Potential contribution of the gut microbiota to hypoglycemia after gastric bypass surgery

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Abstract
Obesity has become a global health problem. Lifestyle modification and medical treatment only appear to yield short-term weight loss. Roux-en-Y gastric bypass (RYGB) is the most popular bariatric procedure, and it sustains weight reduction and results in the remission of obesity-associated comorbidities for obese individuals. However, patients who undergo this surgery may develop hypoglycemia. To date, the diagnosis is challenging and the prevalence of post-RYGB hypoglycemia (PRH) is unclear. RYGB alters the anatomy of the upper gastrointestinal tract and has a combined effect of caloric intake restriction and nutrient malabsorption. Nevertheless, the physiologic changes after RYGB are complex. Although hyperinsulinemia, incretin effects, dysfunction of β-cells and α-cells, and some other factors have been widely investigated and are reported to be possible mediators of PRH, the pathogenesis is still not completely understood. In light of the important role of the gut microbiome in metabolism, we hypothesized that the gut microbiota might also be a critical link between RYGB and hypoglycemia. In this review, we mainly highlight the current possible factors predisposing individuals to PRH, particularly related to the gut microbiota, which may yield significant insights into the intestinal regulation of glucose metabolic homeostasis and provide novel clues to improve the treatment of type 2 diabetes mellitus.

Keywords: Roux-en-Y gastric bypass surgery; Hypoglycemia; Gut microbiota; Obesity

Introduction
Overweight and obesity have become global epidemics. Recently, the World Health Organization announced that the prevalence of obesity had nearly tripled worldwide between 1975 and 2016, leading to a prevalence of overweight or obesity among adults of 39%. Obesity is characterized by abnormal or excessive fat accumulation and the development of a wide variety of comorbidities, such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, non-alcoholic fatty liver disease, musculoskeletal disorders, and several types of cancers. Therefore, the prevalence and rapid growth of obesity have resulted in a tremendous health and economic burden and call for powerful interventions to alleviate not only body weight but obesity-related comorbidities.

Lifestyle interventions, such as modification of dietary intake and increasing physical activity, can result in a 5% to 10% reduction of body weight in obese patients. However, weight regain usually occurs after 3 to 9 months, and almost 90% will return to their original body weight after 1 to 5 years or gain more weight. The combination of anti-obesity medical treatment and lifestyle management can lead to an additional 2 to 8 kg of weight loss. Given the complex etiology and pathogenesis of obesity, including genetic, environmental, physiological, socioeconomic, and epigenetic factors, a combination of pharmacology and lifestyle management to treat obesity seems to be limited and lacks long-term effectiveness. Over the last two decades, bariatric surgery has emerged as an effective tool for fighting obesity, and it leads to long-term weight loss and remission of obesity-related complications.

It is estimated that there are 350,000 bariatric operations done worldwide every year. Currently, clinical practice guidelines recommended bariatric surgery for patients with a body mass index (BMI) ≥40 or ≥35 kg/m² with one or more obesity-related metabolic disorders such as T2DM, hyperlipidemia, hypertension, or obstructive sleep apnea. Bariatric surgery reduces body weight by changing the anatomy of the gastrointestinal tract to restrict energy intake and/or decrease nutrient absorption. Laparoscopic
Roux-en-Y gastric bypass (RYGB) is one of the most common and effective weight-reduction procedures, and it creates an upper 15 to 30 mL gastric pouch based on the lesser curvature, which is completely divided from the gastric remnant and then anastomosed to the distal jejunum. Thus, RYGB has a combined effect of caloric restriction and nutrition malabsorption.[16] Many obese patients with diabetes experience sustained weight loss and remarkable remission of glucose metabolic disorders after RYGB.[17,18] However, post-bariatric surgery hypoglycemia is the most frequent and disabling adverse event after RYGB. Although hypoglycemia is also observed after sleeve gastrectomy and other bariatric surgeries, this review is focused on RYGB, given the greater number of published clinical studies on RYGB at present. The specific mechanism underlying post-RYGB hypoglycemia (PRH) is complex and largely unclear.[16] The incretin effects and neudioblastosis do not completely explain the phenomenon.[19] It is well known that the gut microbiota plays an important role in metabolic health, whereas microbial dysbiosis occurs in patients with obesity and T2DM.[20,21] Dysbiosis occurs in patients with obesity and T2DM.[20,21] Recently, a growing number of studies have shown that the gut microbiota significantly changes after RYGB,[22] which indicates that the intestinal microbiota might be a crucial factor in explaining PRH. This review summarizes the current possible mechanisms mediating PRH, with a focus on the gut microbiota.

**The Diagnosis and Prevalence of PRH**

Hypoglycemia is generally diagnosed by the Whipple triad and is defined by a plasma glucose level below 2.8 mmol/L and a combination of clinical symptoms and signs (autonomic or neuroglycopenic) of hypoglycemia and resolution by carbohydrate administration.[23] The autonomic symptoms caused by activation of the autonomic nervous system include anxiety, higher heart rate, shakiness, hunger, and sweating. The neuroglycopenic symptoms are derived from brain glucose deprivation and range from cognitive impairments, behavioral changes, psychomotor abnormalities, blurred vision, difficulty speaking and thinking, seizure to coma.[24] PRH typically occurs after meals and thus might be misdiagnosed as other postprandial hypoglycemia diseases. Additionally, the levels of blood glucose for PRH are largely controversial.[25] Therefore, there is still a lack of consensus in defining and diagnosing PRH. In the latest review summarized by Dr. Patti et al,[26] a diagnosis flowchart for PRH was recommended. They proposed that after ruling out other causes of hypoglycemia, patients should be diagnosed with PRH with the following conditions: postprandial neuroglycopenia occurring 1 to 3 h after meals with a history of bypass surgery at least 6 to 12 months before symptom onset; documented hypoglycemia (venous glucose level of 54 mg/dL) at the time of neuroglycopenic symptoms and relief of symptoms after glucose administration; and no hypoglycemia after a prolonged fasting period of at least 12 h. The oral glucose tolerance test (OGTT) is not well-tolerated for patients experiencing upper-gastrointestinal surgery, which would result in severe dumping syndrome. In contrast, solid and liquid mixed meals containing protein, carbohydrates, and fat have been used to evaluate glucose tolerance and induce hypoglycemia for the diagnosis of PRH in clinical practice and research studies. Nevertheless, there is no currently accepted standard for meal testing. Continuous glucose monitoring (CGM) has gained increasing popularity and has become a helpful and promising tool to identify patterns of glycemic excursions and diagnose PRH in patients with a history of RYGB surgery.[26]

In light of the unstandardized diagnosis of PRH, the reported prevalence of PRH is also inconsistent [Table 1]. The first report about the incidence of PRH was from a national cohort of 5040 patients undergoing gastric bypass in Sweden from 1986 to 2006. They found that incidences of hospitalization for hypoglycemia after gastric bypass surgery were significantly increased (hazard ratio, 2.7; 95% confidence interval, 1.2–6.3), although the proportion of gastric bypass patients with hypoglycemia was very low (0.2%).[27] Two subsequent studies also evaluated the prevalence of self-reported PRH. The Bariatric Outcomes Longitudinal Database study in the US reported that the incidence of PRH was 0.1% among 145,582 patients.[28] However, another study in Edinburgh showed that 34.2% of 1119 patients who underwent RYGB or vertical sleeve gastrectomy (VSG) reported postprandial symptoms potentially indicating post-surgery hypoglycemia.[29] Recently, several smaller studies used OGTT to assess the frequency of postprandial hypoglycemia in patients who underwent RYGB. Pigeyre et al showed a prevalence of 10.4% in patients with PRH 12 months after the RYGB, which was defined as 120 min plasma glucose <50 mg/dL.[30] However, Brix et al[31] reported that 32.6% of patients 2 years after RYGB developed hypoglycemia based on the same diagnosis as that used by Pigeyre et al.

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**Table 1: Summarization of the incidence of PRH in different studies.**

| References | Patient numbers | Assessing methods | Months after RYGB | Glucose standard (mg/dL) | Incidence rates (%) |
|------------|-----------------|-------------------|-------------------|--------------------------|---------------------|
| [27]       | 5040            | Hospitalization   | –                 | –                        | 0.2                 |
| [28]       | 145,582         | Self-reported     | –                 | –                        | 0.1                 |
| [29]       | 1119            | Questionnaire     | –                 | –                        | 34.2                |
| [30]       | 351             | OGTT              | 12                | <50                      | 10.4                |
| [31]       | 175             | OGTT              | 24                | <50                      | 32.6                |
| [32]       | 957             | OGTT              | 12 and 60         | <50                      | 9.1 and 7.9        |
| [33]       | 1206            | OGTT              | 12 and 60         | <60                      | 2.7 and 13.3       |
| [34]       | 40              | CGM               | 86                | <55                      | 75                  |

PRH: Post-RYGB hypoglycemia; OGTT: Oral glucose tolerance test; CGM: Continuous glucose monitoring; –: Not applicable.
Another two longitudinal studies assessed the prevalence of PRH in patients 1 and 5 years after surgery through OGTT. Raverdy et al.\(^\text{[32]}\) reported a PRH (<50 mg/dL) incidence of 9.1% and 7.9% at 1 year and 5 years following RYGB, respectively, whereas Lee et al.\(^\text{[33]}\) showed PRH (<60 mg/dL) of 2.7% and 13.3%, respectively, in a cohort of non-diabetic patients who underwent RYGB, which indicated that the incidence of PRH might be associated with the glucose and insulin levels before surgery. Additionally, CGM was also used to evaluate hypoglycemia and was performed in a total of 40 patients 86 months after RYGB. Surprisingly, the results showed that 75% of the patients developed PRH based on 5-day CGM.\(^\text{[34]}\) Overall, the prevalence of PRH is largely inconsistent given the differences in diagnostic glucose level standards, assessment strategy, individual variation in patients, sample numbers, and time course. Thus, large cohort studies with the same diagnostic standards for PRH are necessary in the future.

**Currently Possible Mechanisms Underlying PRH**

**Incretin effects**

Understanding the mechanism of PRH is important to prevent this disabling event and provide evidence and targets for the treatment of glucose abnormalities. However, the underlying mechanism of hypoglycemia after surgery is complex and incompletely elucidated.\(^\text{[19,26]}\) In light of the altered upper gastrointestinal structure and the dominant timing of hypoglycemia after RYGB, factors regulating postprandial glucose homeostasis might play essential roles, especially the gut factors. Multitudes of evidence show that food intake leads to a larger glycemic excursion with earlier and higher peaks as well as lower nadir of glucose in patients who underwent RYGB, which is caused by fast nutrient emptying from the remnant stomach pouch to intestine.\(^\text{[35,36]}\) In parallel with altered postprandial glucose pattern, the response of food-induced insulin secretion and gut hormone production are also changed.\(^\text{[36,37]}\) Inappropriate postprandial hyperinsulinemia and approximately ten-fold elevation of glucagon-like peptide 1 (GLP-1) after meal were observed in patients with PRH.\(^\text{[33]}\) GLP-1 is an insulino-metric gut peptide and contributes to meal-induced insulin secretion in patients after RYGB, which were inversely validated by decreased postprandial insulin levels in subjects post-RYGB compared with non-surgical controls after blocking GLP-1 by the GLP-1 receptor antagonist exendin 9-39.\(^\text{[36,38,39]}\) Patients with PRH had higher glucose, insulin, and GLP-1 levels but similar GLP-1 receptor levels after meals than those without hypoglycemia.\(^\text{[35,36,40]}\) GLP-1 receptor antagonist could reverse hypoglycemia along with decreased insulin secretion in PRH patients.\(^\text{[36,41]}\) However, the elevated glucose appearance after meal intake could not be inhibited by exendin 9-39, which indicated that there might be some other factors contributing to PRH other than GLP-1.\(^\text{[36]}\)

**Dysfunction of β-cells and α-cells**

In normal conditions, hypoglycemia leads to decreased insulin secretion by β-cells and increased glucagon production by α-cells. However, for patients with PRH, β-cell suppression is decreased in patients after RYGB when the glucose level is reduced during hyperinsulinemia hypoglycemic clamp than in non-surgical controls.\(^\text{[42,43]}\) Additionally, reduced insulin clearance is also observed in patients with PRH compared with non-hypoglycemia patients.\(^\text{[33]}\) Additionally, a placebo-controlled, randomized, double-blind, crossover study proposed a role for glucose-induced interleukin (IL) 1β in hypoglycemia after gastric bypass surgery, which could be improved by sodium-glucose transporter 2 inhibitors and IL-1 antagonism. Elevated IL-1β leads to an exaggerated postprandial insulin release.\(^\text{[44]}\) A previous study reported that β-cell mass also increased in patients with PRH.\(^\text{[45]}\) However, another study was designed to reduce β-cell mass by partial pancreatectomy, but it had no effects on improving hypoglycemia in patients with PRH, which indicated that β-cell mass was not the dominant contributor to hypoglycemia.\(^\text{[46]}\) In addition to β-cell function, studies also showed that α-cell function, which is characterized by glucagon secretion, was also impaired in response to PRH.\(^\text{[36,40,43,47]}\) Therefore, the dysfunction of β-cells and α-cells might play some roles in mediating PRH. However, a recent clinical study of RYGB reversal surgery in six patients with severe PRH showed that all of the subjects had improved hypoglycemia after reversal of RYGB along with diminished postprandial glucose, insulin, and GLP-1 excursions. At the same time, insulin secretion and clearance were improved. This study further indicated that the pathophysiology of PRH was not inherent to β-cell hyperplasia or hyperfunction but primarily due to altered anatomical structures and associated other changes.\(^\text{[48]}\)

**Other potential factors**

Other factors that regulate glucose homeostasis might also contribute to PRH. A recent study showed that non-insulin dependent glucose disposal (glucose effectiveness) was also significantly increased in patients with PRH.\(^\text{[49]}\) Increased adiponectin and decreased leptin might also play a role in mediating the decreased glucose levels after RYGB.\(^\text{[50]}\) The independent effects from weight loss of RYGB on energy homeostasis also included systemic repression of growth hormone receptor signaling, which might be a mechanism for PRH, but needs further exploration.\(^\text{[51]}\) However, all of the above factors cannot completely explain the incidence and development of PRH. There might be some other factors mediating this event. It is true that RYGB dramatically changes and reconstitutes the upper gastrointestinal structure, which is definitely the origin of hypoglycemia. The gut microbiome is recognized as a forgotten metabolic organ and are located in the intestine. The gut microbiome has been reported to be intimately associated with systemic metabolism, gut hormones, and bile acid (BA) metabolism. Does the gut microbiome change after RYGB? Does the intestinal microbiome also play some roles in PRH?

**The Gut Microbiota is Significantly Altered After RYGB**

The gut microbiota of humans consists of trillions of microorganisms, including bacteria, viruses, and eukaryotes. The genome of the gut microbiome is more than 100
times larger than the human genome. Bacteroides, Firmicutes, and Actinobacteria are the predominant phyla, and the major genera includes *Prevotella*, *Bacteroides*, *Clostridium*, *Faecalibacterium*, *Lactobacillus*, and *Bifidobacterium*. A neonate may procure its microbiota from the intrauterine environment, the delivery method, and breastfeeding. The gut microbiome develops as a newborn grows up according to dietary and environmental factors such as drug intake, infections, and lifestyle patterns. Although the gut microbiome appears to be stable during adulthood, some factors, such as host’s diet, lifestyle, and antibiotic use, can still alter its composition. It has been well established that the gut microbiome plays physiological roles in absorption of fats and fat-soluble vitamins in the host diet, digestion of complex carbohydrates and plant polysaccharides, and regulation of BA-related metabolism. Additionally, gut microbiota also helps to maintain the intestinal epithelial barrier, regulate intestinal permeability, and regulate innate and adaptive immunity. A balanced and healthy gut microbiota is necessary for the metabolic health.

Numerous experimental and clinical studies have reported changes in gut microbiota diversity and composition after RYGB, a topic which has been reviewed before. In this review, we briefly summarize recently published reports that detected alterations of gut microbiota after RYGB. The first study implemented by Dr. Zhang et al discovered an increase in Gammaproteobacteria and a decrease in Firmicutes in patients after RYGB compared with normal-weight controls and obese patients. Several subsequent human studies and experimental animal models validated and showed similar post-RYGB changes in the gut microbiome. In addition to the alterations in microbial components, an increase in the gut microbial richness after RYGB was also uncovered in a clinical trial. For the starting point and duration of the altered intestinal microbiome, a clinical trial detected and followed the alterations in gut microbiota in morbidity obese patients after RYGB. They showed that increased microbial diversity and altered composition could be observed within 3 months of RYGB and more than half of the changed bacteria were stable in relative abundance 1 year later. Another human study also demonstrated that changes in the gut microbiota occur within 3 months and are stable even 9 years after RYGB. In summary, microbial remodeling after RYGB does happen, and it mainly includes increases in gut microbiota richness, reduction in the Firmicutes, and increase in Gammaproteobacteria/Proteobacteria. However, discrepancy also exists among the published studies. Some studies reported decreased Bacteroidetes at the phylum level after RYGB, while others showed the opposite changes. The inconsistency among these studies might be attributed to differences in obesity severity, analysis methods, and timepoints studied after surgery. It should be mentioned that the sample sizes are small, with less than ten cases in most studies. More studies with larger sample sizes would be helpful to confirm the alterations in gut microbiota after RYGB.

Multiple factors may contribute to the changes in gut microbiota after RYGB. The RYGB procedure leads to restriction of the amount and types of food, nutrient malabsorption, and changes in acid exposure to the gastric remnant and proximal small intestine, all of which might be expected to alter the gut microbiota. By comparing changes in microbial composition at different timepoints after RYGB, Li et al demonstrated that the surgical effect on gut microbiota was at least partially independent of food intake. Importantly, studies have suggested that BMI before and weight loss after RYGB are unlikely to have great impact on the gut microbial changes. Many studies reported that intestinal rearrangement after RYGB is a vital factor for the gut microbial changes. Nevertheless, proton pump inhibitor therapy during the first 3 months after surgery and antibiotics used during the peri-operative period can also influence the gut microbiota, which clinicians should be aware of. Does the changed gut microbiota have some effects on metabolic alterations after RYGB?

Altered gut microbiota could be involved in the regulation of glucose metabolism in patients after RYGB. Studies have reported a possible association between RYGB-induced microbial changes and human metabolic indices in plasma. Murphy et al found that there were no phyla level changes in patients with persisting diabetes 1 year after RYGB; in those who achieved diabetes remission after RYGB, there were three significant changes at the phyla level (increases in Firmicutes and Actinobacteria, decrease in Bacteroidetes) and 13 significant changes at the species level. In another study, significant correlations were found between plasma glucose with *Faecalibacterium prausnitzii*, as well as HbA1c with *Trichothecium roseum* and *Veillonella parva*. In all, a clear correlation exists between microbial composition and gene function with metabolic parameters. Furthermore, Arora et al transferred microbiota from sham or RYGB-treated *fa/fa* rats to germ-free mice and found that postprandial glucose levels were lower in mice that received the cecal microbiota from RYGB rats versus that from sham-operated rats, which indicated that changes in the gut microbiome after RYGB could be a mediator for its glucose reduction effect. Through transplantation of the RYGB-associated gut microbiota into germ-free mice, Liou et al showed that the altered gut microbiota was sufficient to trigger decreases of host weight and adiposity. Similarly, Tremaroli et al demonstrated that surgically altered microbiota promoted reduction of fat deposition in recipient mice by colonizing germ-free mice with stool from the patients. Therefore, microbial changes might also be a potential mechanism in PRH. What factors mediate these effects?

**Potential Factors Mediating the Effects of the Intestinal Microbiome on PRH**

Evidence has shown that the gut microbiome plays important roles in glucose metabolism. Many studies have reported significant differences in intestinal microbiota between metabolic disorders and healthy individuals. The role of the microbiome in the progression of T2DM and metabolic syndrome is becoming clear and acknowledged. Conversely, probiotics have been shown to affect gut microbiota and improve glucose homeostasis. How does the gut microbiota influence...
metabolism? Studies have indicated that the microbiota modulates inflammation, interacts with dietary constituents, regulates the circadian clock, and affects gut permeability, insulin sensitivity, and even overall energy homeostasis. For example, microbial products such as lipopolysaccharide can drive low-grade inflammation, which has been recognized as a potential cause of insulin resistance, and the metabolic benefit of fiber is at least partially mediated by the gut microbiota. Furthermore, gut hormones produced by the gut and regulated by the intestinal microbiota are important mediators in the crosstalk between the gut and other metabolic organs.

In this review, we mainly review the role of BA metabolism and microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), in the metabolic adaptation and changes after gastric bypass surgery.

**BAs might be a link between the gut microbiota and metabolic changes after RYGB**

BAs, which are water-soluble, cholesterol-derived amphipathic molecules of saturated hydroxylated C-24 sterols produced by human hepatocytes, constitute approximately 50% of the organic component of bile. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the main primary BAs synthesized in humans. They are conjugated to either taurine or glycine. The primary BAs are secreted into the bile and stored in the gallbladder until secretion in the duodenum. In the intestine, they are deconjugated and transformed into “secondary BAs” by the gut microbiota. Most BAs are recaptured in the ileum and return to the liver via the portal vein, in a process named enterohepatic recirculation. BAs regulate their own synthesis and transport via the nuclear farnesoid X receptor (FXR) in the intestine, through which they regulate glucose metabolism as a hormone. Evidence has shown that BAs are involved in the regulation of glucose metabolism by controlling insulin signaling, hepatic glucose production, glucose utilization, and the secretion of GLP-1.

Alterations in gut microbial communities, which play a crucial role in the transformation of primary BAs to secondary BAs, result in changes in BA metabolism, and thus may influence glucose metabolism. Although studies on relationships between circulating BA concentrations and changes in gut microbiota after RYGB are scarce, a relationship has been reported between increased circulating BA concentrations and changes in gut microbial composition after VSG. In RYGB, the shortened route of enterohepatic recirculation expedites the contact of luminal BAs with the ileum where gut microbiota regulates the transformation of secondary BAs, leading to earlier and more active BA reabsorption. Clinical studies have indicated that circulating BA concentrations, especially for secondary BAs, significantly increase following RYGB, while a simultaneous decrease in blood glucose levels has frequently been observed. BAs bind to FXR and induce synthesis of fibroblast growth factor 19 (FGF-19) in humans, which further circulates into the liver to inhibit hepatic BA production through decreasing 7α-hydroxylase. In the liver, FGF-19 activates glycogen synthesis and inhibits gluconeogenesis, which subsequently leads to a decrease in circulating glucose concentrations. Activation of FXR in the muscles and adipose tissue also leads to improvements in insulin sensitivity, contributing to reduced plasma glucose. In patients after RYGB, coordinated increases in BAs and FGF-19 and decreases in blood glucose levels have been reported. At the same time, increased GLP-1 levels and insulin production were observed in patients who underwent RYGB. Subsequently, Sachdev et al also showed that RYGB elevated the concentrations of BAs and FGF-19 in patients with T2DM compared with those with intensive medical management, and this was negatively associated with their HbA1c levels. Similarly, patients with diabetes resolution after RYGB had larger increases in serum levels of FGF-19 and BAs (CA and deoxycholic acids) than patients without diabetes remission. CDCA intake stimulated GLP-1 secretion in patients after RYGB through activation of G-protein-coupled bile acid receptor (TGR5). Recent-ly, a clinical study performed proteomic analysis of blood samples in patients with PRH and asymptomatic post-RYGB to explore the mechanisms contributing to glucose reduction after RYGB. They showed that FGF-19 levels were 2.4-fold higher in patients with PRH compared with asymptomatic controls. However, a clinical study showed that the total BA and FGF19 levels cannot explain the acute decreases in blood glucose, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol or increases in GLP-1 secretion 1 week after RYG.

Therefore, gut microbiota regulation of BA metabolism might be an important mechanism for PRH (summarized in Table 2). However, this cannot be concluded with the few studies on relationships between BAs and changes in gut microbiota after RYGB and the complicated interaction between gut microbiota and BAs. More studies are required to clarify how gut microbiota influence BAs and contribute to the hypoglycemia after RYGB.

**SCFAs might be another mediator**

SCFAs, which mainly include acetate, propionate, and butyrate, are gut microbiota-derived metabolites mainly produced in the colon by fermentation of non-digestible polysaccharides. They act on G-protein-coupled receptors (GPCRs) such as free fatty acid 2 (FFA2) and FFA3, which are widely expressed in many tissues, to regulate host energy expenditure and appetite and to inhibit histone deacetylation. It has been reported that SCFAs play an important role in glucose metabolism. Both FFA2 and FFA3 are normally expressed in pancreatic cells, and studies have shown activation of these GPCRs may result in insulin secretion. Furthermore, butyrate increases the production of GLP-1 and peptide YY, and it is also involved in reducing appetite, activating brown adipose tissue, and diminishing diet-induced obesity. In T2DM patients, butyrate levels decreased while other SCFAs increased, and a deficiency in overall SCFAs production was also reported. Conversely, SCFAs supplementation is associated with beneficial effects in T2DM.

It is a reasonable hypothesis that gut microbiome remodeling results in changes in SCFAs, which might mediate hypoglycemia in post-RYG patients. The effect of RYG on increasing energy expenditure is well-established, and it
may contribute to hypoglycemia after RYGB.\[95,96\] As SCFAs are involved in host energy expenditure, this effect could be due to altered microbial signaling that increases host energy expenditure. Liou et al.\[57\] reported an increased resting energy expenditure along with increased concentration of the SCFA propionate in the cecum in RYGB microbiota-recipient mice. Similar results were found by Tremaroli et al.\[55\] who colonized germ-free mice with the fecal microbiota collected from humans 9 years post-RYGB. Therefore, SCFA changes resulting from altered gut microbiota after RYGB may mediate host energy expenditure and then contribute to hypoglycemia. Whether other mechanisms are involved in SCFA regulation of glucose metabolism in PRH needs to be further explored.

Overall, the composition and diversity of the intestinal microbiota are dramatically reshaped after RYGB, and this leads to changes in BA metabolism and metabolites, especially SCFAs. BAs and the associated FGF-19 pathway, in which intestinal bacteria is involved, have been shown to play an important role in mediating the glucose levels and incretin effects after RYGB. Additionally, altered SCFAs also influence energy metabolism in patients who underwent RYGB. However, studies comparing the gut microbiota and associated BA and SCFAs between patients with hypoglycemia and non-hypoglycemia after RYGB are limited. Future studies are required to further decipher their roles and specific mechanisms in mediating glucose-lowering effects and to validate their influence on the PRH.

**Conclusions**

Overall, there are no other strategies to sustain weight loss and yield remission of metabolic disorders for obese individuals other than bariatric surgery. RYGB is one of the most popular bariatric procedures. However, patients who undergo RYGB may develop hypoglycemia, which is a disabling and challenging complication. To date, the pathogenesis of PRH is incompletely understood. Incretin effects, dysfunction of β-cells and α-cells, non-insulin dependent glucose disposal, adipokines, growth hormone receptor signaling, and the gut microbiota, as summarized in this review, might be potential mediators of PRH [Figure 1]. Dietary modifications, including carbohydrate restriction and avoidance of high glycemic index foods,\[87-100\] and medical/surgical intervention are currently used but are limited in ability to treat and prevent this hypoglycemia.\[48,101-103\] Therefore, clarifying the underlying mechanism linking hypoglycemia to RYGB and developing promising measures to prevent and treat PRH is urgently needed. Future studies are needed to further elucidate the pathophysiology of this condition as well as the diagnostic standard and treatment approaches,

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**Table 2: The role of BAs and FGF-19 in mediating the effects of metabolic changes after RYGB.**

| Subjects | Comparisons | BAs and FGF-19 | Metabolism | References |
|----------|-------------|----------------|------------|------------|
| Obese patients after RYGB | After RYGB vs. BMI-matched unoperated control | BAs ↑ | GLP-1 and PYY ↑ | \[76\] |
| Obese patients (33.8 months after surgery) | RYGB vs. weight-matched unoperated controls | Postprandial total BAs and FGF-19 ↑ | TG ↓ apoB48 ↑ | \[77\] |
| RYGB-operated subjects (1 year after) | Diabetes vs. without diabetes; Diabetes remission vs. non-remission | FGF-19 and BAs ↓; FGF-19 and BAs ↑ | CYP7A1 gene ↑ | \[78\] |
| Obese patients with T2DM | 1 year after vs. before | Secondary, unconjugated BAs ↑ FGF-19 ↑ | HbA1c ↓ Weight loss | \[79\] |
| Morbidly obese patients | 3 months after vs. before | Bile salts and FGF-19, FGF-21 ↑ | Improved insulin resistance and hepatic fat ↓ | \[80\] |
| Obese subjects | 6-week after vs. before | FGF-19 and total BAs ↑ | GLP-1 and PYY ↑ | \[83\] |
| Obese women with T2DM | 2 year after vs. before | FGF-19 and BAs ↑ | Weight ↓ GLP-1 and PYY ↑ HbA1c ↓ | \[84\] |
| Patients with uncontrolled T2DM | 1 year after vs. before | FGF19 and BAs ↑ | – | \[85\] |
| RYGB-operated participants | Chenodeoxycholic acid vs. placebo | Total BA ↑ FGF-19 ↑ | GLP-1, PYY, C-peptide and glucagon ↑ | \[86\] |
| Patients after RYGB | Hypoglycemia vs. asymptomatic | FGF-19 ↑ | – | \[87\] |
| T2DM subjects | 1 week after vs. before | No changes in fasting total BAs and FGF19 | Glucose, LDL-C and HDL-C ↓ GLP-1 ↑ | \[88\] |

**Notes:**
- **RYGB**: Laparoscopic Roux-en-Y gastric bypass;
- **T2DM**: Type 2 diabetes mellitus;
- **BMI**: Body mass index;
- **BAs**: Bile acids;
- **FGF-19**: Fibroblast growth factor 19;
- **↓**: Decrease;
- **↑**: Increase;
- **CYP7A1**: Cytochrome P450 family 7 subfamily A member 1;
- **HbA1c**: Hemoglobin A1c;
- **GLP-1**: Glucagon-like peptide 1;
- **PYY**: Peptide YY;
- **TG**: Triglyceride;
- **apoB48**: Apolipoprotein B48;
- **LDL-C**: Low-density lipoprotein cholesterol;
- **HDL-C**: High-density lipoprotein cholesterol.
which could target the gut microbiome and associated factors to develop novel therapeutics for PRH. Furthermore, this could yield significant insights into the intestinal regulation of glucose metabolic homeostasis and provide novel clues on how to improve hyperglycemia.

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**Conflicts of interest**

None.

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