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Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery

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Abstract

Bariatric and metabolic surgery (BMS) is the most effective treatment for obesity, type 2 diabetes (T2D) and comorbidities, including nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). The beneficial effects of BMS are beyond the primary goal of gastric restriction and nutrients malabsorption. Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are the two most commonly performed procedures of BMS. Both surgeries lead to physiological changes in gastrointestinal tract; subsequently alter bile acids pool and composition, gut microbial activities, gut hormones and circulating exosome; and ultimately contribute to the improved glycemic control, insulin sensitivity, lipid metabolism, energy expenditure, as well as weight loss. The mechanisms underlying the benefits of BMS likely involve the bile acids signaling pathway mediated mainly by nuclear farnesoid X receptor (FXR) and the membrane Takeda G protein-coupled receptor (TGR5), bile acids-gut microbiota interaction, and exosomes. In this review, we focus on recent advances in potential mechanisms and aim to learn novel insights into the molecular mechanisms underlying metabolic disorders.

Abstract

FXR and TGR5 differentially contribute to the metabolic improvement associated with RYGB and VSG.

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Keywords

Bariatric and metabolic surgery; bile acids; FXR; TGR5; NAFLD; T2D

1. Introduction

The global prevalence of obesity (Body mass index, BMI ≥30 kg/m^2) was estimated to be 13% of adult population [1]. In the United States, 39.6% of adults were obese according to NHANES data from 2015–2016 [2]. The epidemic of obesity has led to a parallel increase in the prevalence of type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) [3, 4]. NAFLD is present in up to 75% of patients with overweight and in 90–95% of patients with grade 3 obesity [5]. Bariatric and metabolic surgery (BMS) has proven to be an effective and durable therapy for grade 3 obesity (BMI ≥40 kg/m^2) as well as for patients with BMIs between 35–39.9 kg/m^2 with poor glycemic control. The criteria for surgery have been expanded to include some patients with a BMI ≤ 35 kg/m^2 [6, 7].

Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are the two most commonly performed procedures in BMS, and they comprise 76% of currently performed procedures [8]. Work from a recent study involving 1,156 patients with grade 3 obesity showed that total body weight loss achieved by RYGB was 35%, 28% and 26.9% at 2, 6 and 12 years post-procedure, respectively. Moreover, T2D was resolved in 75%, 62% and 51% of patients at 2, 6 and 12 years, respectively [7]. In addition, a recent meta-analysis demonstrated the efficacy of BMS in the treatment of NAFLD, as shown by a biopsy-confirmed resolution of steatosis, inflammation, ballooning degeneration, and fibrosis in 66%, 50%, 76%, and 40% of patients, respectively [9]. Moreover, both RYGB and VSG have similar effects on the attenuation of NAFLD regardless the potential different mechanisms [10, 11]. Importantly, BMS also resulted in new or worsened NAFLD in 12% of patients [9]. Currently, BMS is not recommended by American Association for the Study of Liver Diseases (AASLD) to specifically treat nonalcoholic steatohepatitis (NASH) due to the safety issue [12]; but it may be considered an option for obese patients (BMI ≥35 kg/m^2) with one or more severe obesity-related complications (ORCs) remediable by weight loss, including NAFLD and NASH [8, 12].

Nonetheless, the mechanisms underlying the benefits of BMS are of great importance for understanding the pathogenesis of metabolic diseases. Although the primary goal of BMS was designed for gastric restriction and malabsorption to produce weight loss, a growing body of evidence indicates that the beneficial effects of BMS (improvement of hyperglycemia, insulin sensitivity, and hyperlipidemia as well as steatosis) are beyond weight loss [13–15]. Thus, understanding the underlying mechanisms is of significant importance. In this review, we focus on the recent advances in BMS, including altered physiology, mechanistic studies involving bile acid and bile acid receptors, gut microbiota, gut hormones, and exosome.

2. Physiology

VSG is now the most commonly performed procedure of BMS, and it reduces gastric volume by approximately 70–80% through removal of a large portion of stomach along the greater curvature (Figure 1) [16, 17]. By doing so, VSG removes ghrelin-producing cells in the stomach resulting in decreased circulating ghrelin, accelerated gastric emptying, and increased secretion of the intestinal hormones, glucagon-like polypeptide 1 (GLP-1) and peptide YY (PYY) [18]. A recent study compared several procedures with different gastric volume reductions with standard VSG in rats. They found that gastric volume was negatively correlated to gastric emptying rate, glucose, and GLP-1 response. Therefore, significant gastric volume reduction is required to achieve the goal of metabolic improvement [19].

RYGB is the combination of gastric reduction with intestinal rearrangement, including generation of a small gastric pouch and bypass of the stomach and upper gastrointestinal tract, leading to accelerated nutrients flow to the middle jejunum (Figure 2) [16, 17]. While both RYGB and VSG lead to metabolic improvement, they change gut physiology in different ways. A recent clinical trial showed that RYGB and VSG differentially altered nutrient absorption and gut hormone secretion after 12 months. RYGB was associated with accelerated postprandial absorption of glucose and amino acids compared to controls, as shown by stable isotope tracers. However, altered amino acid absorption was not observed in patients after VSG. Moreover, gut hormones secretion rates, such as GLP-1, PYY and cholecystokinin (CCK), were enhanced after RYGB compared to VSG, highlighting the potentially different mechanisms underlying the metabolic benefits of these two procedures [20].

3. Bile acid and bile acid receptors

Increased systemic bile acid levels and altered bile acid composition were observed after both RYGB and VSG, particularly after RYGB [21, 22]. In addition to the role as a surfactant, bile acids act as signaling molecules for a number of nuclear receptors and plasma membrane receptors, including farnesoid X receptor (FXR), pregnane X receptor (PXR), constitutive androstane receptor (CAR), vitamin D receptor (VDR) and the membrane Takeda G protein-coupled receptor (TGR5, also known as GPBAR1) [23]. Among them, FXR and TGR5 are the most studied in BMS research. Ryan et al. found that VSG-induced weight loss and improvement of glucose tolerance were significantly blunted or abolished in *Fxr* knockout mice compared to wild type mice fed with high-fat diet, suggesting that FXR plays an essential role in the metabolic benefits of VSG [24]. Of note, the metabolic effects of FXR signaling are diet- [25, 26] and tissue-dependent [27–29]. While *Fxr* null mice develop a deleterious metabolic phenotype on chow diet [25], they display improved glucose tolerance when fed with a high-fat diet [26]. Although global activation of FXR is beneficial in improving metabolic disorders [27, 30–32], the role of intestinal FXR signaling is mixed [28, 29, 33]. To understand intestinal FXR signaling in the benefits of BMS, intestine-specific *Fxr* null mice were fed with a high-fat diet for twelve weeks before and after bile diversion surgery, which diverts bile flow from the gallbladder to the ileum without gastric reduction and had similar effects as RYGB. As a result, bile diversion-induced weight loss and glucose tolerance improvement were abolished in

intestine-specific *Fxr* null mice fed with a high-fat diet, but not in *Tgr*5 knockout mice fed the same diet [34], suggesting that the beneficial effects of BMS are mediated by intestinal FXR signaling. However, TGR5 is required for the metabolic improvement and GLP-1 secretion produced by VSG [35], indicating distinct mechanisms might be involved in RYGB and VSG. This concept was supported by clinical studies [20, 36]. In addition, the glucoregulatory effects of bile diversion surgery were abrogated by either GLP-1 receptor (GLP-1R) antagonist or by the bile acids sequestrant, cholestyramine, as well as in *Glp-1r* knockout mice [34], indicating the essential role of GLP-1 in glucose homeostasis. To determine the role of FXR and TGR5 in GLP-1 secretion, mice were treated with a FXR agonist (obeticholic acid, OCA), a TGR5 agonist (INT-777), or a dual agonist of FXR and TGR5 (INT-767). Glucose-induced GLP-1 secretion was markedly increased by all three agonists, with the dual agonist being the strongest stimulator. Conversely, serum GLP-1 levels were significantly reduced in both *Fxr* and *Tgr5* knockout mice. Moreover, INT-767 stimulated GLP-1 secretion was observed in *Tgr5* knockout mice, but not in the *Fxr* knockout mice, suggesting that FXR is required for the GLP-1 secretion. Further, a FXR-response element was identified on the *Tgr5* gene promoter, suggesting FXR is upstream of TGR5 [37]. In another study, the intestine-restricted FXR agonist, fexaramine (FEX), markedly increased glucose-induced GLP-1 secretion in wild type mice, but not in *Fxr* or *Tgr5* knockout mice, suggesting both FXR and TGR5 are required in bile acid-stimulated GLP-1 secretion [38]. Collectively, intestinal FXR and GLP-1 signaling pathways are key players in the beneficial role of BMS.

TGR5 is a transmembrane G-protein coupled bile acid receptor [39, 40]. Recent studies revealed that TGR5 is required for the beneficial role of VSG in the improvement of glucose control, weight loss, hepatic steatosis, and energy expenditure in a diet-induced obesity mouse model [35, 41]. Investigators found the mRNA expression of *Tgr5* and its target gene, *proglucagon,* in the ileum were significantly upregulated after VSG in wild type mice, but not in *Tgr5* knockout mice, indicating activated TGR5 signaling by VSG. They further demonstrated that glucose clearance was significantly enhanced after VSG compared to sham-operation in wild type mice in response to an oral glucose load, and this was associated with increased GLP-1 and insulin secretion. However, these effects were blunted in *Tgr5* knockout mice, suggesting that TGR5 is required in the regulation of GLP-1 and insulin secretion following VSG [35]. Primary bile acids are synthesized in the hepatocytes and secreted to the intestine where they are deconjugated to secondary bile acids by the gut microbiota. Therefore, bile acids can modulate the abundance and the composition of gut microbiota. Conversely, gut microbiota can modulate bile acids composition via microbial enzyme activities [42]. However, the relative abundance of gut microbiota did not differ between wild type and *Tgr5* KO mice after VSG; therefore, it is questionable as to whether VSG-induced bile acids alterations were attributable to gut microbiota [35, 41]. How bile acid levels and composition are altered by BMS remains elusive. While primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are FXR agonists [42], tauro-β muricholic acid (TβMCA) (in mice) is a FXR antagonist [43]. Secondary bile acids, lithocholic acid (LCA) and deoxycholic acid (DCA), are potent ligands for TGR5 [42]. Research in mice showed that serum total and unconjugated, as well as taurine-conjugated, bile acids were increased by VSG, whereas fecal taurine-conjugated bile acids, including

TβMCA, were decreased in a high-fat diet induced obesity mouse model [35]. However, it is unclear whether and how decreased fecal TβMCA and/or altered bile acids composition contribute to the metabolic improvement by BMS.

Although both FXR and TGR5 are essential in the beneficial effects of BMS, their roles in the regulation of lipid and glucose metabolism are divergent. To understand the differential roles of FXR and TGR5 in the regulation of lipid and glucose homeostasis, bile acid sequestrants were administered to either *Fxr* or *Tgr5* null mice. The results revealed that the beneficial role of bile acid sequestrants on cholesterol and triglyceride metabolism is mediated by FXR [44, 45], whereas the improvement on glycemia control is dependent on TGR5/GLP-1 [45]. An FXR mutation led to improved glucose tolerance and adipose tissue insulin sensitivity, but aggravated hepatic steatosis, and had no effect on hepatic insulin sensitivity in either genetic or diet-induced murine model of obesity [26]. Conversely, CA, a natural ligand of FXR, protected against hepatic steatosis and attenuated hypertriglyceridemia in KK-Ay mice, characterized with hyperglycemia, hyperlipidemia and hepatic steatosis [46]. In support of this concept, a FXR agonist, OCA, showed beneficial effects on NASH patients [30, 32, 47].

Several studies examined the role of TGR5 on the development of diet-induced hepatic steatosis. The results from different groups uniformly showed that *Tgr5* knockout mice developed comparable hepatic steatosis compared to wild type mice in response to a high-fat or a high-fat/high-fructose diet [35, 41, 48], suggesting TGR5 is not required in diet-induced hepatic steatosis. However, debate exists regarding the role of TGR5 in mediating the benefits of VSG on hepatic steatosis. While Ding et al.'s study showed that TGR5 is required for the beneficial role of VSG in reducing liver fat accumulation [35], McGavigan et al.'s results did not [41]. The discrepancy likely relates to the age of mice, dietary fat proportion and the duration of the experiment [35, 41]. TGR5 is expressed in a variety of tissues and cells, including liver sinusoidal endothelial cells [49], adipose tissue, skeletal muscle [50], ileum and colon enteroendocrine cells [40]. Future studies with tissue- or cell-specific *Tgr5* knockout animals will lead to a better understanding of the role of TGR5 in metabolic diseases.

4. Gut Hormones

Increased gut hormone secretion after BMS contributes to appetite and glycemic control, including proximal intestine derived hormones, such as CCK and glucose-dependent insulinotropic polypeptide (GIP), and distal intestinal hormones, such as GLP-1, PYY and neurotensin (NT). Yet, the specific role of a particular macronutrient in stimulating gut hormones secretion after BMS is unclear. A recent study showed that distal, but not proximal gut hormones, were significantly increased in RYGB patients compared to controls in response to dietary long-chain fatty acids (LCFAs) [51].

Fibroblast growth factor 19 (FGF19) has been proposed as a potential therapeutic target from the beneficial effects of BMS. FGF19 (in humans and its mouse ortholog FGF15) is a target gene of FXR. Once FXR is activated by bile acids in the ileum, FGF15/19 is released from the enterocytes of the small intestine and enters the liver via the portal vein, where

FGF15/19 binds to FGF receptor 4 (FGFR4), and consequently suppresses cholesterol 7α-hydroxylase (CYP7A1) expression and inhibits bile acids synthesis. Not only does FGF15/19 promote glycogen synthesis and reduce gluconeogenesis, it also decreases hepatic triglycerides. While circulating FGF19 was decreased in NAFLD patients, it was increased after BMS, indicating that FGF19 may be a mediator for the beneficial effects of BMS [52].

5. Gut Microbiota

Gut microbiota dysbiosis is increasingly recognized as an important mechanism leading to obesity and the metabolic syndrome. BMS-induced weight loss is associated with alterations of the gut microbiome characterized by increased microbial gene richness (MGR) [53], Gammaproteobacteria [54–56], *Akkermansia muciniphila* [55, 57, 58] and a decreased ratio of Firmicutes to Bacteroidetes [54, 59, 60]. However, the alterations of the gut microbiota are likely independent of calorie restriction [55, 61]. Fecal microbiota transplantation (FMT) from RYGB-treated mice to non-operated germ-free mice resulted in weight loss and reduced fat mass in recipient mice compared to the sham-operated recipient mice [55], suggesting that the beneficial role of BMS in improving metabolic diseases is mediated, at least partially, by gut microbiota. Consistent with this, germ-free mice that received fecal microbiota from patients 9-years post RYGB or VSG exhibited significantly less body fat accumulation (43% and 26%) in 2 weeks compared to mice that received microbiota from severely obese patients. Moreover, mice colonized with RYGB microbiota gained more lean body mass, while the body weight gain and food intake did not differ compared to controls. In addition, mice with RYGB microbiota displayed a lower respiratory quotient (RQ, ratio of CO_2 produced and O_2 consumed), suggesting increased lipid oxidation and decreased carbohydrate oxidation [62]. This study further validated that the long-term beneficial effects of BMS are through functional gut microbiota. However, only modest effects were achieved in the patients with the metabolic syndrome who received gut microbiota from donor-RYGB patients compared to those who received gut microbiota from metabolic syndrome donors. The FMT recipients of RYGB gut microbiota exhibited a trend toward faster intestinal transit time, altered fecal bile acids profile and decreased adipose tissue C-C motif chemokine ligand 2 (CCL2) mRNA as well as decreased plasma CCL2 levels. The discrepancy between human and mice studies is likely due to the greater variation of external environment and individual gut microbiota composition in humans [63]. Although the role of gut microbiota in the beneficial effects of BMS has been established, the underlying mechanisms remain largely unknown. Despite significantly improved metabolic effects and weight loss, MGR was only restored in a small portion of patients undergoing BMS and remained low [53]. Moreover, Proteobacteria are considered potentially pro-inflammatory bacteria [64] and a hallmark of gut microbiota dysbiosis [65], which is a signature of gut microbiota alteration after BMS. Therefore, future research is necessary to understand how the altered gut microbial activity following BMS improves host metabolism.

6. Exosomes

Adipose tissue is a major source of circulating exosome microRNAs (miRNAs). Adipose tissue-derived circulating exosome miRNAs regulate gene expression in the liver [66]. It has been demonstrated that adipose tissue-derived exosomes activate peripheral monocytes and

subsequently release inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which contribute to the pathogenesis of insulin resistance [67]. Therefore, it is plausible that adipose tissue-derived exosomes are a potential mediator of beneficial effects after BMS. In fact, a growing body of evidence demonstrated that distinct alterations of circulating miRNAs occurred after BMS [68–71]. A recent study showed that BMS-responsive miRNAs were found from circulating adipocyte-derived exosomes identified by fatty acid binding protein 4 (FABP4), a specific marker for adipocytes. Further, they showed that the insulin signaling pathway was a target of 10 miRNAs and that the changes in levels of these miRNAs correlated to the improved insulin signaling after BMS [72]. In line with this, markedly reduced serum C-reactive protein (CRP), TNF-α and IL-6 were observed after BMS, suggesting improved systemic inflammation [57, 73]. However, the link between the altered miRNA profiles and improved systemic inflammation as well as other metabolic phenotypes remains to be established concerning the beneficial effects of BMS. Future studies identifying specific circulating miRNAs as biomarkers for the prediction of successful BMS would be of great interest.

7. Glucose Metabolism

The changed anatomy of GI tract due to RYGB leads the undigested nutrients going directly to the Roux limb (Figure 2), which reprograms intestinal glucose metabolism associated with the hypertrophy of Roux limb and renders the intestine as a major site for glucose disposal, consequently leading to improved glucose tolerance. This effect is mediated by the upregulation of glucose transporter-1 which leads to increased glucose uptake from circulation and concomitant increased glycolysis. Not only were these findings demonstrated in a rat model [74], but they were also verified in human studies [36]. Paradoxically, Baud's study showed that glucose uptake from the alimentary Roux limb was decreased after RYGB in minipigs, owing to deprived bile in the Roux limb. Addition of bile to the Roux limb restored glucose uptake. Mechanically, bile diversion results in the concomitant diversion of salt which contributes a functional defect in sodium glucose cotransporter 1 (SGLT1), consequently reducing glucose absorption [75]. Although both RYGB and VSG improve glycemia, the mechanisms underlying the two approaches are different. While RYGB increases intestinal glucose disposal, VSG decreases alimentary glucose absorption without intestinal hypertrophy, and is associated with increased density of GLP-1 secreting cells [36]. A human study showed that gastric bypass surgery was superior to VSG for the remission of type 2 diabetes [76]. To understand the mechanisms underlying VSG-induced improvement in glucose homeostasis, Harris et al. evaluated tissue-specific glucose uptake using 18-FDG PET/CT in a mouse model. They found VSG resulted in a significant increase in glucose uptake by visceral adipose tissue, which was associated with the upregulation of transcripts involved in energy metabolism, suggesting increased glucose utilization in adipose tissue after VSG [77]. However, these results were from a non-obese mouse model and need to be validated in obese mouse models as well as in humans.

8. Lipid Metabolism

Dyslipidemia is one of manifestations associated with obesity and the metabolic syndrome as shown by elevated blood total cholesterol, low-density lipoprotein (LDL), triglycerides

and decreased high-density lipoprotein (HDL), all of which were reversed by BMS [70, 78–80]. However, the underlying mechanisms are not clear. A recent study showed that intestinal LDL receptor (LDLR) was significantly upregulated at both mRNA and protein levels in jejunal biopsies from patients after RYGB. This was accompanied by the upregulation of Niemann-Pick C1-like protein 1 (NPC1L1), acetyl-coenzyme A acetyltransferase 2 (ACAT2), sterol regulatory element-binding protein 2 (SREBP2), and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), implicating the enhanced intestinal cholesterol absorption, uptake, and synthesis. Consistent with this, mice with intestine-specific overexpression of LDLR displayed significantly decreased circulating total cholesterol and LDL cholesterol levels, as well as body weight, either on regular chow diet or high-fat, high-cholesterol (HFHC) diets. Moreover, increased fecal cholesterol as well as total lipids levels were observed when intestine-specific *Ldlr* overexpression mice were fed with HFHC diet, highlighting that the reprogrammed intestinal cholesterol metabolism might produce at least some of the beneficial effects of RYGB [81].

Conclusions

While RYGB and VSG are effective in the improvement of metabolic phenotypes, they likely involve different mechanisms. Tissue-specific roles of FXR and TGR5 in the mediation of the metabolic benefits of RYGB and VSG, as well as in the metabolic disorders, remain elusive. The benefits of BMS are transmissible through FMT in rodents. However, again, the underlying mechanisms are largely unknown. Circulating exosomes and miRNA profiles were substantially altered by BMS. The specific roles of miRNAs on the regulation of gene expression involved in metabolic signaling pathways are not clear. Future studies are warranted to decipher how BMS confers its benefits.

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Abbreviations:

BMS	bariatric and metabolic surgery
RYGB	Roux-en-Y gastric bypass
VSG	vertical sleeve gastrectomy
FXR	farnesoid X receptor
TGR5	Takeda G protein-coupled receptor

NAFLD	nonalcoholic fatty liver disease
BMI	body mass index
T2DM	type 2 diabetes
NASH	nonalcoholic steatohepatitis
AASLD	American Association for the Study of Liver Diseases
ORCs	obesity-related complications
GLP-1	glucagon-like polypeptide 1
PYY	peptide YY
PXR	pregnane X receptor
CAR	constitutive androstane receptor
VDR	vitamin D receptor
GPBAR1	G protein-coupled bile acid receptor 1
GLP-1R	GLP-1 receptor
OCA	obeticholic acid
FEX	fexaramine
CA	cholic acid
CDCA	chenodeoxycholic acid
TβMCA	tauro-β muricholic acid
LCA	lithocholic acid
DCA	deoxycholic acid
GIP	glucose-dependent insulinotropic polypeptide
NT	neurotensin
LCFAs	long-chain fatty acids
FGF19	fibroblast growth factor 19
FGFR4	FGF receptor 4
CYP7A1	cholesterol 7α-hydroxylase
MGR	microbial gene richness
FMT	fecal microbiota transplantation
CCL2	C-C motif chemokine ligand 2

miRNAs	microRNAs
TNF-α	tumor necrosis factor-α
IL-6	interleukin-6
FABP4	fatty acid binding protein 4
CRP	C-reactive protein
SGLT1	sodium glucose cotransporter 1
18FDG	^{18}F-fluorodeoxyglucose
PET	positron emission tomography
CT	computed tomography
LDL	low-density lipoprotein
HDL	high-density lipoprotein
LDLR	LDL receptor
NPC1L1	Niemann-Pick C1-like protein 1
ACAT2	acetyl-coenzyme A acetyltransferase 2
SREBP2	sterol regulatory element-binding protein 2
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HFHC	high-fat, high-cholesterol diet

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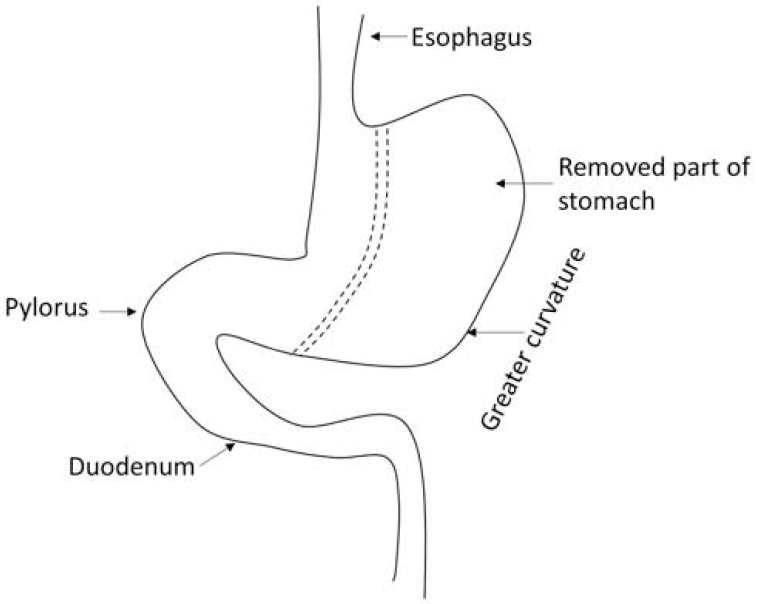

Figure. 1. Vertical sleeve gastrectomy (VSG).

Schematic diagram of VSG. VSG creates a tube-like stomach with the majority (approximately 70–80%) of stomach is removed along the greater curvature. The dotted line denote where the excision is made (in between).

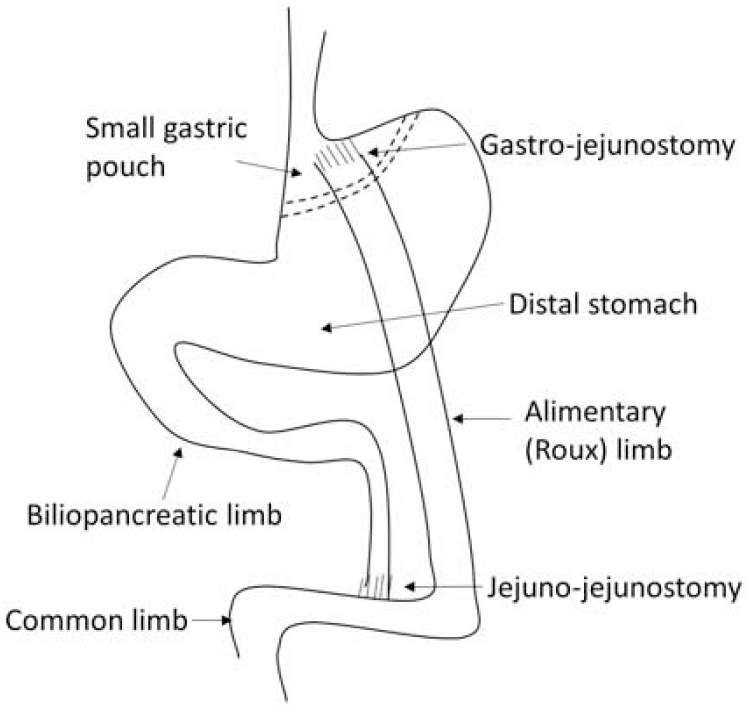

Figure. 2. Roux-en-Y Gastric Bypass (RYGB).

Schematic diagram of RYGB. The stomach is divided into a small gastric pouch and a distal stomach along the dotted lines. The jejunum is transected and the distal part is connected to the gastric pouch through a gastro-jejunostomy, which creates a Roux limb or alimentary limb, as indicated. The continuity of the gastrointestinal tract is re-established by connecting biliopancreatic limb to the jejunum through a jejunojejunostomy. The small intestine distal to the jejuno-jejunostomy is called common limb. RYGB leads ingested food to bypass the distal stomach, duodenum and proximal jejunum, and rapidly go through the small gastric pouch and flow into the jejunum. Therefore, nutrients are present in the Roux limb without bile, whereas bile and pancreatic secretions are present in the biliopancreatic limb, but no nutrients. Nutrients are mixed with bile and pancreatic secretions in the common limb.