remission of diabetes (84). Interestingly, GLP-1 showed variable response to SG, with studies showing GLP-1 decrease (44), no change (90), an increase less than RYGB (37, 39, 49), or an overall increase (38, 40, 42, 48, 89, 94, 95, 97). The preponderance of the evidence suggests that SG increases GLP-1; since simple restriction in the setting of diet or AGB does not increase GLP-1, this seems to be specific to the removal of a portion of the stomach, though still could be a secondary effect. Overall, one clear contribution of altered anatomy in bariatric surgery is an incretin effect due to increased GLP-1.

The effects of bile acid on GLP-1 are important in the outcomes of bariatric surgery. Pharmacologic bile acid sequestration (via colestipol, cholestyramine, or colesevelam) has been shown to increase circulating GLP-1 levels and reduce hyperglycemia in both humans (98–100) and rodents (101–103). One study showed no change in incretins due to colesevelam, though there was still an improvement in oral, but not intravenous, glucose tolerance (104). The bile acid sequestrants all decrease serum bile acids (not surprisingly) (105–107), while the malabsorptive procedures increase them (see bile acids section and Table 2 below). The common mechanism of action, if one exists, is thus likely the alteration of bile flow in the intestine, but this has not been proved. One elegant study showed that enteric bile acids signal through the receptor TGR-5 in the intestine to increase GLP-1 production (108). Overall, these data show that altered bile acid flow in malabsorptive procedures is likely one reason for their resultant incretin effect. Still, Steinert et al. showed that increases in serum bile acid after RYGB lagged behind the increase in GLP-1 by several months (95); clearly, more work is needed to elucidate the exact mechanism.

Glucagon functions opposite insulin to increase circulating glucose via decreased uptake and increased glycogenolysis. Generally, glucagon levels are not well studied after bariatric surgery. The studies that have been done show somewhat conflicting results; there may be a trend towards increased glucagon production after malabsorptive procedures. Patients undergoing medical weight loss show decreased glucagon production (109–111). After AGB there is no change in glucagon production (68, 91, 93), and after SG there is evidence of both early increase (42, 94) and late decrease (44, 112). With the exception of one study showing no change (91), both BPD and RYGB show evidence of increased glucagon production (44, 68, 94, 110, 113). BPD and RYGB methods also tend to have the highest increases in insulin; it is possible that the increased glucagon observed after RYGB and BPD are compensatory increases for significantly lowered blood sugar in these cases.

Peptide YY is released by the ileum and colon and is known to inhibit gastric motility, reduce pancreatic exocrine secretion, and may reduce appetite directly through NPY receptors in the brain. It also may inhibit appetite through secondary effects of reduced GI motility. Studies have shown that PYY either decreases (58) or does not change after medical weight loss (52, 53, 55, 87). Both AGB and SG show a general trend towards increased PYY, with 18 studies reporting a range of decreased (44), unchanged (8, 41, 42, 56, 57), and increased (21, 28, 37–40, 49, 50, 92, 97, 114, 115) PYY after intervention. Interestingly, the malabsorptive procedures show a uniform increase in PYY (8, 21, 30, 37–39, 42, 44, 49, 56, 57, 87, 92, 96, 116). The mechanism of how PYY is increased is unclear, but may be related to early contact with nutrients or altered bile flow; bile acid sequestration shows mixed effects for PYY (decreased (117), no change (104), increased in rats (101)). The overall effect on PYY on weight loss and diabetes resolution is thus unclear, but appetite reduction due to increased PYY may contribute to the anti-obesity effects of malabsorptive procedures.

Bile acid changes in bariatric surgery

The normal enterohepatic circulation is that primary conjugated bile acids are secreted into the duodenum in response to fatty meals, where they mix with fatty acids. Some are dehydroxylated to secondary bile salts by lower GI bacteria. Most are reabsorbed in the ileum and flow back to the liver. The level of postprandial bile excretion is decreased in obese compared to lean patients (118); serum bile acids are higher in obesity, and decrease after medical weight loss (119–121). The studies done in AGB and SG are conflicting, showing serum bile acid levels that are increased (122), decreased (95, 123), and unchanged (41, 57) in response to restrictive procedures. No serum bile acid data could be found for DJB or BPD. In RYGB, 9 of 10 studies showed in increase in some fraction of serum bile acids (57, 96, 123–129); the other study showed an initial decrease prior to a late increase (95) (see Table 2 for references). Overall, the increased serum bile acids seen in RYGB are well-known, and the increase is believed to be due to the fact that excreted bile acids have less time to mix with food prior to transit through the ileum, leaving more bile acids free for ileal reuptake. See Table 2 for an overview of alterations in bile flow in bariatric surgery.

As discussed above, increased free ileal bile acids activate TGR-5, leading to increased GLP-1 production. A separate incretin effect from bile follows the bile->FXR->FGF-19->CYP7A1 pathway (130). Briefly, luminal bile acids bind the Farnesoid X Receptor (FXR) in the intestine, which activates fibroblast growth factor (FGF)-19; FGF-19 then activates CYP7A1 in the liver, which produces bile acid from cholesterol; it is thus a somewhat rare example of a feed-forward mechanism. FGF-19 is decreased in diabetes; after RYGB, it was shown that both FGF-19 expression and bile acid production increase to a greater degree in diabetic patients, possibly contributing to the increased bile acid levels and hence the incretin effect of RYGB (126, 131). On the other hand, some data suggest that FGF-19 is not increased by RYGB (128). Interestingly, FGF-19 was previously found to be decreased by bile acid sequestrants and increased by oral bile acid supplementation (132); this FGF-19 pathways is thus somewhat at odds with the finding of an incretin effect with bile acid sequestrants.

Increased bile acids have a complex relationship with gut microbiota. An increase in free bile acids may encourage overgrowth of bile-tolerant bacteria in phylum proteobacter (such as Bilophila wadsworthia); at the same time, a change in gut bacteria may change the degree to which bile acids are metabolized in the gut (133). Moreover, some evidence shows that the gut microbiota directly regulate the production of bile acids by conjugating bile acids to activate FXR->FGF signaling (134). Sorting out the cause and effect of change in bile acid flow and change in gut bacteria remains an active area of study.

Gut microbiota changes in bariatric surgery

The gut microbiome changes significantly after both medical weight loss and bariatric surgery (5). In particular, recent research has repeatedly shown persistent phyla-level differences in obesity, and after medical weight loss and RYGB. Generally, the Firmicutes:Bacteroides ratio is increased in obese individuals (135–138), and decreases after medical weight loss (135, 139, 140), though one study reported no significant difference between healthy and obese patients (141). A similar decrease in the Firmicutes:Bacteroides ratio is induced after RYGB (138, 142, 143). Moreover, several studies have now shown an increase in Proteobacteria after RYGB (142–145). Unfortunately, our comprehensive literature search found no studies of the microbiome in any of the other interventions discussed here.

The taxonomic changes observed after medical weight loss and after RYGB have in common a decreased Firmicutes:Bacteroides ratio; however, RYGB shows a persistent increase in Proteobacter that is not observed in medical weight loss. Moreover, David et al. showed that a change in diet to less carbohydrates and higher protein and fat produced a very fast (within a day) significant shift towards increased gut bile-tolerant phylum Proteobacter (133). One possibility is thus that RYGB patients ingest more animal products than their medical weight loss counterparts, and this induces a shift towards Proteobacteria. However, a more likely scenario is that the greater amount of free bile acids seen by the lower intestine after RYGB creates an environment more hospitable to bile-tolerant bacteria such as in phylum Proteobacter. Perhaps even more fascinating is that a recent study of the gut microbiome after oral vancomycin administration showed that the vancomycin selectively killed off Firmicutes bacteria, which lead to an overgrowth of Proteobacter; this in turn caused a decrease in secondary bile acids, leading to increased serum primary bile acid levels with a resulting incretin effect (146). Putting these data together, then, the increase in free primary bile acids in the lower intestine after RYGB has both a direct incretin effect through TGR-5 signalling, but also an indirect feedforward effect in serum bile acids caused by changes in the gut microbiome. These synergistic changes may be partly responsible for the magnified incretin effect seen after RYGB. As an aside, it should also be noted that a recent study linked increased Proteobacter to a higher incidence of gallstones; thus changes in the gut microbiome may also be linked to the increase in gallstones after RYGB (147). Finally, it has also been shown that administering oral lactobacillus post-RYGB leads to increased weight loss; there may thus be benefits to modulating gut microbiota to induce weight loss (148).

A mechanistic proposal of interplay between hormones, bile, and the microbiome

Taken together, the complex interplay between change in diet, bile flow alteration, hormonal change and altered gut microbiota cannot be easily understood. Still, some cause and effect relationships are clear, even if the exact mechanisms remain unknown. First, leptin is decreased and adiponectin is increased in rough proportion to weight loss, and they do not appear to change according to type of intervention. Second, SG is the only intervention which appears to show a sustained decrease in ghrelin, and this may be partly responsible for its greater weight loss success than AGB. Third, some of the anorectic effect seen in malabsorptive procedures may be due to increases in PYY. Fourth, GLP-1 is significantly increased in malabsorptive procedures, at least partially due to a direct effect from increased unbound luminal bile acids acting through intestinal TGR-5. Moreover, the incretin effect from GLP-1 can be reproduced in part by oral administration of bile acid sequestrants. Fifth, RYGB causes an increase in free bile acids in the lower intestine and increases in serum bile acids not seen with restrictive procedures or medical weight loss; this may contribute to its incretin effect through TGR-5 signalling to increase GLP-1 expression. Finally, RYGB induces an increase in Proteobacter in the gut microbiome not seen in medical weight loss, and this may induce a feedforward mechanism towards increasing serum bile acids and an incretin effect.

In each intervention discussed here, the diet is changed. Moreover, the diets between the different interventions may be changed in different ways; malabsorptive procedures, in particular, often create an aversion to dietary fats. The effects discussed above thus cannot be untangled, as of yet, from their possible dietary changes. Still, some elegant mechanistic studies of bile flow, gut bacteria and incretins have helped explain, at least in part, why malabsorptive procedures are so successful in reversing type 2 diabetes.

Weaknesses

This review has some weaknesses. First, the exact time courses of the changes in hormones with respect to the procedures are not reviewed here. Second, the choice of hormones reviewed is not comprehensive. The actions of other hormones, such as insulin, thyroid hormones, GIP, and FGF-19 were not reviewed. Third, medical weight loss was not reviewed systematically, and so our results may have bias. Finally, this study is not a formal meta-analysis; although we aimed to be comprehensive in our literature search, simple ‘vote-counting’ of studies should not take the place of a formal statistical meta-analysis; we hope that others will use this work as a starting point for more formal analyses.

Conclusions

Obesity and type 2 diabetes remain as epidemics. Modern bariatric surgery is safe, reliable, and effective for weight loss and reduction of insulin resistance. While both restrictive and malabsorptive procedures are effective for weight loss, RYGB in particular is known to induce greater weight loss with a higher cure rate of type 2 diabetes. The so-called BRAVE effects of RYGB (altered Bile flow due to exclusion of the biliary limb, Reduced gastric size in the RYGB , Anatomic gut rearrangement (as explained in the introduction), Vagal alterations secondary to the gut rearrangement, and Enteric hormone alterations as reviewed

here) have been known for some time, but only recently have mechanistic studies in bile flow and gut microbiota shed light on how RYGB causes such a significant incretin effect.

Still, more work is needed. Important questions include whether and how the gut microbiome might change in purely restrictive procedures, and to what degree this depends on diet. Also important to reconcile is the exact mechanism of action of bile acids in the incretin effect; although intestinal TGR-5 signaling may cause at least part of this effect, it doesn't explain why bile acid sequestrants and anatomic bile-rerouting both have an incretin effect through GLP-1. Regarding hormonal changes, enough studies have been done that a formal meta-analysis of hormonal changes after bariatric surgery, including time series, would be both feasible and beneficial. As the questions of timing of changes in diet, hormones, bile flow, gut bacteria, and weight loss become clear, causative models will be established, giving unparalleled insight into the physiology of obesity and weight loss.

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Practice Points

- Bariatric surgery is now recognized as having profound metabolic effects.
- Comparative effectiveness of bariatric surgery varies with gastric bypass providing the most effectiveness and gastric band the least effectiveness with corresponding metabolic changes
- Changes in the microbiome and their role in weight loss following bariatric surgery require more definition

Research Agenda

- The role of the microbiome, bile acid metabolism, and hormonal changes following bariatric surgery needs to be further defined.
- The impact of the microbiome upon weight loss should be determined to be associative or causative.
- The mechanism of bile acid metabolism upon weight changes requires further study.

Table 1

Review of studies on hormonal changes across different interventions. If one group of studies formed a majority, the number is listed, and their references are found in the cell at right.

	Leptin	Ghrelin	Adiponectin	GLP-1	Glucagon	PYY
Medical Weight Loss	Decrease (26, 47, 52, 58, 109), No Change (55)	No Change (46, 47, 54, 55), Increase (35, 52, 53, 58)	Decrease (85), No Change (55), Increase (47, 64, 67, 85)	Decrease (58), No Change (54, 55, 71, 87–90)	Decrease (109–111)	Decrease (58), No Change (52, 53, 55, 87)
AGB	Decrease (9–28), No Change (29,30), Immediate Increase (31,32), Late Increase (8,33,34)	Decrease (34) No Change (8, 14, 20, 21, 29, 56, 57), Transient Increase (16), Increase (11, 25, 27, 51), Late Increase (10)	Increase (17, 19, 22, 28, 33, 65, 68)	No Change (8, 20, 21, 56, 57, 68, 91–93), Increased Less Than RYGB (29)	No Change (68, 91, 93)	No Change (8, 56, 57) Decreased fasting level, Increased total production (27, 92, 114), Increased Less Than RYGB (20, 29)
SG	Decrease (40, 41, 43, 47, 49, 73, 75, 77)	Immediate Decrease (97) Decrease (35–38, 40, 41, 44–49), Late Decrease (42), No Change (43)	Increase (41, 45, 47, 73, 77)	Decrease (44), No Change (90) Increase Less Than RYGB (37, 39, 49), Increase (38, 40, 42, 48, 89, 94, 95, 97)	Late Decrease (44, 112), Early Increase (42, 94)	Early Decrease (44) No Change (41,42), Increase Less Than RYGB (37–40); Increase (97, 115)
RYGB	Decrease (8, 11, 20, 26, 29, 33, 43, 49, 72, 74, 77)	Decrease (37, 38, 42, 54, 56), No Change (8, 11, 20, 35, 43, 49, 57), Higher than SG (61), Increase (62, 74, 76)	Increase (29, 33, 45, 68–71, 74–79, 81–84)	Decrease (92), Increase (8, 20, 37–39, 42, 49, 50, 56, 57, 68, 71, 84, 87, 90, 91, 94–96)	No Change (91) Increase (68, 94, 110, 113)	Increase (20, 29, 37–39, 49, 56, 57, 87, 92, 96), Late Increase (8, 42)
BPD	Decrease (23, 72, 73)	Decrease (59), No Change (44)	Increase (73)	Early Increase (44)	Early Increase (44)	Increase (44)
DJB	Decrease (86)	Decrease (60) No Change (36)	No Change (86)	Increase (36, 61, 86, 116)	Decrease (86) Increase (61)	Increase (116)
Bile Acid Sequestrants	not studied	not studied	not studied	No Change (104), Increased in Humans (98–100), Increased in Rodents (101–103)	No Change (98–100)	Decreased (117), No Change (104), Increased in rats (101)

Table 2

Review of studies on bile acid changes across interventions.

	Serum Bile Acids
Medical Weight Loss (late)	Decreased postprandial in obesity (118) Higher in obesity, Decreased during weight loss (119–121)
AGB	Decreased (123), No Change (57), Increased in AGB+SG (122)
SG	Early Decrease (95); No Change (41); Increased in AGB + SG (122)
RYGB	Increase (57, 96, 123–129); Initial Decrease, late Increase (95)
BPD	Not studied
DJB	Not studied
Bile Acid Sequestrants	Decreased (105–107)

Table 3

Review of studies on gut microbiome changes across different interventions.

	Gut Microbiota
Obesity vs Normal	Firmicutes:Bacteroides ratio increased in obesity (135–138), No change in phyla (141)
Medical Weight Loss	F:B ratio decreased after weight loss (135, 139, 140) Diet profoundly changes microbiome (133)
AGB	Not Studied
SG	Not Studied
Post-RYGB	F:B ratio decreased (138, 142, 143); Administration of lactobacillus increases weight loss (148); Proteobacter increased (142–145)
BPD	Not Studied
DJB	Not Studied
Bile Acid Sequestrants	Not Studied