# Proceedings of the 2017 ASPEN Research Workshop— Gastric Bypass: Role of the Gut

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## Abstract

The goal of the NIH funded A.S.P.E.N. 2017 research workshop (RW) "Gastric Bypass: Role of the Gut", was to focus on the exciting research evaluating gut-derived signals in modulating outcomes post bariatric surgery. Though gastric bypass surgery has undoubted positive effects, the mechanistic basis of improved outcomes cannot be solely explained by caloric restriction.

Emerging data suggest that bile acid metabolic pathways, luminal contents, energy balance, gut mucosal integrity as well as the gut microbiota are significantly modulated post bariatric surgery and may be responsible for the variable outcomes, each of which were rigorously evaluated.

The RW served as a timely and novel academic meeting that brought together clinicians and researchers across the scientific spectrum, fostering a unique venue for inter-disciplinary collaboration among investigators.

It promoted engaging discussion and evolution of new research hypothesis and ideas, driving the development of novel ameliorative, therapeutic and non-surgical interventions targeting obesity and its co-morbidities.

Importantly, a critical evaluation of the current knowledge regarding gut modulated signaling post bariatric surgery, potential pitfalls and lacunae were thoroughly addressed.

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## Introduction

Obesity is a global health problem and its ameliorative strategies remain a major research focus[1,2]. Though several interventions have been trialed, the mainstay of current therapy anchors on lifestyle modification inclusive of nutrition and exercise[3–5]. While clinically meaningful weight loss may be achieved with lifestyle intervention, such weight loss is generally not sustained and its efficacy in modulating comorbidities has been questioned[6]. Thus, there remains an ongoing need for effective and durable therapeutic options, including bariatric surgery.

With surgical advances patients with obesity tend to have significant improvement in obesity related co-morbidities with gastric bypass surgery. While several variations for such bariatric surgery are in practice, one of the earliest was the Roux-en-Y gastric bypass (RYGB)[7]. Post-surgery improvement in most organ systems affected by obesity have been noted[8].

In keeping with significant health benefits, the number of patients undergoing bariatric surgery has reached unprecedented levels, with over 300,000 bariatric surgery procedures being undertaken annually[9,10]. Given the remarkable success, the underlying mechanisms leading to improved outcomes after bariatric surgery are the focus of a burgeoning field of research that may lead to novel non-surgical interventions.

Recent data suggests that post-surgery improvement may not merely be an effect of weight loss; there may be a significant influence of altered gut derived signals in modulating the disease pathology. Alterations in gut anatomy also induce adaptive changes to the morphology of the gut, which affect the absorption of macro and micronutrients. The mechanisms responsible for metabolic and nutritional outcomes following gastric bypass were reviewed as part of the workshop and presented by each faculty member.

### (I) Overview of Enterohepatic Circulation, Gut Microbiota and Metabolic Pathways Relevant to the Gut-liver Axis: (Ajay K Jain)

**Gastric Bypass FXR and Bile Acids—**Emerging studies suggest that bile acid metabolic pathways are disrupted with bariatric surgery with significant alterations to the finely regulated enterohepatic bile acid circulation[11,12]. Bile acids, traditionally considered as toxic agents have emerged as major signaling molecules maintaining several homeostatic pathways involved in insulin, glucose metabolism, lipid regulation as well as regulators of hepatic steatosis[13,14]. Marked increases in serum bile acids and its sub-fractions have been noted post RYGB in comparison to weight matched controls[12,15]. New research provides evidence that enteral bile acid treatment activates the nuclear receptor, Farnesoid X Receptor (FXR) in gut epithelial cells[16,17]. Such activation stimulates the production of the growth factor, Fibroblast Growth Factor – 19 (FGF19). FGF19 is subsequently delivered via the portal system to the liver and is known to modulate bile acid, glucose and lipid metabolism[18,19]. In fact, intravenously delivered FGF19 has been shown to reverse or prevent diabetes, improve glycemic control and reduced hepatic steatosis and triglyceride levels[20–22]. FGF19 thus functions as a secretory signal from the gut to the liver, regulating bile acid synthesis[23].

This seems to provide evidence that hepatic bile acid synthesis; glucose and lipid metabolism is modulated via gut FXR signaling[24–26]. Indeed, higher levels of FXR and FGF19 have been noted several months post RYGB in human subjects[27].

Both large animal studies and human studies have shown that exogenously delivered FXR agonist improve glycemic control, lipid metabolism and hepatic steatosis[28,29]. Additionally surgical procedures involving ileal transposition (where sections of the ileum are inserted into the jejunum), result in a significant increase in bile acids levels, improvement in body mass and obesity related co-morbidities[30].

A postulated mechanism has been a short circuiting of the normal enterohepatic circulation brought about by the altered anatomy, as the ileum is the primary site of bile acid absorption. Improved glycemic regulation, reduced hepatic steatosis, increased bile acid levels, as well as weight loss have been noted in animal models with biliary diversion[31,32]. The recapitulation of the benefits of gastric bypass using such procedure raises the thought provoking idea that anatomic alteration during bariatric surgery may explain some of the mechanistic basis of improved outcomes. However, while this data is encouraging it has also been noted that there are differences in post prandial bile acids after RYGB or Vertical sleeve gastrectomy (VSG) which points to a differential enterohepatic signaling based on the type of surgery[33,34].

Further exploration of such bile acid regulated key signaling pathways with a potential for pharmacological and nutritional intervention was a major focus of the 2017 RW.

**Gastric Bypass and role of Glucagon Like Peptide-1 (GLP-1) and TGR5 axis—**
A further mechanistic link is again through bile acid regulated pathways. Bile acids activate TGR5 – a cell surface G-protein-coupled receptor[35]. TGR5 is known to be present in the intestines, brown adipose tissue and the liver[36]. There is an increase in intracellular cAMP upon bile acid stimulation of TGR5 with variable effects dependent on the cell type expressing TGR5[37]. The role of bile acids in regulation of glucose homeostasis is further strengthened by the secretion of GLP-1 upon TGR5 activation[38,39].

We now know that plasma GLP-1 rapidly increases after RYGB[40]. GLP-1 has been implicated in glycemic homeostasis. Along with glucose dependent insulinotropic polypeptide (GIP), GLP-1 is a major gut hormone which enhances the insulin response to nutrient ingestion[41]. In non-obese individuals with normal glucose tolerance GLP-1 is released in response to nutrient intake. However, this GLP-1 response is significantly diminished in those with obesity[42]. It is known that post RYGB there in an increased TGR5 signaling[12]. Given that GLP-1 is secreted from enteroendocrine L cells in the intestine, it is plausible that manipulation of the gastro-intestinal tract as in RYGB alters GLP-1 secretion.

Further highlighting this pathway is data that postoperatively there is enhancement of postprandial GLP-1 response[43,44]. GLP-1 response is known to be greater after RYGB than after Sleeve Gastrectomy[45]. Additionally, such increase in GLP-1 response was not noted in calorie restricted obese patients; mimicking the post-surgery diet[46] or in obese patients on a low-calorie diet experiencing a similar weight loss. It has also been shown that there is a

progressive increase in GLP-1 level during the first year postoperatively with a sustained response noted in some individuals[47–49].

Given the above data it appears plausible that alterations to GLP-1 and the TGR5-GLP axis, brought about by the surgical procedure of Gastric bypass exert significant beneficial influence and the therapeutic potential needs to be explored.

**Gut Microbiota FXR and TGR5**—While the bacterial mass in any individual is a small percent of body weight[50], the bacterial genome exceeds by several folds the human genome. Ironically this makes us genetically 1% human and 99% bacterial[51,52].

When viewed as a whole, this "super gut microbial organism" can perform vital physiologic functions[53]. These typically benefit the host in educating the mucosal immune system, nutrient extraction from undigested carbohydrates, production of short chain fatty acids, production of vitamins and metabolism of bile acids[54,55].

A large human study evaluating fecal microbial colonies in dizygotic and monozygotic twin pairs addressed the role of host genetic factors, adiposity, environment and its influence on the gut microbiota[56]. Although the human gut microbiota was shared among family members, it was specific for each individual. A comparable co-variation between dizygotic and monozygotic twin pairs excluded difference based on genetic factors. Obesity was associated with intestinal microbiomes showing reduced diversity at a phylum level[56].

In rodent studies, delivery of cecal microbiota from ob/ob mice into wild germ free animals resulted in a modest fat gain. Such bacterial transfer also increased food calorie extraction in comparison to animals receiving gut bacteria from lean animal donors[57]. Several studies evaluating Nonalcoholic steatohepatitis (NASH), have noted improvement in steatosis, glucose intolerance as well as lipid profiles[58,59] with exogenous gut bacterial modulation[60,61].

These studies further support the belief that gut bacteria modulate and play an important role in human disease. Several rodent and human studies have shown that post RYGB there occurs a restructuring of the gut microbiota[62,63]. An exogenous transfer of the gut microbes from RYGB mice to un-operated, germ-free mice resulted in significant reduction in fat mass gain as well as less weight gain in comparison to such a transfer from mice that underwent sham surgery[64].

Given that gut microbes are intimately involved in gut nutrient processing and their alterations are noted with RYGB, it is reason to believe that altered gut microbiota secondary to gastric bypass influences positive outcomes post RYGB surgery.

### (II) Gut Hormones and Bariatric Surgery: (Carel Le Roux)

Gut hormones have been implicated as part of the mechanisms of how bariatric surgery reduces bodyweight and maintains long term weight loss[65].

RYGB and VSG might alter signaling from the gut to the hypothalamus and brainstem. Markedly higher postprandial levels of the anorexigenic hormone peptide YY (PYY)[66] are

noted after both RYGB and VSG, but not after calorie restriction or adjustable gastric banding (AGB)[67,68]. After a meal, PYY is released from the L cells in the distal small bowel in proportion to consumed calories. It decreases food intake by acting at the arcuate nucleus of the hypothalamus[69], and also via vagal afferents ending at the nucleus of the solitary track, thus signaling satiety. PYY has been shown to delay gastric emptying and increase energy expenditure[70]. Patients with increased PYY after RYGB have more weight loss[71,72]. Blocking the release of PYY with octreotide increased food intake in humans and rats after RYGB, but not AGB. Mechanistic studies have also shown the physiological importance of PYY in rodent studies. GLP-1 responses are similar to those of PYY after both RYGB and VSG[73]. GLP−1 is secreted by the L cells of the small bowel together with PYY, with higher concentrations in the colon and distal ileum. It acts on the GLP−1 receptors in the hypothalamus, striatum, substantia nigra and brainstem[74]. In response to a meal the peptide is produced, which decreases food intake via its effects on the brainstem and hypothalamus[75]. GLP−1 delays gastric emptying, inhibits the release of glucagon and acts on the pancreas to promote secretion of insulin[76]. Whether GLP−1 alone is necessary for VSG-induced weight loss has been questioned. The procedure was effective equally in GLP−1 receptor wild-type and knockout mice[77] but the potential synergy of GLP-1 along with other gut hormones post these operations may hold the key. The rapid nutrient delivery to the distal ileum after RYGB might be responsible for the exaggerated increase of both GLP-1 and PYY levels[78]. In the absence of a shorter small bowel in VSG, the rise in levels of these gut hormones has been attributed to rapid gastric emptying[79]. However, this finding is probably just part of the story as nutrient sensing in the proximal segment of the small bowel can produce signal to the distal small bowel to release gut hormones[80]. Recent data also suggests that post RYGB there is an increase in the post prandial responses for cholecystokinin and glucagon and a decrease in ghrelin and leptin[81]. It is also known that gut hormones are elevated within days after surgery and remain elevated for at least a decade after RYGB[47]. However, although they play an important role the gut hormones are only part of the mechanistic explanations for why bariatric surgery is able to reduce weight and maintain weight loss.

## (III) Role of Bile Salts and Key Hepatobiliary Receptors in Modulating Gut Structure and Signaling Post Gastric Bypass Surgery (Puneet Puri)

Weight loss in the management of obesity is plagued by the lack of effective long term sustainability and translation into improved outcomes[6,82]. The most notable obesity related liver condition is nonalcoholic fatty liver disease (NAFLD). More concerning is the fact that NASH, the aggressive phenotype of NAFLD, is emerging as the leading cause of cirrhosis, liver cancer and liver transplantation[83,84].

Bariatric surgery remains a very important approach to combat obesity and its co-morbidities[85]. The benefits of bariatric surgery extend beyond weight loss and are postulated to occur via modulation of glucose and lipid homeostasis, which in turn are also regulated by bile acids[86]. Given alterations noted in serum bile acid levels following gastric bypass surgery in both human and animal studies[12,87], several authors have postulated that the beneficial effects post-surgery are a result, at least in part, due to changes in enterohepatic circulation of bile acids[88].

Experimental approaches such as 'ileal transposition' or bile diversion have been used in preclinical studies. Ileal transposition studies in rodent models demonstrate diminished food intake, significant weight loss and resolution of the features of the metabolic syndrome[89]. These improvements are linked to adaptation of the interposed segment as evident by greater length of jejunum-like villi, enhanced mucosal surface area, as well as increase in mRNA expression of transcription factor GATA4/ileal lipid binding protein (GATA4/ILBP)[30]. Additionally, ileal transposition short-circuits enterohepatic recycling of the bile acids that lead to protective effects against the metabolic syndrome[30]. Importantly, weight loss alone does not improve the metabolic effects as is seen in rodents with similar weight loss on food restriction, but are observed in surgical weight loss procedures that alter serum bile acids and have been noted to help in the resolution of NASH[90].

While data translated from these studies is certainly helpful in defining mechanistic links, it is plausible that additional bile acid pathways are modulated by current bariatric surgery procedures as there is a known variability in the serum bile acid levels based on the kind of surgery performed[34,91].

In fact, VSG with gastroduodenal continuity is becoming the preferred surgical option for obesity in recent years[92]. In addition to weight loss, VSG can produce changes in bile acids and their receptor mediated molecular actions confer the metabolic benefits[93]. We now know that FXR is "a" target for the beneficial weight-loss dependent and independent effects of VSG, similarly its downstream targets small heterodimer partner (SHP) and indirect entero-hepatic signal FGF15/19 also merit future investigation as potential therapeutic targets[94]. Further mechanistic insights into bile acid signaling and regulation of entero-hepatic circulation will advance our understanding of bariatric surgery related metabolic benefits. In future, this will allow translation of these metabolic benefits through non- or minimally invasive "bariatric-mimetic" interventions that would bridge the current vast therapeutic gap in patients suffering from obesity and other related comorbidities including NASH[95].

## (IV) Changes in intestinal metabolism and portal signaling (Ali Tavakkoli)

Mechanisms leading to the anti-diabetic effects of bariatric surgery remain poorly elucidated. Understanding these mechanisms can lead to development of less invasive surgical or medical alternatives that can be offered to a wider patient population. There has been a broad interest in the changes in intestinal function that occurs after RYGB surgery, with studies showing increase in intestinal glucose utilization after surgery[96]. Furthermore, studies have also shown a decrease in intestinal glucose absorption after RYGB[97,98]. It has been postulated that these changes in intestinal function, alter fasting and post-prandial portal vein milieu which can alter hepatic glucose handling and lead to the early reduction in hepatic insulin resistance that is seen after bariatric surgery. To support this hypothesis, studies using portal vein infusions in a rodent model, have shown post-infusion changes in expression of hepatic enzymes involved in glucose homeostasis, through a neutrally mediated process that likely involves SGLT3 as a portal glucose sensor[97]. The authors concluded that the portal vein was not only capable of sensing its glucose levels but responded to it by altering hepatic glucose handling.

The portal vein delivers the intestinal venous drainage to the liver and as such provides a direct communication between the bowel and the liver. The above mentioned studies which show that the portal vein is more than a simple conduit between the bowel and the liver, and the observation that changes in portal vein glucose levels can lead to changes in hepatic pathways involved in glucose homeostasis[97,99], through a neutrally mediated pathway, highlight an important role for this structure in post-operative glucose improvement.

To this effect studies have documented a decrease in fasting and post-prandial glucose levels after RYGB surgery in rodents, with associated decrease in hepatic gluconeogenesis and glycolysis. Interestingly, some of these changes are uniquely seen in RYGB and not VSG, which may explain the more potent anti-diabetic effects of RYGB. Further research may provide insights into the mechanistic basic of these responses.

### (V) Gut Nutrient Sensing: Gut Remodeling and Adaptation to Gastric Bypass and Effects on Absorption of Macro and Micronutrients (Nana Gletsu-Miller)

Gastric bypass surgery is traditionally considered to be malabsorptive[100], however, from the stand point of nutrition this characterization is simplistic. Several mechanisms contribute to the risk of malnutrition observed following RYGB. One major issue is the reduced dietary intake of macro and micronutrients, secondary to decreased energy intake and to food intolerances that develop after surgery[101,102]. In addition patients decrease their intake of dietary factors that enhance absorption including fat and vitamin C, which leads to decreased bioavailability of nutrients such as vitamin D, iron and copper. Besides changes in dietary intake, anatomical changes result in reduced nutrient bioavailability and intestinal absorption. Resection of the stomach antrum decreases gastric acid secretion[103,104] and loss of absorptive surface in the duodenum and proximal jejunum reduces access to nutrient transporters[105]. At the same time, the adaptive response to changes in the anatomy result in growth of the remaining small intestine, similar to the adaptation of the gut that occurs after resection of the intestine, referred to as short gut syndrome[106]. The result of these changes is an increase the absorption of some nutrients but not others after RYGB[107]. Therefore the impact of RYGB on nutritional status is mixed with respect to macro and micronutrients.

**Impact on macronutrient status—**As aforementioned changes in gut anatomy, accompanied by intestinal hyperplasia[106,108] lead to changes in macronutrient absorption. Over the long term, the gut retains or enhances its ability to absorb glucose[109], fatty acids[110] and amino acids[111,112]. Elegant studies in rodents and humans demonstrated that gut adaptations can lead to improvements in glucose metabolism, as the intestine assists with glucose disposal from the periphery[109]. At one and six months post gastric bypass, it has been demonstrated that even though patients decreased their dietary intake of fat, they did not exhibit deficiencies in essential fatty acids[113]. However, enhanced absorption of amino acids does not compensate for the fact that many patients do not meet the dietary intake of 60 g of protein that is recommended for this population[114,115]. The evidence supporting this recommendation was rated as low; information on the impact of dietary protein on protein status during surgically-induced weight loss is mostly observational[116] and evidence from randomized clinical trials is extremely limited[117]. This is an important issue since sarcopenia is common after surgery, with patient losing 10 to 28% of lean mass[116]. The

clinical manifestations of a reduction of lean body mass and sarcopenic obesity include decreased energy expenditure[118], muscle strength[119], and bone density[118], adverse outcomes that have the potential to reduce the benefits of surgery over the long term.

**Impact on micronutrient status—**Unlike macronutrients, patients undergoing RYGB are more vulnerable to deficiencies in micronutrients, primarily minerals and fat soluble vitamins. It has long been appreciated that nutritional complications such as hair loss, bone loss, anemia, fatigue, neuropathies[120], and more severe symptoms including bone fractures[121], blindness[122] and paralysis[123], associated with deficiencies in micronutrients can occur following gastric bypass. Unfortunately, the literature regarding the micronutrient status of RYGB is incomplete due to the lack of patient follow-up and nutritional screening. Our best knowledge is that deficiencies in iron, calcium and vitamin D are common, ranging from 25 to 75%[120]. Deficiencies in vitamins A, $B_{12}$ and other B vitamins occur less frequently with incidences of around 10%[124,125] The mechanisms responsible are complex since obesity per se, prior to surgery, is a risk factor for deficiency in specific nutrients, such as vitamin D[126] and iron[127]. In the obese state, the bioavailability of iron and vitamin D is reduced due to obesity-induced inflammation[128] and sequestration in adipose tissue[129], respectively. Following surgery, as patients experience weight loss, this alleviates the adverse impact on the nutritional status that is related to obesity[130,131]. Despite the favorable impact of weight loss, research shows that the nutritional status of vitamin $B_{12}$, iron, zinc, copper, and calcium worsens after surgery[120]. This may be due to resection of the stomach and the resulting decrease in gastric acid secretion[59,60.] Gastric acid is needed to digest the minerals from food, and solubilize them, so that they are bioavailable for absorption. Moreover, to reduce the risk of stomach ulcers after surgery, patients increase their use of proton pump inhibitors[132], and hypogastric acidity impairs the absorption of nutrients[133]. Bypass of the proximal intestine, which is where the majority of the transporters of minerals are located, also contributes to the reduced absorption of iron[105], zinc[105], and vitamin D[134] that has been observed after surgery. It is not clear whether gut adaptation, over the long term, can rescue the defects in intestinal absorption of micronutrients[135–138].

**Strategies for prevention and treatment—**The risk of malnutrition following RYGB reduces its safety profile. Adverse outcomes related to function and quality of life[139,140] would be reduced if nutritional support of these patients was improved. Therefore patients, practitioners, and other stakeholders need to know the best practices for the treatment and prevention of nutritional deficiencies[114]. Studies have demonstrated that sufficient intake of protein and iron, can realistically be obtained from diet especially if it is nutrient dense[115,141]. Use of dietary supplements is also an effective way to manage status of protein[142], calcium, iron[141,143], and vitamins D[115] and $B_{12}$[144] after gastric bypass. For treatment of deficiencies, although clinical trial are limited, data suggest that high-dose supplementation of iron[145], vitamins D[142,146] and $B^{12}$ and protein[117] is effective. Taken together, since oral ingestion of food and supplements can be used to prevent and treat malnutrition, this suggests that sufficient capacity of the gut remains for digestion and absorption of micronutrients after surgery. However, it has also been advocated for patients to undergo intravenous administration of nutrients, as a second line of therapy[114,147]. In summary, more research is needed to determine optimum strategies for treatment and

prevention of nutritional deficiencies post gastric bypass surgery. This information will improve nutritional outcomes so that more patients can benefit from this life-saving procedure.

## (VI) Effect of Microbiota on Digestion and Absorption: Integrity of the Mucosal Barrier (Bruce M. Wolfe)

The extent to which obesity contributes to the development and severity of obesity-related comorbid conditions such as type 2 diabetes, hypertension, dyslipidemia, and obstructive sleep apnea generally increases with the severity of obesity but is highly variable[148]. There are both genetic and environmental factors which contribute to obesity-related comorbid disease, including certain alterations of the composition of the microbiome. Efforts to determine causality are the subject of ongoing research.

In addition, weight loss is highly variable among people with obesity following interventions including lifestyle intervention, pharmacotherapy, and bariatric surgery/gastric bypass[149]. Efforts to explain or predict the extent of this variable weight loss following gastric bypass remain largely unknown. While, the NIH multi-center consortium, Longitudinal Assessment of Bariatric Surgery, identified changes in eating behaviors that contribute modestly to this variation[150], further research is necessary into the potential contributions by genomic factors as well as changes of the microbiome induced by gastric bypass to identify appropriate candidates. Though mechanisms indicating a direct relationship between gut microbiota changes and response to gastric bypass remain a major focus of research, we know that the gut microbiota in mammals plays an important role in the digestion, absorption, and extraction of energy from ingested nutrients[151]. The importance of this energy extraction varies among mammalian species. For example, in cows, as much as 70% of total energy extraction from the diet results from fermentation production of short-chain fatty acids. Germ-free mice require approximately 30% greater energy intake in order to achieve comparable growth to normally colonized mice. The contribution from microbiota digestion of nutrients in humans is estimated to represent approximately 10% of total energy, a figure that potentially varies widely.

The mammalian proximal intestine absorbs simple carbohydrates efficiently, especially glucose. Disaccharides are also absorbed and, to a limited extent, polysaccharides. Otherwise indigestible carbohydrates in the proximal intestine pass distally for digestion and metabolism by luminal microbiota. Fermentation in which polysaccharides are metabolized to short-chain fatty acids is an important pathway. Pyruvate is metabolized to acetyl-CoA and ultimately acetate, butyrate and propionate[152]. Butyrate and acetate are readily absorbed and contribute to energy supply, particularly for enterocytes. Butyrate has been identified as a modifier of cytokine production by CT cells and to enhance the integrity of the intestinal epithelial barrier. Metabolic signaling is also attributed to absorbed butyrate[153]. Acetate has a role in enhancing the resolution of intestinal inflammation and protection from intestinal pathogens.

In summary, gut microbiota is responsible for the digestion of otherwise indigestible carbohydrates and, to a lesser extent, protein and lipids. The contribution of these processes to total energy supply will vary as functions of dietary intake, microbiome composition, and

other factors involved in digestion of nutrients including bile salts, and pancreatic and other enzymes[154]. One measure of qualitative detection of the microbiota effect on digestion is the production of both methane and hydrogen. These gases are excreted in the breath and may be detected qualitatively if not quantitatively, reflecting bacterial digestion. Since gut anatomy is altered post bariatric surgery there is data confirming an associated change in the microbiota. Whether such change this is a cause or has a major effect post bariatric surgery needs further investigation.

Low levels of chronic inflammation are variably associated with obesity. This low level inflammation is associated with atherosclerosis, insulin resistance, type 2 diabetes as well as non-alcoholic steatohepatitis[152]. The activation of inflammatory cells in fat stores involves the action of cytokines, chemokines, and acute phase reactants. Triggers of inflammatory cells include adipocyte apoptosis, saturated free fatty acids, ceramides, glucose, and low levels of endotoxemia (LPS).

LPS-binding protein (LPB) serves as a surrogate marker of underlying low-grade endotoxemia induced by LPS from the gut. The absorption of LPS is attributed to increased permeability of the intestinal barrier induced by alterations of the microbiome among other factors. Levels of LPB, BMI, and obstructive sleep apnea have all been shown to be associated in children[155]. New data also shows that short term decrease in LPS is additionally dependent on the type of the surgical procedure as well as on the glycemic status of a patient[156]. In mice, a high fat diet induced changes of the microbiome are associated with endotoxemia, suggesting a relationship between diet-induced changes of the microbiome, intestinal permeability to endotoxins, and related systemic inflammation[157]. This may provide a link between the association of the gut microbiome and cardio/metabolic health[158]. As changes in the flow of the food stream post bariatric surgery can alter the microbiota, it seem intuitive to believe that these microscopic organisms may prove formidable players in outcomes post such surgery.

**Microbiome-obesity research challenges—**It is apparent that many associations of the descriptive findings of the microbiome with metabolic phenomena and related human disease have been established including gastric bypass. Most of these studies use feces, which may or may not be an appropriate representation of the composition of the microbiome throughout the intestinal tract. Additional challenges arise from the incomplete status of bacterial genome databases and the high number of polymorphisms. There are species differences among the animal models. Finally, obesity, as noted above, is a heterogeneous condition. Thus, establishing a cause-and-effect relationship and a basis for therapeutic interventions will require sorting out multiple aspects of the relationship of the microbiome to obesity and related comorbid disease. These investigations generate exceedingly large data files which require rapidly evolving skillsets among computational biologists for analyses.

### (VII) Gut Microbial Symbiosis and Key Enterocyte Derived Signals Influencing Health and Disease: Microbial Metabolomics (Blandine Laferrère)

We know that specific composition of the gut microbiome associates with pathological conditions such as cardio vascular disease, inflammatory bowel disease or asthma and with certain phenotypes like obesity and insulin resistance[159]. However, the mechanism by which the gut microbiome maintains health or contributes to diseases is unknown. Metabolomics is the quantitative analysis by mass-spectrometry or nuclear magnetic resonance spectroscopy of large numbers of low molecular weight metabolites, substrates and products in metabolic pathways, in bio specimens (fluids or tissue)[160]. Identifying metabolomic signatures and circulating biomarkers associated with the metabolism and functions of gut bacteria is an important step to understand the pathways and mechanisms by which the gut microbiome contributes to the development of diseases. These metabolomic biomarkers could also be used to track response to treatment. Discussed below are four examples of targeted metabolomics to the measure circulating biomarkers of microbiome metabolism: short chain fatty acids (SCFA), bile acids, branched chain amino acids (BCAA) and trimethylamine-N-oxide (TMAO), and how they relate to outcomes post bariatric surgery.

**SCFA – fuel and anti-carcinogen—**The SCFAs are fatty acids with 2 to 6 carbons, bacterial metabolites produced during the colonic fermentation of indigestible oligosaccharides, dietary plant fibers, non-digested proteins and intestinal mucin, that are at the interface between the diet, the microbiota and the host[161]. SCFA (and medium chain FA) are primarily absorbed through the portal vein during lipid digestion, while long chain fatty acids go through chylomicrons, the lymphatic canal and the subclavian vein. SCFAs have many positive functions. Butyrate is the major energy source for colonocytes[162–164]. SCFAs stimulate the production of the satiety hormones GLP-1 and PYY via activation of the G-protein-coupled receptor FFAR2[165,166], a mechanism by which SCFA may modulate food intake[167]. Propionate is largely metabolized in the liver, and acetate is the main circulating SCFA[168]. SCFAs play a role in lipid metabolism and inflammation, improve insulin sensitivity and modulate the risk of cardio vascular disease, in part by activation of a subset of G protein-coupled receptors[169,170]. The administration of inulin-propionate ester, a dietary fiber, to 60 overweight humans reduced body weight, intra-abdominal adipose tissue, liver fat and improved insulin resistance in a 24-weeks randomized clinical trial. The targeted colonic delivery of inulin-propionate increased circulating PYY and GLP-1 concentrations during a test meal and reduced subsequent food intake[171]. This *in vivo* data confirm the *in vitro* stimulation of PYY and GLP-1 from a colonic cell line by butyrate and propionate[166]. Colonic infusions of SCFA mixtures, in concentrations and ratios similar to the ones reached after fiber intake, increased fat oxidation, energy expenditure and PYY, and decreased lipolysis in overweight/obese men[172]. The systemic availability and metabolism of colonic-derived SCFAs in healthy subjects has been demonstrated using stable isotopes. The quantification of SCFA production from ^{13}C-labelled fibers in the human colon can be done by measurement of ^{13}C-labelled SCFA concentrations in blood[173][174]. In that study, the systemic availability of colonic-administered acetate, propionate and butyrate was 36%, 9% and 2%, respectively. Conversion of acetate into butyrate (24%) is the most prevalent interconversion by the colonic microbiota. Little administered acetate was incorporated into cholesterol (<1%) and less than 15% in fatty acids. On average, 6% of colonic propionate

was incorporated into glucose. Most of SCFAs excretion occurred via the lungs after oxidation to $^{13}CO_2$, and almost no SCFAs (less than 0.05%) were excreted into urine. There is no report to our knowledge of levels of circulating SCFA after bariatric surgery. However, fecal SCFA concentration and microbial composition was shown to be altered after biliopancreatic diversion and related to change in metabolism[175].

**Bile acids and microbiota – symbiotic relationship—**Bile acids are synthesized in the liver from cholesterol under the control of key enzymes, stored in the gall bladder and excreted in the intestine upon ingestion of meals high in fat. Historically, their main function is to facilitate the emulsification of dietary fats and the intestinal absorption of lipids and lipophilic vitamins[176]. Bile acids undergo further transformation by the gut microbial enzymes, including bile salt hydrolase, through deconjugation and dehydroxylation reactions that generate unconjugated and secondary bile acids[177]. Apart from regulating secondary bile acid metabolism, gut microbiota also reduce the synthesis of bile acids in the liver, by a mechanism involving the suppression of FXR expression in the ileum[178]. Therefore, the gut microbiota contributes to the diversity and composition of the bile acid pool[176,179]. The activity of bile salt hydrolase may be modified in colon cancer and or liver disease. In the gut, bile acids control bacterial overgrowth and microbiome composition[180–182]. We also know that bile acids have carcinogenic potential[183,184,185]. In addition to their role in lipid digestion and as bacteriostatic agents, bile acids signal a variety of systems in the liver and intestine by interaction with multiple nuclear receptors[186] and play a role in glucose and lipid metabolism[187,188]. Dietary factors such as prebiotics play important roles in the growth of intestinal microbiota and bile acids metabolism. Fecal bile acid profiling, as opposed to circulating bile acids, may be a better non-invasive tool to monitor the intestinal environment[189]. Many studies have shown an increase of circulating bile acids pool after RYGB[15,190,191]. However, the increased concentration of circulating bile acids and the change in the composition of conjugated bile acids do not seem to parallel the observed GLP-1 rise after the same surgery as noted in some studies[191].

**Protein and amino acids—**Bacterial fermentation of proteins in distal colon can produce ammonia which can act as tumor promotor. Fermentation of aromatic amino acid tyrosine and tryptophan by colonic bacteria can produce phenols and indoles respectively. Phenols, such as p-cresol, may be pro-carcinogen in colon CA[192]. Essential amino acids, not synthesized in the body, are provided by the diet and de novo biosynthesis by gut bacteria. The intestinal microbiota is involved in the utilization and catabolism of several amino acids originating from the diet and from endogenous proteins. These amino acids can serve as precursors for the synthesis of bacterial products such as SCFAs. Gut bacteria may contribute to the branched chain amino acid (BCAA) signature associated with insulin resistance. Circulating BCAAs have long been associated with obesity and insulin resistance[193,194,195,196,197] and can predict future type 2 diabetes[198]. Their concentration decreases after interventions that improve insulin sensitivity, such as surgical weight loss by RYGB[199]. Circulating BCAA concentrations are modulated by their metabolism in adipose tissue[200] and, perhaps, also by the microbiome[201]. The altered gut bacterial composition in individuals with obesity and type 2 diabetes may contribute to their dys-metabolism by influencing amino acids and SCFAs bioavailability to the host. Individuals with insulin

resistance who have a serum metabolome characterized by increased levels of BCAAs, have a gut microbiome with an enriched biosynthetic potential for BCAAs and deprived of genes encoding bacterial inward transporters (from blood to gut) for these amino acid. Specific bacterial species driving this association were shown to induce insulin resistance, aggravate glucose intolerance and augment circulating levels of BCAAs in mice[201].

**The importance of the TMA/TMAO microbiome-host axis in health and disease**
—Dietary phosphatidylcholine (lecithin), the major source of choline, is metabolized by intestinal lipases to form glycerophosphocholine, phosphocholine, and choline[202]. Choline containing nutrients that reach the cecum and the large bowel serve as fuel for intestinal bacteria, producing trimethylamine (TMA). TMA is oxidized to trimethylamine-N-oxide (TMAO) in the liver. TMAO enhances the accumulation of cholesterol in macrophages, the deposition of foam cells in arterial walls and the formation of atherosclerosis, all factors associated with an increased risk of cardiovascular disease and death[203,204]. Circulating choline can also be oxidized to betaine, a metabolite involved in methylation reactions and detoxification of homocysteine, in the liver and in the kidneys. In humans, elevated plasma concentrations of TMAO, choline and betaine are associated with an increased risk of a major adverse cardiovascular event, even after adjusting for traditional risk factors. The role of the gut microbiota in TMAO production was demonstrated in vivo. The acute rise of circulating TMAO after an oral phosphatidyl challenge can be suppressed with antibiotics[205206]. Paradoxically, circulating TMAO levels are elevated after RYGB, a surgery associated with large weight loss, decreased inflammation and cardiovascular risk[207].

## (VIII) Microbiome Host Mucosal Interactions: The Role of Epigenetics (Richard Kellermayer)

Epigenetics defines molecular mechanisms that influence pre-translational gene expression independently from the genetic code. Epigenetic processes can respond to environmental changes and have been implicated as important participants in the developmental origins of human diseases[208]. Secondary to environmental plasticity, the host epigenome in mammals carries the potential to communicate with the commensal microbiota through direct and indirect mechanisms[209].

With respect to obesity, epigenetic regulation of body composition[210] and physical activity[211] through prenatal/early life exposures are intense areas of research. Intermediates of energy metabolism are co-factors in epigenetically mediated chromatin, and secondary gene expression modifications. Therefore, gene regulation underlying phenotypic determinants of adult metabolic health may be influenced by maternal and early postnatal diet[212]. Maternal (by communicating maternal nutritional influences to the emryo) and individual (own) commensal microbiota are inherent participants in this environment-diet associated developmental programming. In fact, early developmental modulation of gut microbial composition leads to lasting metabolic consequences in mammals[213]. The clinical relevance of these findings is supported by the association of infantile antibiotic exposure and subsequently increased body mass index in children[214].

The ongoing importance of microbiome composition in obesity and related comorbidities is underscored by the beneficial effects of fecal microbiota transplantation (FMT) from lean individuals to obese patients with metabolic syndrome[215]. This therapeutic intervention is intensely being investigated in ongoing obesity related clinical trials[216]. Importantly, a recent controlled study on FMT from lean donors into obese individuals showed a transient improvement in insulin sensitivity in those recipients who had lower microbiome diversity at baseline (responders)[217].

Recent research is also examining the potentially critical role of the microbiome in regards to bariatric surgery outcomes. Murine model experiments indicate that the microbiome plays a critical role in weight gain following transient loss of obesity[218]. In accordance with this observation, recent human translational research showed consistent increase in the *Roseburia* genus in patients with successful resolution of diabetes following both RYGB and SG surgery[219]. Such microbiome changes associated with fecal metabolite alterations, may be relevant for modulating epigenetic mechanisms. Importantly, *Roseburia* are butyrate producers[220]. Butyrate can promote epigenetic remodeling in intestinal stem cells by acting as a histone deacetylase inhibitor[221]. This example signifies the potential for bariatric surgery induced microbiome modification to alter host physiology, which requires intense exploration in the future.

## (IX) Gut Microbiota and Obesity: Changes Post Bariatric Surgery – Clinical Perspective (John K. DiBaise)

A better understanding of the mechanisms underlying the effectiveness of bariatric operations is important in order to optimize patient selection and clinical outcomes of these operations, and may result in the development of less invasive, novel treatments. The gut microbiota is now recognized to contribute to host energy harvest, storage and the development of obesity[154,222]. The relationship between the intestinal microbiota and obesity/adiposity has generated interest into the potential role of this complex microbial community as a contributing factor to the success or failure of bariatric operations.

### RYGB anatomical and physiological changes may contribute to dysbiosis—

Following RYGB, a variety of environmental, systemic and anatomical changes occur that might directly or indirectly affect the microbial composition of the gut. Reduced gastric size will affect diet composition and acid exposure to the nutrients. Altered nutrient flow due to accelerated transit through the shortened small intestine may affect oxygen and nutrient exposure to the more distal gut. Altered bile acids and mixing of pancreaticobiliary secretions with nutrients will affect gut microbes. Changes in gut hormone production (e.g., GLP-1, PYY) due to altered nutrient exposure in the distal gut, and vagal nerve disruption may also affect gut microbe composition. Finally, other factors that may affect gut microbial populations post-RYGB[64] include the occurrence of postoperative complications (some of which may require altered diet and exposure to antibiotics), altered diet (e.g., food intolerances), pre-existing disordered eating behaviors and, potentially, changes in exercise and mood.

**Gut microbe changes after RYGB—**To date, only a handful of studies have been reported. A small pilot study, using pyrosequencing on fecal samples from morbidly obese individuals, normal weight subjects and patients who had successful weight loss after RYGB showed that RYGB resulted in increased abundances of *Gammaproteobacteria* and *Verrucomicrobia* and decreased *Clostridia*[62]. Higher numbers of the $H_2$-producing *Prevotella* and $H_2$-consuming Archaea in the obese subjects were found, suggesting a syntrophic relationship between certain microbes that improves the efficiency of fermentation and contributes to the development of obesity. In a study of 30 obese individuals and 13 lean controls, fecal samples were collected at baseline in all subjects and 3 months and 6 months after RYGB in the obese individuals[223]. Real-time quantitative PCR was performed to examine seven bacterial groups. After RYGB, *Escherichia coli* levels were significantly elevated at both 3 and 6 months compared to baseline and lean controls. *Faecalibacterium prausnitzii*, a bacteria suggested to have anti-inflammatory activity, also increased in abundance after RYGB but only in those individuals who were diabetic preoperatively. The same research group then performed deep sequencing on the same patients and found an increase in richness and diversity of the microbiota after RYGB with 37% of the increased bacteria belonging to Proteobacteria[224]. Seven dominant genera identified post-surgery, were independent of reduced calorie intake and were associated with markers of anti-inflammation and insulin sensitivity. Using a non-obese rat model comparing RYGB to a sham control, Li et al. performed pyrosequencing and metabolite profiling of fecal samples[63]. Similar to the studies in humans, they found a 52-fold increase in Proteobacteria (bloom in E*nterobacter hormaechei*) with smaller decreases in both Firmicutes and Bacteroidetes. Increased oligosaccharide fermentation (and increased short-chain fatty acids), biogenesis of p-cresol, and amine generation were also detected post-RYGB. The same group demonstrated that this shift in microbial composition post-RYGB correlated with an increased cytotoxic environment highlighting a potential long-term cancer risk after RYGB[225]. It has been shown that RYGB alters the microbiota along the length of the gut but these changes were most substantial in the Roux limb and common channel suggesting that changes in microbes in the small bowel may regulate the beneficial effects post-surgery[226]. In another study using a mouse model of RYGB and comparing microbial and metabolite changes among two groups of mice following sham surgery with or without caloric restriction[64] increases in Proteobacteria (*Escherichia*), Verrucomicrobia (*Akkermansia*) and Bacteroidetes (*Alistipes*) were found. These changes occurred by 1 week post-op, were consistent regardless of diet, were similar with both luminal and mucosal samples, and were detectable along the length of the gut. Moreover, when the authors transplanted the microbiota from all mouse groups into germ-free mice, RYGB feces recipients significantly decreased in body weight compared to the other groups[64] providing for the first time empirical support for the claim that the changes in gut microbes post-RYGB contribute to reduced weight/adiposity.

**Gut microbe changes after other bariatric operations—**Important insight into the role of the gut microbes in the success or failure of RYGB may be obtained by studying changes in gut microbes occurring after other bariatric operations with less drastic alterations in gut anatomy and physiology. Vertical sleeve gastrectomy results in the resection of about 80% of the greater curvature portion of the stomach and causes a

restriction of food intake, acceleration of gastric emptying and alteration of gut hormones affecting satiety and appetite. VSG was noted to produce only modest microbial changes compared to RYGB[219] but did lead an increase in the Bacteroidetes/Firmicutes ratio and a decrease in *Eubacterium rectale, Ruminococcus obeum, Lachnospiraceae bacterium* and *F. prausnitzii* (in those with impaired glucose tolerance only)[227]. VSG also led to an increase in malabsorption due to loss of energy-rich fatty acids in the stool, impaired bile acid circulation[227] and resulted in greater capacity for metabolism of amino acids[219]. A human study compared gut microbial changes about 9 years after either RYGB or vertical banded gastroplasty (VBG), a predominantly restrictive operation[228]. They found significant differences in microbe composition between RYGB and obese patients but not between VBG and obesity or VBG and RYGB[228]. Furthermore, the two operations resulted in alterations of fecal and circulating metabolites in comparison to obese controls. Finally, they investigated a causal link by performing microbiota transplantation of human stool from the three groups into germ free mice. Mice colonized with RYGB and VBG microbiota accumulated 43% and 26% less body fat, respectively, than mice colonized with obese microbiota. Additionally, RYBG colonized mice had lower respiratory quotient than the other groups suggesting a decreased utilization of carbohydrates and an increased utilization of lipids. Finally, results from a retrospective study comparing RYGB and adjustable gastric banding (AGB), another mostly restrictive operation, to lean and obese control subjects found that RYGB and lean patients had higher microbial diversity and evenness than the other groups[229]. *Bacilli, Gammaproteobacteria*, and *Prevotellaceae* were the microbial signatures discriminating RYGB microbiota from lean and obese controls. *Gammaproteobacteria* and *Bacilli* also discriminated RYGB from AGB while *Flavobacteriia* and *Porphyromonadacea* discriminated AGB subjects from the non-surgical subjects. RYGB had higher butyrate, propionate and branch chain fatty acids[230] (saturated fatty acids which have methyl branches on the carbon chain, usually noted in bacteria) than the other groups, implicating fatty acid signaling, which stimulate appetite regulating peptides, as a mechanism of action of RYGB. The available data, while encouraging, are limited by the small number of subjects, relatively short duration of follow-up, lack of standardization for obesity-related comorbidities and medication use, and different techniques used to probe the microbial communities present.

### (X) Understanding the Clinical Implications of Therapeutic Bariatric Interventions (Robert G. Martindale)

The numerous potential interventions in the management of obesity are almost limitless today. Endeavors focused at weight loss and metabolic management of obesity using interventions ranging from behavioral modification, to pharmaceutical agents[28], to endoscopic devices like intra-gastric balloons[231], absorption barriers and various methods of gastric plication to the bariatric surgical procedures make decisions on the optimal choice of weight loss method difficult. Weight management now requires a very individualized approach[232]. Of these interventions the bariatric surgical procedures are currently the most durable with 20 year outcome data now available for RYGB and BPD and 10 year outcome data for sleeve gastrectomy[233,234]. Continued follow-up of these patients and well-designed trials have shown the co-morbidities associated with obesity are dramatically decreased following successful weight loss including type 2 DM, obstructive sleep apnea,

hypertension, several cancers and even mortality. Although successful in managing weight loss bariatric surgery is not without significant complications which are often ignored or understated by the "business" of bariatric surgery[235].

The previous concept of bariatric surgery being a decision between malabsorption procedure and restrictive procedure is very naive and the metabolic changes associated with bariatric surgery are much more complex than ever anticipated. The future is bright for the study and management of obesity with the recent exponential increase in understanding of the complexity of obesity. With "Big Data", a better understanding of the >30+ peptides involved in appetite control, the importance of bile salts and the microbiome in metabolic regulation has offered a new focus for the metabolic management of obesity[236,237]. The potential for therapeutic interventions with bile salts or their receptor antagonist[30,39,238] has changed the focus and approach to the bariatric patient. Emerging data also points to a rebalancing of satiety signals post-surgery via resensitization of the gut-brain axis which could be a contributor to the improved outcomes[239]. Mechanistic pathways mediating such signaling remain a major research focus.

Potential answers and approaches to the global obesity crisis are within reach but this will take a concerted effort on not only with the health care professionals but also the general public. Government incentives and sponsored education to all levels of the public focused to draw attention to the problem of obesity will be needed. The importance of major dietary changes and exercise cannot be understated in any successful approach to weight management.

## Final Remarks

The theme of the A.S.P.E.N. 2017 RW was to focus on research evaluating the role of the gut gut-derived signals in modulating outcomes post Bariatric Surgery. Gastric Bypass results in significant loss of fat mass. Additionally there is improvement in glucose/insulin signaling, hepatic steatosis and NAFLD, which by far outweigh the benefits of associated weight loss.

Manipulation of the gastro-intestinal tract as in RYGB results in marked increase in bile acids and its sub-fractions, which in gut epithelial cells activate Farnesoid X Receptor (FXR) followed by stimulation of Fibroblast Growth Factor – 19 (FGF19) signaling to liver, thus in turn regulating bile acid synthesis. Additionally GLP-1 rapidly increases after RYGB with favorable lipid and glycemic effects. Furthermore, hepatic and gut nuclear factors as well as bile acid pathways, (specifically FXR, TGR5 and GLP axis), modulated post bariatric surgery, are also known to influence gut microbiota colonization.

Recent data also highlights the importance of applied microbial metabolomics to understand the role of gut microbiome as a mediator between diet and metabolism. Coupling microbial analysis with targeted and untargeted metabolomics analysis of not only circulating metabolites but also stool and gut tissue analysis, coupled with sophisticated statistical methods applied to multi-omics analysis, will allow us to discover mechanistic links and pathways associating microbial metabolism with health and disease. However, the

complexity of microbiome metabolism, with multiple cross-talk between bacteria species, represent a challenge to identify novel treatment targets.

Overall, given the remarkable durability, after bariatric surgery in obesity and its related co-morbidities, lessons learned at this workshop point to the irrefutable role of gut derived signals in modulating the post-operative course after bariatric surgery. Efforts exploring this exciting pathway may even lead to novel non-invasive/non-surgical interventions for the worldwide obesity epidemic.

In summary the 2017 ASPEN Research Workshop focused on the novel idea that gut derived signals modulates gastric bypass outcomes. The workshop brought together clinicians and researchers across the scientific spectrum. Such unique interaction and exchange of knowledge between investigators and clinicians greatly promoted an engaging discussion with a great potential for translation of basic findings into clinical practice. Further, the research workshop engaged in direct outreach to other research communities and greatly helped in collaborations across organizations and disciplines.

## Acknowledgments

## MAJOR ABBREVIATIONS

| | |
|---|---|
| **FGF19** | Fibroblast Growth Factor 19 |
| **FXR** | Farnesoid X Receptor |
| **SHP** | Small heterodimer partner |
| **RYGB** | Roux-en-Y gastric bypass |
| **VSG** | Vertical sleeve gastrectomy |
| **AGB** | Adjustable gastric banding |
| **NASH** | Nonalcoholic Steatohepatitis |
| **NAFLD** | Non Alcoholic Fatty Liver Disease |

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