MANAGEMENT OF ENDOCRINE DISEASE

Which metabolic procedure? Comparing outcomes in sleeve gastrectomy and Roux-en-Y gastric bypass

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Abstract

Obesity and its associated comorbidities have become one of the largest challenges for health care in the near future. Conservative therapy for obesity and related comorbidities has a very high failure rate and poor long-term results. Similarly, the conservative and medical management of the majority of metabolic diseases such as type 2 diabetes mellitus are only able to slow down disease progression but have no causal effect on the disease process. Obesity surgery has evolved as a highly effective therapy for severe obesity achieving long-lasting weight loss. Furthermore, several studies have demonstrated the beneficial effects of obesity surgery on reduction of overall mortality, reduction of cardiovascular events and superior control of obesity-related diseases such as type 2 diabetes mellitus, dyslipidemia and also the non-alcoholic steatohepatitis compared to medical therapy. Based on these findings, the term 'metabolic surgery' with the focus on treating metabolic diseases independent of body weight has been coined. Of great interest are recent studies that show that even existing complications of metabolic diseases such as diabetic nephropathy or the non-alcoholic steatohepatitis can be reversed by metabolic surgery. Although metabolic surgery has proven to be a safe and effective treatment for obesity, resolution of comorbidities and enhancing quality of life, it is still uncertain and unclear, which surgical procedure is the most effective to achieve these metabolic effects. The aim of this review is to compare the effects of the two currently most widely used metabolic operations, the Roux-en-Y gastric bypass and the sleeve gastrectomy in the treatment of obesity and its related comorbidities.

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Invited Author's profile

Beat Müller-Stich has been chief of the Minimally Invasive and Metabolic Surgery since 2010 at the University of Heidelberg and became a senior attending surgeon in 2012. His research focus is on metabolic surgery and minimally invasive oncological surgery. The main area of research in metabolic surgery is the treatment of type 2 diabetes and non-alcoholic fatty liver disease with metabolic surgery and other obesity-related disease. Clinical studies consist of large multi-center trials and also translational research including the investigation of the mechanisms by which metabolic surgery improves obesity and diabetes-related mechanisms.

Review	A T Billeter and others	Sleeve vs RYGB for Metabolic Surgery	179:2	R78
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Introduction

During the last decades, obesity has become a worldwide epidemic and is one of the largest challenges for health care in the near future (1, 2). Obesity itself but especially obesity-associated diseases such as type 2 diabetes (T2DM), cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD) along with steatohepatitis (NASH) and renal failure are strongly increasing and are responsible for a large amount of the current and future health care spending (2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Conservative treatment options for obesity and its comorbidities suffer from a high failure rate and are limited to slowing down disease progression without an impact on the cause of the disease (1, 12, 13, 14). Weight loss with lifestyle change is usually limited to 10% body weight in the short term while after 1 year, the failure rate, i.e. weight regain and often even the gain of additional weight occurs in >95% of patients (15). The treatment of diabetes aims to control blood sugar levels although there is clear evidence that tight blood sugar control with insulin does not affect overall and cardiovascular-related mortality or the progression of kidney disease to renal failure (16). Also, lifestyle interventions do not reduce cardiovascular events despite weight loss and improved glycemic control (17). The real-world value of newly developed antidiabetic medication such as glucagon-like protein (GLP-1) agonists, the dipeptidyl peptidase-4 inhibitors or sodium/glucose cotransporter 2-blockers, which have shown some promise in at least some subgroups of diabetic patients, still needs to be determined (18, 19, 20). Regarding NAFLD, and in particular NASH, the mainstay of therapy remains lifestyle changes since no effective medical treatment has yet been introduced (3, 21, 22, 23). Currently, there are several on-going studies on this topic and will show whether these newly developed drugs will provide an effective therapy option for NAFLD/NASH (22, 23). As of now, medical therapy for obesity and its related comorbidities is still largely supportive, ineffective and has little effect on severe complications such as the development of cardiovascular events, kidney failure, dyslipidemia or progression of NAFLD/NASH to liver cirrhosis or hepatocellular carcinoma (HCC) (12, 16, 17).

In contrast, obesity surgery has been shown to achieve sustained weight loss over decades in many patients while also effectively treating obesity-associated diseases. Due to these strong effects on obesity-associated diseases, the focus for indications for obesity surgery is shifting toward comorbidities and away from weight or

BMI-based indications. The work by Sharma *et al.* clearly showed that the obesity-related comorbidities are more relevant for the long-term survival than the BMI (24, 25). The concept of metabolic surgery is of high relevance since conservative, multimodal therapy does not impact survival and cardiovascular events, even when the surrogate parameters such as HbA1c, weight and waist circumference are improved, as has been shown in the LookAHEAD trial (17). These findings from non-operative therapy of metabolic diseases are strongly contrasted by the data from metabolic surgery. The data from the Swedish obese subject (SOS) study as well as from the United States show that obesity surgery results in a long-lasting weight loss over 12 years and more in severely obese patients with a BMI >35 kg/m² (26, 27, 28, 29). Often accompanied is a remission of T2DM in 20–80% of patients, an important improvement and possible remission of dyslipidemia, as well as cardiovascular disease-related mortality (26). Furthermore, data from the SOS study and other publications showed a significantly reduced incidence of diabetes-associated microvascular complications but also macrovascular complications in general during a mean follow-up time of 17.6 years (28, 29, 30, 31). Regarding T2DM, there is ample high-class evidence from randomized controlled trials (RCTs) that suggest that obesity surgery, and in particular the Roux-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), achieve superior control of T2DM and metabolic syndrome, including dyslipidemia compared to even very intensive lifestyle changes and optimal medical therapy (32, 33, 34, 35, 36, 37). A recent meta-analysis using only RCTs confirms that obesity surgery achieves superior diabetes remission and resolution of the metabolic syndrome than lifestyle intervention and medical therapy in patients with a BMI >27 kg/m² (38). Another meta-analysis has also concluded that obesity surgery even in nonseverely obese patients with a BMI of 25–35 kg/m² is superior to medical and lifestyle interventions (39). Therefore, it is nowadays justified to refer to obesity surgery as metabolic surgery. And even more importantly, metabolic operations can also improve an already existing diabetic nephropathy at the time of the operation (30, 40, 41, 42, 43). Additionally, some studies from our group along with other publications indicate that metabolic surgery improves not only diabetic nephro- and neuropathy, but also retinopathy (42, 44, 45, 46, 47, 48). Thus far, sustained remission and improvement of existing microvascular complications cannot be achieved with medical therapy.

Lastly, obesity surgery is also highly effective in treating NAFLD and NASH resolving the histological features in the majority of patients, even in advanced NASH fibrosis (49, 50).

Although bariatric surgery has proven to be a safe and effective treatment for obesity, resolution of comorbidities and enhancing quality of life, to date, it is still uncertain and unclear, which surgical procedure is the most effective to achieve these metabolic effects. The aim of this review is to compare the effects of the two currently most widely used metabolic operations, the RYGB and SG in the treatment of obesity, but especially on the effects of T2DM, dyslipidemia and NAFLD/NASH.

Overview of surgical procedures for obesity and metabolic disease

Obesity surgery is not a new field as it has been around for over four decades, but it has become widely used to treat obesity and its associated comorbidities in the last two decades (1). It has traditionally been divided into restrictive procedures and a combination of restrictive and malabsorptive procedures (51). Laparoscopic gastric plication, laparoscopic adjustable gastric band (LAGB) and laparoscopic SG could be considered restrictive procedures, although there are many additional metabolic effects, which go beyond the effects of pure restriction of food intake. This is especially true for the SG, which has well-described changes in intestinal hormones, bile acid metabolism, microbioma and the gut–brain signaling (52, 53). The RYGB has a small gastric pouch and bypasses the stomach, duodenum and first part of the jejunum. The malabsorptive effects of the RYGB however are limited (54). The biliopancreatic diversion (BPD) in contrast, is mainly a malabsorptive procedure with only about 100 cm of common channel for resorption of food.

Currently, RYGB and SG are the most commonly performed bariatric procedures in the last decade (55). According to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) registry report 2017, there were 89,662 bariatric surgeries reported worldwide between 2013 and 2017. Of those, 46.3% (41,508) were RYGB, while 43.6% (39,137) were SG (55, 56). The popularity of the LAGB, which used to be the most frequently used bariatric procedure in the first decade of the 2000s, has drastically decreased in recent years due to the unfavorable safety profile in the long-term and the poor long-term weight loss in comparison with the other bariatric procedures (57, 58, 59). Throughout the years,

both surgeries have been demonstrated to be safe and effective for the treatment of obesity (60, 61, 62, 63).

Mechanisms of metabolic surgery

The mechanisms by which metabolic operations affect metabolism are still poorly understood. Food restriction and weight loss is certainly an important part for the beneficial effects of metabolic procedures as demonstrated by the effects of the LAGB, the only purely restrictive bariatric procedure, which also achieves significant weight loss and remission of T2DM (64, 65). Furthermore, some of the effects of metabolic procedures on T2DM can be mimicked by a very-low-calorie diet in the very short term for about 6 months (66, 67, 68). However, the recurrence rate of T2DM after an initial very-low-calorie diet of 8 weeks followed by a stepwise return to an isocaloric diet was >60% after 6 months (66). Although these findings are important and help to shed light on the mechanisms of metabolic surgery, there is ample evidence that food restriction plays a lesser role than initially expected (69, 70). In line with these findings are recent studies showing that the fibroblast growth factor, a hormone that is relevant for energy consumption and mitochondrial function and the hypothalamic–adrenal axis is very differently affected by metabolic surgery than very-low-calorie diets (71, 72). Further supporting the role of hormonal changes after metabolic surgery is the fact that the LAGB is clearly inferior to both SG and RYGB regarding long-term weight loss and T2DM remission (73, 74). These findings are further supported the study of Purnell *et al.*, which showed that the chances for T2DM remission after RYGB is significantly higher for any given weight loss compared to LAGB (75). Several theories about the hormonal changes are intensively under investigation but none of them currently stand out as the leading mechanism. Early studies found that gastrointestinal hormones such as GLP-1, ghrelin, peptide-YY (PYY) and others are affected by metabolic surgery. RYGB as well as SG induce similar changes in these hormones except for ghrelin (76, 77, 78, 79, 80). Ghrelin is reduced after SG due to the resection of large parts of the stomach, whereas ghrelin may increase or remain stable after RYGB. Other mechanisms of action are the changes in bile acid metabolism and signaling, changes in the microbioma as well as changes in food perception and appetite (52, 76, 81, 82). For a detailed review of the current understanding of the mechanisms of metabolic surgery, we refer to current specific reviews on this topic (76).

Roux-en-Y gastric bypass

RYGB (Fig. 1A) is one of the most common bariatric surgeries performed worldwide. In the mid 1960s, Edward Mason described the first experience with open gastric bypass surgery for weight loss (83). In response to the gastric bypass, less complicated gastric restrictive procedures were developed in the 70s, and these procedures were known as 'gastroplasties'. In the mid-90s, the first laparoscopic RYGB was first successfully performed laparoscopically by Alan Wittengrove (84). The success of laparoscopic surgery in other procedures led to the widespread adaption of laparoscopic surgery also in obesity surgery resulting in significantly reduced complications and therefore increased acceptability of obesity surgery (85). In the current form of the RYGB (Fig. 1A), a gastric sleeve pouch is created of approximately 20–30 mL volume using a 36–42 French bougie with an alimentary limb of approximately 120–150 cm in length and a biliary limb of approximately 50–100 cm in length, depending on the individual technique (86). Both gastro-jejunal and jejuno-jejunal anastomosis can be created using stapler devices and sutures. There is currently an on-going debate about the ideal limb length for the Roux- as well as the biliopancreatic limb (87, 88). Some studies have shown that a longer biliopancreatic limb length results in improved weight loss and better T2DM remission (89). However, the most currently presented data of a high-quality RCT with a 150 cm biliopancreatic limb and 75 cm Roux-limb only showed a trend toward better weight loss after 4 years, whereas diabetes remission was not different (Berends *et al.* IFSO 2017 (90)). However, the lengthening of the Roux-limb to achieve a short common channel of 75–100 cm (distal RYGB) as a primary

operation is associated with a high risk of malnutrition as well as vitamin and micronutrient deficiency and is therefore reserved for re-do operations after failed conventional RYGB (91, 92, 93, 94).

An adaption of the classic RYGB is the one-anastomosis or mini-gastric bypass (OAGB, Fig. 1B) in which a long gastric pouch is formed similar to SG without pylorus, but the biliopancreatic limb is not divided and anastomosed to the gastric pouch about 150–200 cm distal from the ligament of Treitz (Fig. 1B). The second anastomosis of the jejunum to the ileum is not necessary. There are only few studies comparing the classic RYGB with the OAGB and the data quality is generally poor. In uncontrolled, retrospective data, the OAGB seems superior in regard to weight loss and diabetes remission, but the only RCT showed no significant difference (87, 88, 89). However, the nutritional complications regarding malnutrition as well as vitamin and micronutrient deficiency are also higher after OAGB, and it remains to be seen whether the OAGB will become a widely used operation (95).

Sleeve gastrectomy

In the last decades, SG has increased its popularity around the world (Fig. 2). Based on Nicola Scopinaro's BPD, Douglas Hess performed a BPD with a duodenal switch (BPD/DS) combined with a tubular stomach (gastric sleeve) instead of the typical 2/3 gastrectomy (96). Since the BPD-DS as well as the RYGB are technically very difficult to perform in super-obese patients with a BMI > 60 kg/m², the concept of two-stage procedures was introduced (97, 98, 99, 100, 101). In this approach, the first step was the SG and after an initial weight loss, the second step with BPD was performed. However, some patients already

Figure 1

(A) Classic Roux-Y gastric bypass. (B) One-anastomosis gastric bypass.

Figure 2

Sleeve gastrectomy.

experienced an extensive weight loss with the SG and the second-stage operation was not necessary anymore resulting in the description of the SG as a stand-alone procedure for weight loss (97, 98, 102). In the SG, an estimate of 75–85% of the stomach is excised by dissecting the greater curvature using linear staples to create a gastric tube. SG has emerged as one of the top surgical treatment options with excellent weight loss, minimal morbidity and negligible mortality (103, 104). Also, the risk for malnutrition or vitamin and micronutrient deficiency is minimal (105, 106, 107).

Short- and long-term weight loss after metabolic surgery

Both surgeries are known to have good short- and long-term results regarding weight loss. Many studies have published short-term results after 2–3 years and a systematic review found no difference in median weight loss (108). Two high-quality RCTs were performed comparing RYGB with SG showing no clinically relevant difference between SG and RYGB 5 years postoperatively even though the difference was statistically different with 3.6 kg weight loss difference in the study by Peterli *et al.* (60, 63). There is a limited amount of studies reporting long-term results (>5 years) after SG (Table 1). Noel *et al.* performed a study to present long-term weight loss results after SG (109). A percentage excess weight loss (%EWL) of 76% at 5 years and 67% at 8 years was reported. They concluded that after 8 years, SG remains as a favorable treatment for obesity. Another study by Sarela *et al.*

analyzed results at 8–9 years after SG, in which 55% of their patients had a %EWL of >50% (110). Regarding RYGB, Mehaffey *et al.* analyzed 316 patients at 10 years after RYGB, with favorable results of percentage excess body mass index lost (%EBMIL) of 52.7% (111). With these results, they concluded that RYGB remains an excellent and durable operation for long-term weight loss. Obeid *et al.* reported similar results 10 years after RYGB with a %EWL of 58.9% (112). In summary, there may be some benefit for more weight loss after RYGB, but the difference is minimal (in the range of 1–2 BMI-points) and clinically most likely not relevant. In 2015, the BariSurg trial was started to investigate EWL rates 2 years after either RYGB or SG (113). As a secondary endpoint, EWL rates 60 months after surgery will be analyzed. The recruitment period is currently ongoing.

T2DM remission and glycemic control after metabolic surgery

Metabolic surgery is the best therapy for T2DM in patients with a BMI >25 kg/m² achieving superior glycemic control compared to even very intensive lifestyle modification and optimal medical therapy. Besides superior glycemic control, metabolic surgery also reduces the incidence of microvascular complications and can improve preexisting diabetic nephropathy. Ultimately, metabolic operations reduce mortality in patients with obesity, especially in patients with T2DM (114, 115). Despite the clear evidence that metabolic surgery is superior to conservative therapy, it remains unclear, which procedure achieves better T2DM-related outcomes. Depending on the quality of data, the results are different. A recent meta-analysis by Li *et al.*, which included all published studies independent of the study quality, found that RYGB achieves more T2DM remission than SG (116). However, when only RCTs are included in the meta-analysis, there are no differences regarding T2DM remission (117). However, the RCT with the longest follow-up, the STAMPEDE-Trial by Schauer *et al.*, found that patients after RYGB need less antidiabetic medication after 5 years compared to SG (118). Glycemic control on the other hand is similar between groups. An overview of the mid-to-long-term results of high-quality studies are shown in Table 2. To better select the ideal patient for RYGB or SG, the patients, enrolled in the future, need to be better classified in terms of their endocrine pancreatic function and insulin resistance as well as the effect of each procedure on these parameters. Aminian *et al.* proposes a score (individualized metabolic surgery

Table 1 Effect of RYGB and SG on weight loss.

Reference	Follow-up (years)	RYGB	SG
(111)	5	68.8 %EBMIL	n/a
	10	52.7 %EBMIL	n/a
(112)	10	70.7 %EBMIL	n/a
(146)	10	63.3 %EBMIL	n/a
(186)	10	69.0 %EWL	n/a
(187)	10	57.1 %EWL	n/a
(63)	5	68.3 %EBMIL	61.1 %EBMIL
(60)	5	57.0 %EWL	49.0 %EWL
(62)	5	67.8 %EWL	60.2 %EWL
(110)	>8	n/a	69.0 %EWL
(188)	11	n/a	62.5 %EWL
(136)	8	n/a	46.0 %EWL
(137)	6	n/a	67.3 %EWL
(138)	5	n/a	62.9 %EWL

%EBMIL, percentage excess body mass index loss; %EWL, percentage excess weight loss; n/a, information not available; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Review	A T Billeter and others	Sleeve vs RYGB for Metabolic Surgery	179:2	R82
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Table 2 Effect of RYGB and SG on glycemic control.

Reference	Surgery	Pre-OP HbA1C (%)	Post-OP HbA1C (%)	Follow-up (years)
(33)	RYGB	8.7 ± 1.4	6.7 ± 0.5	5
(32)	RYGB	9.3 ± 1.4	7.3 ± 1.5	5
	SG	9.5 ± 1.7	7.4 ± 1.6	5
(60)	RYGB	7.8 (7.2–8.5)*	6.6 (6.4–6.8)*	5
	SG	7.5 (6.9–8.1)*	6.6 (6.4–6.8)*	5
(63)	RYGB	7.2 (6.4–8.0)	5.9 (5.7–6.1)	5
	SG	7.6 (6.8–8.4)	6.2 (5.9–6.6)	5
(34)	RYGB	9.6 ± 1.0	6.7 ± 2.0	3
(37)	RYGB	8.5	7.1	3
(189)	RYGB/SG	7.5 ± 1.8	5.7 ± 1.1	>1
(190)	RYGB	7.7 ± 1.3	6.2 ± 0.5	1
	SG	8.3 ± 1.8	5.9 ± 0.9	1
(191)	RYGB	6.3 ± 0.9	5.5 ± 0.5	1
	SG	6.4 ± 1.3	5.5 ± 0.4	1
(192)	RYGB	10.4 ± 1.1	5.9 ± 0.3	1

HbA1c, glycated hemoglobin; post-OP, postoperative; pre-OP, preoperative; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; *Values provided as mmol/L

score (IMSS)) to assess chances of T2DM remission and to select the appropriate procedure (119). The IMSS is based on the STAMPEDE study and was validated in a cohort of Spanish patients. It includes number of preoperative medication, preoperative insulin use, T2DM duration and preoperative HbA1c <7%. Based on these points, T2DM can be divided into three stages and RYGB is suggested for mild disease although SG can also be used since likelihood of complete T2DM remission is high (119). In the intermediate stage, the authors recommend RYGB since more patients are off any anti-diabetes medication after RYGB than SG. In a severe stage, the authors recommend SG since chances for T2DM remission are slim in both procedures and SG is safer and has fewer complications. Another study on prediction of T2DM remission also found that RYGB is associated with slightly better rates of T2DM remission than SG, although other parameters such as insulin use and duration of T2DM play a much stronger role than the type of operation (120). It is very clear however that preoperative BMI is irrelevant whether a metabolic operation achieves T2DM remission or not. Panunzi *et al.* showed that T2DM remission was similar when considering a BMI >35 kg/m² or a BMI of <35 kg/m² with 71% and 72%, respectively (121).

NAFLD/NASH improvement after metabolic surgery

NAFLD and NASH are recognized as a rapidly increasing challenge since they are associated with many other metabolic diseases including T2DM and dyslipidemia

(3, 5, 122, 123). Furthermore, the progression of NASH to liver cirrhosis and ultimately liver failure requiring transplantation is projected to become the most common indication for liver transplantation in the near future (21, 124, 125, 126). The development of HCC directly from NASH without liver cirrhosis appears to be an additional feature of NASH, which requires new surveillance strategies (3, 124, 127). Data from the University of Lille bariatric cohort have clearly demonstrated that metabolic surgery is able to effectively treat NAFLD and NASH while also improving liver fibrosis (49, 50). Epidemiologic data suggest that bariatric operations also reduce the incidence of HCC compared to matched patients who did not undergo such an operation (27, 128). However, there are only few studies comparing the effects of different metabolic operations on NAFLD/NASH and the data are conflicting (Table 3). We have previously reported that in obese patients with T2DM, SG normalizes liver function tests after 12 months, whereas RYGB was not able to achieve normal transaminases (129). These findings are supported by a recent RCT, which also found that SG normalizes liver function tests within 12 months after surgery but not RYGB (130). In contrast to these findings, a very recent analysis from our cohort of all bariatric patients found that the liver stiffness may be better improved by RYGB than SG (131). The main issue with all these studies is that they did not have liver biopsies during the follow-up but only surrogate markers such as transaminases or liver stiffness. Future studies will be necessary to determine whether RYGB or SG have an advantage regarding improvement of NAFLD/NASH. What is clear however is that the gastric band is inferior to RYGB (132).

Review	A T Billeter and others	Sleeve vs RYGB for Metabolic Surgery	179:2	R83
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Table 3 Effect of RYGB and SG on NAFLD/NASH.

Reference	Surgery	ALT, U/L		AST, U/L	
		Pre-OP	At 12 months	Pre-OP	At 12 months
(130)	RYGB	35.1 ± 14.1	32.0 ± 19.3	23.6 ± 7.7	21.4 ± 6.4
	SG	27.8 ± 19.9	21.7 ± 12.9	23.7 ± 12.8	22.5 ± 7.2
(131)	RYGB/SG	42.3 ± 28.9	22.1 ± 11.6	31.5 ± 17.3	21.4 ± 7.2
(129)	RYGB	69.2 ± 29.0	31.1 ± 11.2	43.2 ± 15.5	24.3 ± 5.8
	SG	57.9 ± 17.8	17.8 ± 7.1	42.1 ± 20.7	17.0 ± 8.8
(193)	RYGB	322 ± 16.3*	-10.6 ± -15.5	30.6 ± 21.6*	-5.8 ± -10.0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LSG, sleeve gastrectomy; post-OP, postoperative; pre-OP, preoperative; RYGB, Roux-en-Y gastric bypass. *Values are provided as IU/L.

Metabolic syndrome and insulin resistance after metabolic surgery

Metabolic syndrome is defined by a group of factors that increases the risk of coronary heart disease (CHD), atherosclerotic diseases and T2DM. Its main components are visceral obesity, atherogenic dyslipidemia, insulin resistance in the peripheral tissue as well as in the liver and endothelial dysfunction (133). There are several definitions, which have been updated over the years. Metabolic surgery has been shown in multiple studies to produce significant weight loss and enhance or rectify many of the symptoms of metabolic syndrome including T2DM, hypertension, sleep apnea and dyslipidemia (110, 134, 135). There is a recent publication that compared RYGB and SG for metabolic syndrome resolution (136). The authors reported that at a 4-year follow-up, RYGB had a significant resolution of all metabolic syndromes' factors by 37.6%, while SG also reduced all metabolic syndrome components by 26.8% (except hypertriglyceridemia and hyperglycemia). They concluded that RYGB and SG were associated with similar proportion of resolution of metabolic syndrome. Another study comparing RYGB and SG in metabolic syndrome remission with a 3-year follow-up confirmed these results with 58% for RYGB and 59% for SG respectively (137). Boza *et al.* performed a study reporting metabolic syndrome's remission at a minimum of 5 years of follow-up, but only with RYGB (138). They reported a resolution rate of 86% postoperatively. In summary, there appears to be no relevant difference between RYGB and SG regarding resolution of the metabolic syndrome. The underlying cause of the improvement in the metabolic syndrome is the reduction of the insulin resistance in the peripheral tissue such as adipose tissue and muscle but also in the liver (129, 139, 140, 141, 142, 143). However, there are no studies comparing the effects of RYGB and SG on insulin resistance in the various tissues. Of note, some recent studies showed that the metabolic effects of

metabolic procedures remain even in patients with weight loss failure (144, 145).

Arterial hypertension after metabolic surgery

Arterial hypertension is linked to obesity and other metabolic disease, and it plays an essential role in the development of kidney disease, especially in patients with T2DM. Metabolic surgery has been demonstrated to be an effective procedure for hypertension resolution (115). Since the early 90s, several studies have shown that RYGB is an effective therapy for arterial hypertension in patients with obesity (146, 147) (Table 4). A study by Sugerman *et al.* reported that at 5- to 7-year follow-up, there was a 66% hypertension remission rate in patients who underwent RYGB (148). Several studies also reported the effects of RYGB and SG on resolution of arterial hypertension. A current meta-analysis, which includes all studies independent of their quality, found that RYGB achieves a higher rate of arterial hypertension resolution than SG

Table 4 Effect of RYGB and SG on arterial hypertension.

Reference	Surgery	% Pre-OP (%)	% Remission (%)	Follow-up (years)
(151)	RYGB	21.4	66	5
	SG	19.2	60	5
(60)	RYGB	71*	51	5
	SG	71*	29	5
(63)	RYGB	61.5	70.3	5
	SG	63.4	62.5	5
(150)	RYGB	37.5	75	3
	SG	31.2	50	3
(194)	RYGB	17.2	40	3
	SG	14.3	25	3

*71% of all patients were using medication for arterial hypertension. HTN, arterial hypertension; LSG, laparoscopic sleeve gastrectomy; pre-OP, preoperative; RYGB, Roux-en-Y gastric bypass.

Review	A T Billeter and others	Sleeve vs RYGB for Metabolic Surgery	179:2	R84
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(60% vs 51%, $P=0.001$, OR: 1.43 (95% CI: 1.15–1.77)) (116). In contrast, there are no differences between RYGB and SG when only RCTs are considered (149). However, the follow-up in these studies is short and limited with only two studies having a follow-up >12 months. The recent results from the SM-BOSS trial after 5 years support the finding that there is no difference in resolution of arterial hypertension between RYGB and SG with 71.2% vs 65.2% respectively (61). The remaining patients had all an improvement of their arterial hypertension again with no difference between the two procedures. Taken together, there is currently no evidence that one operation is superior for resolution of arterial hypertension compared to the other until long-term data from RCTs are available.

Dyslipidemia after metabolic surgery

Similar to remission of T2DM and arterial hypertension, metabolic surgery can also efficiently resolve dyslipidemia (51). Also, analyzing uncontrolled data, RYGB appears to have a superior effect on dyslipidemia (116). As in the other obesity-related comorbidities, the benefit of RYGB seems to disappear when only RCTs are analyzed (149). However, in contrast to the other components of metabolic syndrome, RYGB may have a superior impact on dyslipidemia in the long term (Table 5). Yang *et al.* observed a 100% remission of dyslipidemia after RYGB and 75% after SG after 3 years while Zhang *et al.* found a 92.5% and 84.6% remission after 5 years respectively (150, 151). The three-year results of the SM-BOSS trial also indicate that the RYGB may achieve a better improvement of dyslipidemia than SG (61). A complete remission of the dyslipidemia was observed in 71.7% of patients after RYGB compared to 43.8% after SG. A further 35.4% of patients after SG experienced an improvement of the dyslipidemia compared to 26.1% after RYGB. However, dyslipidemia was not changed or worsened in 20.8% of patients after SG (2.2% after RYGB). In summary, RYGB may have a slightly superior effect on dyslipidemia than SG although more long-term data are necessary to ultimately answer this question.

Cardiovascular disease after metabolic surgery

Cardiovascular risk (CVR) is estimated using numerous multivariable risk equations, such as the Framingham risk score and its modifications for assessing the risk of CHD

Table 5 Effect of RYGB and SG on dyslipidemia.

Reference	Surgery	% Pre-OP (%)	% Remission (%)	Follow-up (years)
(151)	RYGB	46.4	92.5	5
	SG	50	84.6	5
(63)	RYGB	51	62.3	5
	SG	67.3	42.6	5
(60)	RYGB	35*	60	5
	SG	35	47	5
(150)	RYGB	56.2	100	3
	SG	65.6	75	3

*35% of all patients had dyslipidemia.

LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass.

(152). According to the American Heart Association, hard atherosclerotic cardiovascular disease (ASCVD) should be focused for estimating CVR instead of CHD alone, also considering atherosclerotic stroke (153). Only few studies assess CVR following metabolic surgery. The randomized, nonblinded, single-center trial of Schauer *et al.* investigated CVR factors, associated medication use and adverse events (fatal myocardial infarction, stroke) as secondary outcomes following RYGB or SG compared to medical treatment alone (118, 154). Triglyceride and high-density lipoprotein cholesterol levels improved significantly following surgery compared to intensive medical treatment at 3 and 5 years of follow-up (118). Also, a significantly reduced use of cardiovascular and glucose-lowering medications was found following metabolic surgery. Neither RYGB nor SG showed a superior improvement achieving these results, although medication use after RYGB was significantly lower compared to SG. There are no randomized trials investigating CVR factors in particular as a primary outcome. Referring to this, a prospective cohort study of 140 patients undergoing either RYGB or SG showed that both procedures are equally effective, reducing estimated CVR based on the Framingham score to half at 1 year after surgery (155). Randomized trials with long-term follow-up are needed to investigate CVR factors and incidence of events following RYGB compared to SG as primary endpoints.

Short- and long-term complications after metabolic surgery

For a widespread application of new therapies such as metabolic surgery, potential side effects need to be acceptable and the benefit of the therapy needs to outweigh potential complications. The clear and long-lasting health benefit of an invasive therapy is also important for patients to choose such a therapy. The efficacy vs safety

assessment is particularly challenging in the treatment of metabolic diseases with operations compared to the conservative medical therapy. It is inherent to operations that they are more invasive and may have more severe complications than non-operative therapies. However, it is very important to realize that the current metabolic operations performed at experienced centers are extremely safe and the mortality rate is < 0.5%, whereas the overall major complication rate is around 2–7% (62, 156, 157).

Non-surgical complications and increased risk for self-harm

Besides the ‘traditional’ complications of surgery, metabolic procedures seem to have additional, unique complications, which need to be addressed. Osteoporosis and an increased risk for fractures has recently been reported after metabolic surgery, especially after malabsorptive operations such as the BPDs (158, 159, 160). Further studies assessing the efficacy of postoperative vitamin and micronutrient supplementation to prevent osteoporosis and nutritional deficiencies are needed to further improve the high safety of metabolic surgery.

A very important area of concern, which has recently been identified, is the increased risk for self-harm and even suicide in patients after bariatric surgery. While the initial studies indicating a higher risk for self-harm and suicide in the post-bariatric patients had a high risk of bias since they compared patients after bariatric surgery with the general population but not with similarly obese patients (161, 162, 163, 164), the study by Neovius *et al.* showed that patients after bariatric surgery have indeed a higher risk for self-harm and suicide compared to matched patients (165). This study analyzing the SOS study and also patients from the Scandinavian Obesity Registry found a three-fold increased risk for suicide after bariatric surgery. Therefore, every health care provider treating patients before and after metabolic surgery must be aware of these complications and a special emphasis on the prevention and therapy of psychological disorders must be taken (166). In order to prevent self-harm and suicide, our institution screens every patient after metabolic surgery for depression or risk for self-harm/suicide, and we recommend that every institution implements such a screening tool.

Nonetheless, it is very important to put these detrimental outcomes of metabolic surgery in perspective. The success rate and health benefits of metabolic surgery are also much stronger and longer lasting than those of medical therapy (28, 29, 30, 31, 167, 168). The reduced

overall long-term mortality, which has been repeatedly shown after metabolic surgery includes mortality from suicide (27, 28, 29, 114), clearly outweighs the potential risks of metabolic operations. Several analyses have confirmed the overall benefit of metabolic operations compared to conservative therapy, especially since the current medical therapy including the newest drugs is not able to reproduce the effects of metabolic surgery (14, 134, 169).

Surgical and operation-related complications

Nonetheless, a safety assessment should also be a concern when RYGB and SG are compared. A recent meta-analysis found that SG has fewer major complications in RCTs than RYGB (3.4% vs 7.5%, $P=0.05$; OR: 0.49 (95% CI: 0.24–1.9)), whereas reoperations or re-intervention occurred with the same frequency (156). These findings are in line with the most recent results from the SM-BOSS and SLEEVEPASS trials, which also found no difference in reoperations after 5 years including the conversions of SG to RYGB due to severe GERD (61, 63). In contrast, Melissas *et al.* found that the long-term complications 5 years after surgery are significantly less in SG patients (1.0%) than after RYGB (3.3%) (62). In summary, both RYGB and SG are very safe operations but SG seems to have less overall complications perioperatively but especially in the long term (Table 6).

Discussion

Metabolic surgery is currently the most powerful and effective therapy for obesity and its associated diseases such as T2DM, dyslipidemia, NAFLD/NASH and arterial hypertension. It seems to have a causal effect since these operations improve insulin resistance as the underlying cause of the metabolic syndrome (142). Metabolic operations not only achieve successful (>50% EWL after RYGB and SG) long-lasting weight loss but they also reduce overall and comorbidity-associated mortality while improving quality of life (27, 28, 29, 114). Such beneficial long-term effects and sustained weight loss cannot be achieved by lifestyle interventions or conservative therapy (1, 12, 17, 26, 28, 167, 170, 171, 172). A recent meta-analysis showed that metabolic operations not only reduce the incidence of diabetes associated complications but can even improve preexisting diabetic complications, especially diabetic nephropathy in a high rate (173). Interestingly, it seems that some of these metabolic effects

Review	A T Billeter and others	Sleeve vs RYGB for Metabolic Surgery	179:2	R86
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Table 6 Perioperative and long-term complications after RYGB and SG.

Reference	Surgery	Perioperative (%)	Long term (%)	Medical treatment (%)	Reoperations (%)
(62)	RYGB	3	3.3	n/a	2.1
	SG	2.1	0.9	n/a	0.5
(151)	RYGB	6.2	25	n/a	n/a
	SG	12.6	0	n/a	n/a
(194)	RYGB	7	3	3.3	10
	SG	26.6	3	3.3	6.6
(150)	RYGB	3.7	n/a	3.1	n/a
	SG	7.1	n/a	6.2	n/a
(60)	RYGB	26.5	26	n/a	14.2
	SG	13.2	19	n/a	8.2
(63)	RYGB	4.5	17.3	n/a	22.1
	SG	0.9	14.9	n/a	15.8

Long term, complications >30 days post-surgery; perioperative, complications within <30 days post-surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

even prevail in patients with failed bariatric surgery and weight regain (144, 145). Based on this clear evidence, the leading societies for diabetes therapy proposed new guidelines with early adaption of metabolic surgery for the treatment of patients with T2DM (174).

RYGB and SG are the most commonly performed metabolic operations worldwide since they combine high safety with good metabolic outcomes and a high quality of life (175). In this review, we compare the impact of RYGB and SG on long-term weight loss, remission of T2DM and other metabolic disease while also assessing safety to determine which operations should be the primary choice. While the RYGB may have a slight advantage regarding weight loss, although one should keep in mind that the difference in long-term weight loss after 5 years is about one BMI point or 7% EWL, there are no relevant differences in the remission of comorbidities. One exception might be the remission of T2DM in the subgroup of intermediately severe patients in whom RYGB may have some advantages although this cohort needs to be better defined and the outcomes need to be evaluated in prospective studies. In contrast, there is clear evidence that SG has a superior short- and long-term safety profile compared to RYGB. Another aspect that should be considered when operations are assessed is what the options are in patients with failure of the metabolic operation regarding weight loss but also remission of comorbidities. It is important to know that weight loss failure does not necessarily translate into failure of improvement of comorbidities. Two recent studies showed that the metabolic effects of such operations can still remain despite weight loss failure (144, 145). However, when a reoperation is necessary, the options after SG are more diverse than after RYGB. The most widely used options after RYGB is the conversion to a long-limb (distal) RYGB, pouch resizing, banding of the

pouch or endoscopic narrowing of the pouch anastomosis (176, 177, 178). However, the conversion of the failed RYGB to BPD-DS have also been successfully reported in two case series (179, 180). The outcomes of these revisions are in the short term acceptable but there are only few long-term results. In the case of sleeve failure, however, there are more options that include the conversion to an RYGB or into a malabsorptive procedure such as the duodenal switch or a single-anastomosis duodenal-ileale switch (181, 182, 183, 184, 185). Similar to the revisions after failed RYGB, the long-term outcome data after failed SG is also strongly limited.

Taking all these considerations into account, both RYGB and SG need to be prospectively evaluated over a long period of time. In such an evaluation, perioperative complications, weight loss and metabolic outcomes, need for revisions independent of the indication but also the complications and outcomes of a revisional surgery need to be considered. After such a thorough analysis, the ideal metabolic operation can be determined. Other avenues of research should also attempt to better characterize patients prior to the first operation, including BMI, comorbidities but also genetic factors, with the aim to develop prognostic scores that allow to select the appropriate procedure.

As of now, both RYGB and SG are the metabolic operations of choice yielding excellent short- and long-term results. The choice of operation should be based on extensive discussion and information about the benefits and drawbacks of each operation together with the patient.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

A T B and B P M helped with concept and design. A T B, J D G H and K M S contributed to data acquisition (literature search). A T B, J D G H and K M S drafted the manuscript. F N, F B and B P M helped in critical revisions.

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