Endotext

SURGICAL PREVENTION AND TREATMENT OF DIABETES

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ABSTRACT

The effective treatment of obesity is challenging. This in part reflects the complexity of the underlying disease process. However, there are a growing number of effective surgical, endoscopic, and pharmacologic treatments which are available. Although there has long been a preference on lifestyle modification such as diet and exercise, there is a relative paucity of evidence to support these interventions as effective long-term treatments for obesity, in producing sustained weight loss and resultant improvements in obesity related disease and mortality. Conversely, bariatric procedures which include sleeve gastrectomy, roux en Y gastric bypass, single anastomosis gastric bypass, biliopancreatic diversion, and several less frequently performed operations have been shown to produce substantial and durable weight loss with significant improvements in obesity related disease, quality of life, and mortality. The mechanisms by which these operations work vary depending on the procedure however they primarily act via alterations in the gut-brain axis and alterations in neurohormonal signaling. These changes produce sustained changes in appetite and hunger and unlike weight loss mediated by diet are not followed by a rebound weight regain in the long term. In addition, there appear to be modifications in bile acid metabolism and the gut microbiome which also play a contributory role in weight loss following bariatric surgery.
The criteria for consideration of bariatric surgery have recently been updated to reflect advances in knowledge, surgical technique, and safety. According to the 2022 guidelines produced by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), people with a BMI >35kg/m^2 should be recommended surgery and those with BMI 30-34.9kg/m^2 with metabolic disease should be considered. It is important to involve the multidisciplinary team in determining suitability for surgery as well as for long-term follow up (1). The multidisciplinary team typically includes a dietician, psychologist, physician, and surgeon. The decision on which procedure should be used is based on patient or surgeon preference, availability of appropriate aftercare and the patient's tolerance of risk and permanent anatomical change.

BACKGROUND

The hallmark of an effective treatment of obesity is not one which can produce clinically weight loss, rather one which can produce weight loss which is sustained in the long term such that there is an improvement in obesity related disease and mortality. Although diet and lifestyle modification has long been the cornerstone of many obesity treatment programs, the

primary concern with such approaches including very low energy diets (VLED) is the durability of weight loss. Randomized controlled trials have shown that weight loss of up to 15% is possible in people living with obesity however less than 10% will maintain this over one year and the majority will return to their pre-diet weight within 3-5 years (2). Conversely, bariatric surgery has been demonstrated to produce weight loss of 20-30% which critically is not only sustained in the long-term but has the effect of modifying the underlying disease process and resetting of the homeostatic weight 'set point', primarily through neurohormonal changes (3, 4).

The concept of the set point suggests that in the majority of adults, there is a pre-determined inherent weight around which each individual will maintain their weight over the long-term with a gradual increase seen over time. Following a period of volitional weight loss with dietary changes, there is a decrease in the overall weight followed by several homeostatic adaptations which see a return to the original baseline weight. Following bariatric surgery, irrespective of the procedure performed, there tends to be an initial period of rapid weight loss for the first 18 months followed by a period of weight stability and a subsequent very gradual weight regain. In spite of the recognized weight regain, what is critical is that overall, following surgery, there is a new, lower set point with a similar weight gain trajectory as to what is seen in the general population.

It was initially felt that bariatric procedures could be classified according to the mechanism by which they were thought to act, resulting in the description of 'restrictive' and 'malabsorptive' procedures however subsequent mechanistic studies have demonstrated this to be incorrect as they were recognized to act via alterations in neurohormonal signaling, bile acid metabolism, and changes in the microbiome (5).

The longest-term data establishing the role of bariatric surgery as a treatment for obesity compared to traditional lifestyle interventions comes from the landmark Swedish Obese Subjects (SOS) study (3). With more than 25 years of follow up, this case-control series demonstrated that irrespective of the procedure performed, bariatric surgery produces sustained weight loss which is maintained long term and supports a reduction in all-cause mortality due to cardiovascular causes and cancer compared to matched controls receiving standard care at the time (6). Critically, in addition to producing sustained weight loss, evidence from randomized controlled trials (RCTs) have consistently supported the efficacy of bariatric surgery in the treatment of obesity related disease, specifically type 2 diabetes mellitus (T2DM) compared to medical treatment (7-18).

In light of improvements in glycemic control and even remission of diabetes in a subset of people with obesity, bariatric surgery forms a central element in the treatment algorithm as endorsed by the American Diabetes Association (ADA) and International Diabetes Federation (IDF) for those with obesity and T2DM. Early views of gastrointestinal surgery as a means of permanently curing diabetes have been replaced by a more realistic view that it is more likely a means of inducing remission and improving long term glycemic control. Longer-term data from studies has now demonstrated that one in four people who initially go into remission will experience a relapse of T2DM (7). Despite this, it is essential to recognize that although some of the metabolic improvements associated with surgery dissipate with time, glycemic control is still very good compared to those treated with medication alone. As demonstrated by the UK Prospective Diabetes Study (UKPDS), there is a legacy effect of even a short period of improved glycemic control on the development of diabetes-related complications, cardiovascular endpoints and mortality (19). Thus, even individuals who do not meet the ADA criteria for diabetes remission, these improvements in glycemic control should not be dismissed as they may have important implications for morbidity and mortality.

A HISTORICAL PERSPECTIVE OF BARIATRIC SURGERY

Surgical procedures involving the upper gastrointestinal tract have long been recognized to result in substantial and sustained reductions in weight, albeit most often to the detriment of the patient. Although the mechanisms producing this weight loss were at the time very poorly understood, it became apparent that this effect could be used within the context of obesity to potentially produce surgically mediated weight loss with an improvement in metabolic disease.

Small Bowel Bypass Procedures (1950-1970)

Surgical management of obesity began with the introduction of the jejunoileal bypass (JIB) in 1954 (20). In this procedure, the proximal jejunum was diverted to distal part of the gut, leaving a long segment of excluded small intestine and a marked reduction in absorptive capacity. Although the JIB offered substantial and sustained weight loss with improvements in lipid metabolism, it was associated with serious side-effects including diarrhea, electrolyte imbalances, oxalate calculi in the kidneys, and progressive hepatic fibrosis with eventual liver failure (21-25). Given the seriousness of these complications, these procedures were generally abandoned by the 1970s in favor of so-called stomach stapling procedures

Stomach Stapling Procedures (1970-1990)

The Roux-en-Y gastric bypass (RYGB) operation was introduced by Edward Mason in 1960 (26) and gastroplasty in 1973 (27). Numerous variations of this procedure have followed, the most significant variant being the vertical banded gastroplasty (VBG) which was first described by Dr Mason in 1982 (28) . It was hoped that this group of operations would provide greater short- and long-term safety and yet retain the power of gastric bypass. Unfortunately, both randomized controlled trials and observational studies have consistently shown that it failed in both aspirations (29-32).

In the meantime, there was a resurgence of hypoabsorptive surgery with Italian surgeon, Nicola Scopinaro, introducing the biliopancreatic diversion procedure (BPD) in 1976 (33). The basic procedure involves distal gastrectomy leaving a proximal gastric pouch of 200 – 500 ml, a 200 cm length of terminal ileum anastomosed to the gastric pouch, and the biliopancreatic limb entering at 50 cm from the ileocecal valve (34). The most notable remodeling of the procedure has been the so-called duodenal switch variant (BPD-DS) proposed by Picard Marceau's group in 1993 (35, 36) in which a longitudinal gastrectomy (sleeve gastrectomy) enabled retention of the gastric antrum for controlled gastric emptying, and the ileal limb was anastomosed to the proximal duodenum.

Adoption of the Laparoscopic Approach

One of the most remarkable advances in bariatric surgery came with the near universal adoption of a laparoscopic approach. The reduced invasiveness resulted in major improvements in safety with regard to morbidity and mortality, irrespective of the procedure performed. This contributed to a major rise in the use of bariatric surgery for obesity across the world. According to the most recent IFSO Global Registry Report, 99.7% of all primary bariatric procedures undertaken worldwide are done laparoscopically (37).

One of the first laparoscopic procedures to gain widespread acceptance was the laparoscopic adjustable gastric band (LAGB) which had been specifically designed as a standalone laparoscopic procedure in 1993. Proponents of the LAGB felt the

procedure offered two primary benefits; there was an improved safety profile as it did not require the formation of any gastrointestinal anastomoses while also providing the option of a procedure which could be specifically tailored to individual needs; and allowing for band filling and deflation without requiring further surgery. LAGB became the most commonly performed bariatric procedure worldwide throughout the 1990s with only the United States not seeing widespread adoption due to regulatory restrictions which were only resolved in 2001. The adoption of laparoscopic RYGB started within a similar timeframe as LAGB however, the technical challenge associated with the formation of two gastrointestinal anastomoses contributed to a slower uptake. As surgical techniques advanced, in part due to the development of more advanced stapling devices, RYGB became the most commonly performed bariatric procedure worldwide. The adoption of sleeve gastrectomy (SG) has steadily risen in recent years, now accounting for approximately 60% of procedures world-wide, therefore overtaking RYGB which accounted for 29.5% as of 2023 (37).This increase is in part driven by the perception that it is less technically challenging than procedures such as RYGB as no anastomosis is formed.

Although RYGB and SG continue to account for the majority of procedures, the adoption of laparoscopic surgery has not only increased safety associated with bariatric surgery but has also contributed to the development of several new operations. One anastomosis gastric bypass (OAGB) is particularly noteworthy with regard to its increasing popularity and growing evidence base to support it as both safe and effective in terms of weight loss and resolution of metabolic co-morbidity. OAGB currently accounts for approximately 4% of procedures world-wide although the number has steadily risen in recent years (37).

Overall, the availability of several safe and effective laparoscopic bariatric procedures allows for greater ability to choose an operation that meets both the expectations and need of the individual while matching this with the skill set of the surgeon and moving the field closer to an era of precision medicine.

CURRENT METHODS IN BARIATRIC SURGERY

Sleeve Gastrectomy

The sleeve gastrectomy (SG) has become the most commonly performed bariatric procedure worldwide. Although initially conceived as part of the two-stage duodenal switch procedure SG has become a standalone operation having recognized the substantial weight loss it produces as well as improvement in obesity associated disease. SG involves excision of approximately 80% of the stomach by using multiple firings of a linear stapler/cutter to separate a narrow tube or sleeve of the lesser curve of the stomach from the greater curve. The initial firing starts approximately 4-7cm proximal to the pylorus which is preserved to maintain gastric emptying. A bougie (usually >32Fr) is placed in the lesser curve segment during the resection to maintain adequate lumen size. Although there is variability in the precise size, a 2012 consensus statement recommended the use of a bougie between 32-40Fr (38).

SG is relatively contraindicated in those with significant gastro-esophageal reflux disease (GERD) due to the high risk of worsening of pre-existing reflux and which can be difficult to manage symptomatically and may also play a role in the development of Barrett's esophagus. Due to this potential risk, it is advised by the International Federation for the Surgery of Obesity (IFSO) that any person undergoing SG have surveillance endoscopy one year postoperatively and then every 2-3 years thereafter (39). Other recognized complications of SG include staple line leak and bleeding in the early postoperative period as well as de novo or worsening of GERD and stricture. As the gastric remnant is removed, SG is not a reversible procedure.

Although initially and incorrectly classified as a procedure that acted via mechanical restriction, mechanistic studies have demonstrated that SG acts by modifying key neurohormones including GLP-1 and PYY which regulate hunger, appetite, and satiety via the gut-brain axis (40). SG is also thought to reduce hunger through resection of the gastric fundus which is the site of ghrelin production (41).

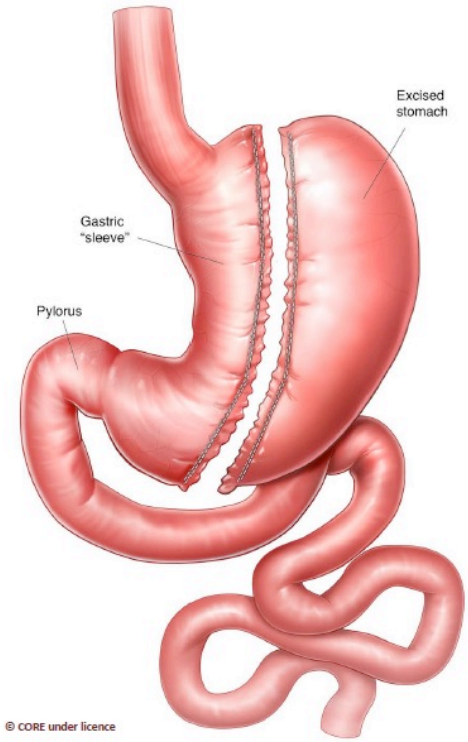

Figure 1. Sleeve gastrectomy.

Laparoscopic Adjustable Gastric Banding (LAGB)

At one time LAGB was one of the most commonly performed bariatric procedures, however, it is now infrequently performed due to the perceived high complication and re-operation rate as well as the mounting evidence to support that that it does not produce equivalent weight loss to procedures such as SG and RYGB. Although previous studies have demonstrated nearly 50% excess weight loss that can be maintained with >15 year follow up, the major caveat was the requirement for very close follow up with regular band adjustments which was not sustainable in real world practice (42).

In spite of the apparent limitations of the LAGB, the less invasive nature of the operation and potential reversibility of the procedure make it a potential consideration for those who are considered higher risk. Recognized complications of LAGB include port site infection, GERD, pouch dilatation, band slippage and erosion. Studies have suggested that up to 50% of those who have a LAGB will require reoperation or band removal (43).

The exact mechanisms of action of the LAGB are unclear however they are thought to act beyond the pure mechanical effect by involving vagal afferents (44). Vagal stimulation may help regulate food intake by promoting satiety.

Figure 2. The band consists of a ring of silicone with an inner balloon. The balloon is connected to an access port.

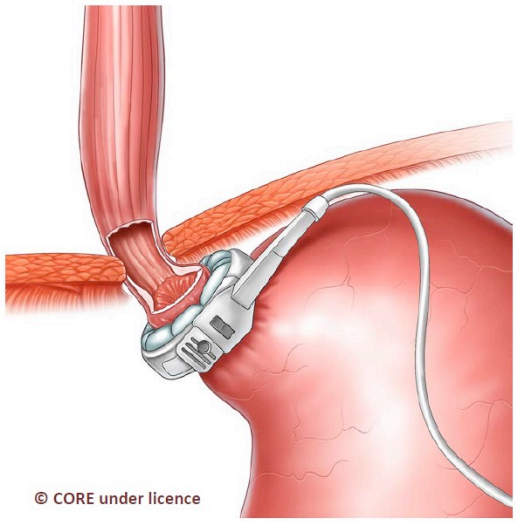

Figure 3. The LAGB is placed over the cardia of the stomach within 1cm of the esophago-gastric junction.

Roux en Y Gastric Bypass (RYGB)

Roux en Y gastric bypass is now less commonly performed than SG due in part to the technical challenge of forming two anastomoses and previous lack of level one evidence demonstrating its superiority in terms of weight loss or resolution of obesity related disease. The emergence of recent data from several RCTs appears to support that RYGB may produce significantly higher weight loss than SG with greater improvements in obesity related disease including dyslipidemia and gastro-esophageal reflux disease (GERD). Overall, there is good long-term evidence to support the efficacy of RYGB as a safe procedure which provides significant and durable weight loss with a significant improvement in metabolic complications such as T2DM (7, 45). It is also the procedure of choice in those with significant pre-existing GERD and obesity rather than SG (46).

Similar to SG, studies have shown that RYGB produces weight loss through changes in gut hormones, namely GLP-1 and PYY, an effect which is believed to be in part the result of early delivery of

nutrient in the terminal ileum and passage of undiluted bile in the bypass and the proximal jejunum (4, 5). These changes appear within days of surgery and as well as producing long-term reductions in weight are also responsible for the weight-loss independent improvements in glucose homeostasis which occur in the immediate postoperative period.

RYGB involves the formation of a small gastric pouch with an excluded gastric remnant. A loop of jejunum is then brought up and anastomosed to the gastric pouch to form the gastro-jejunostomy with the alimentary limb distal to this. Within the alimentary limb, ingested food is excluded from mixing with any digestive enzymes as the proximal jejunum has been bypassed. Approximately 100-120cm distal to the gastro-jejunostomy, a second anastomosis is formed between the biliary limb and the alimentary limb to form the jejuno-jejunostomy. It is only distal to this anastomosis that there is mixing of food and bile.

Although this is overall a very safe procedure, the most potentially serious complication which may arise is bowel obstruction or ischemia secondary to an internal hernia as two mesenteric defects are created during the procedure. Both mesenteric defects are typically closed intraoperatively, however, they may increase in size over time following weight loss and as the fat content of the mesentery decreases. Studies would support the routine closure of mesenteric defects but doing so is associated with an increased risk of complications associated with small bowel obstruction at the jejunojejunostomy (47). Additional complications include the possibility of anastomotic leaks or stricture and staple line bleeding. A small minority of people may also develop chronic abdominal pain which may be challenging to treat. It is also worth noting that due to the anatomical changes produced by RYGB, future procedures such as ERCP may require alternative approaches to accessing the excluded proximal duodenum via the remnant stomach. This may also be of concern in populations where there is concern about gastric cancer as the remnant stomach cannot be assessed by standard esophagogastroduodenoscopy.

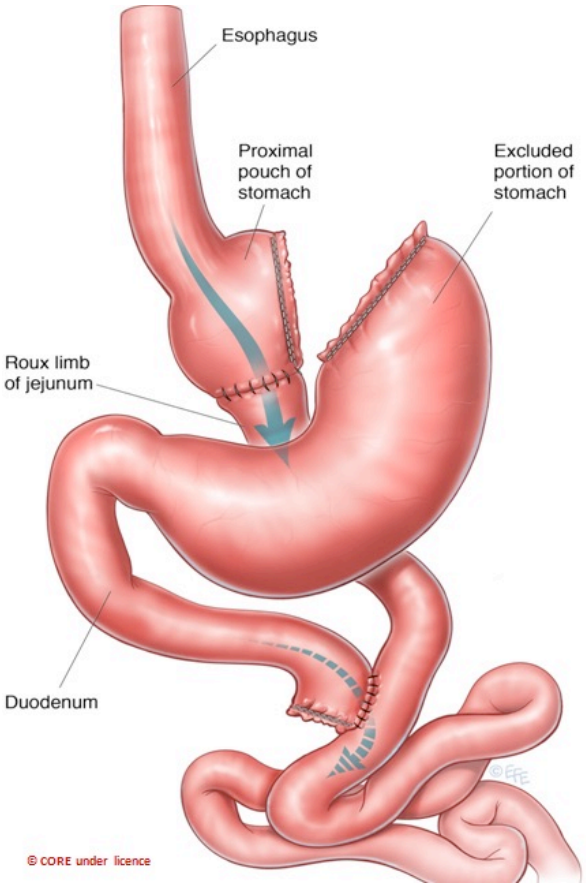

Figure 4. RYGB showing a small gastric pouch, a narrow gastrojejunostomy and exclusion of foods from the duodenum and proximal jejunum.

One Anastomosis Gastric Bypass (OAGB)

The one gastric bypass is increasingly popular as an alternative to the RYGB owing in part to the fact that it produces significant weight loss but requires the formation of only one anastomosis. OAGB involves the formation of a small gastric pouch to which a loop of jejunum is anastomosed to form a gastro-jejunostomy. Unlike the RYGB, there is only one anastomosis and the length of duodenum and proximal jejunum which is bypassed is much longer, typically up to 150cm (48, 49). (figure 5).

The mechanism of action is thought to be very similar to that of RYGB in that it results in changes in gut hormone signaling via bypass of the proximal duodenum and studies to date would suggest that weight loss outcomes as a result are comparable (48). These changes are also responsible for the improvements in glucose homeostasis and resolution or improvement of T2DM.

Given the relative lack of long-term follow up on OAGB, there are concerns regarding the potential implications of chronic bile acid reflux and the possibility of inducing gastric and esophageal malignancy, however, there is no high-quality evidence at present to support these concerns.

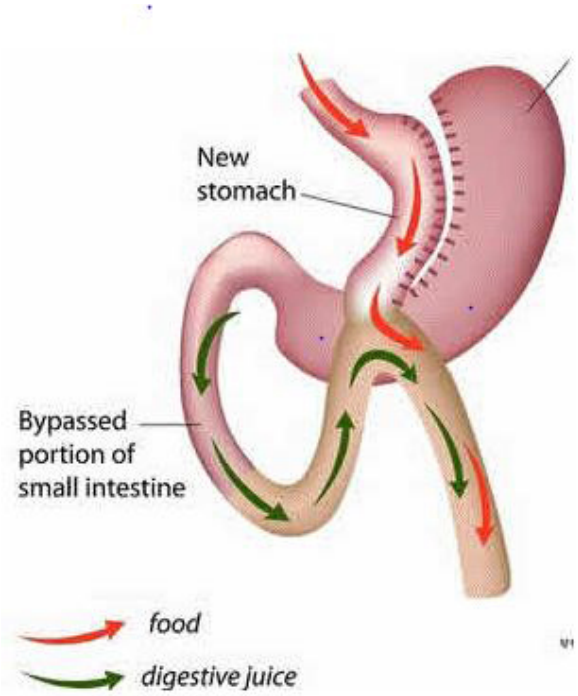

Figure 5. OAGB showing the gastric pouch as a sleeve of lesser curve of stomach and the loop gastrojejunostomy.

Biliopancreatic Diversion / Duodenal Switch (BPD/DS)

Although BPD/DS is not amongst the most commonly performed bariatric procedures, accounting for only ~1% of operations worldwide, it is noteworthy for the amount of weight loss it induces as well as the resultant improvements in metabolic dysfunction. The operation is a two-stage procedure with the initial operation involving the formation of a sleeve gastrectomy with preservation of the pylorus. In the second stage, the duodenum is mobilized and divided at D1 and subsequently anastomosed to the distal ileum. The duoden-ileal anastomosis forms the alimentary limb through which ingested food will pass, without mixing with digestive enzymes. A second anastomosis is then formed between the biliary limb and the distal ileum, approximately 80-100cm proximal to the ileocecal valve. The second anastomosis creates a short common channel for mixing of ingested food and digestive enzymes.

The weight loss and metabolic improvements following BPD/DS are significantly greater than RYGB/OAGB and SG, however, it remains an infrequently performed procedure not only due to the technical challenges but primarily owing to significant long-term complications. As a result of the very short common channel, micronutrient and fat-soluble vitamin deficiencies are expected and long-term supplementation and monitoring is essential. The potential complications resulting from nutrient deficiency can be severe and in cases irreversible, including night blindness and Wernicke's encephalopathy. Up to 10% will remain deficient despite adherence to dietary and nutritional guidelines and supplementation and will require re-operation (50).

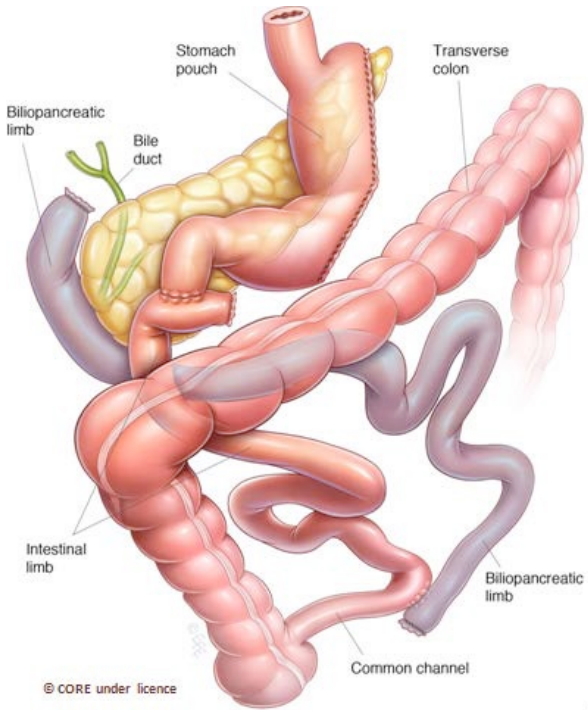

Figure 6. The ds variant of bpd with a sleeve gastrectomy, retention of the gastric antrum, diversion of food into the mid small gut and diversion of pancreatic and biliary secretions to the distal small gut. Note both limbs are passing behind the transverse colon and a color difference is added to help follow the respective pathways. The common channel is the normal ileum terminating at the ileo-cecal junction.

Single Anastomosis Duodenal-Ileal Bypass with Sleeve (SADI-S)

The SADI-S procedure is seen as a potentially simplified version of the BPD-DS procedure. Similar to BPD-DS, the procedure involves the mobilization of the duodenum followed by sleeve gastrectomy with division of the duodenum. A duodenojejunal anastomosis is subsequently formed between the duodenal stump and a loop of ileum 250-300cm proximal to the ileocecal junction which is brought up in an antecolic fashion (51). Weight loss and metabolic outcomes following SADI-S have been shown to be very good at five years with 40% total weight loss with 60-80% of individuals in T2DM remission (52-54). As there is a longer common channel, the risk of nutritional deficiencies is lower than seen with BPD-DS and were similar to RYGB (55).

Experimental Bariatric Procedures

In recent years, there has been growing interest in non-surgical treatments for obesity including endoscopic approaches. Although long-term data is more limited, the ability to offer less invasive procedures may further broaden the population to which effective obesity treatment is available. EndoBarrier is an endoscopically placed 60cm duodenal-jejunal bypass liner which aims to replicate the effects of RYGB. Once placed within the duodenal bulb, the liner allows the flow of gastric content to the jejunum via the lumen while pancreatic content flows along the outside, preventing any mixing until the end of the liner is reached. The device can be left in situ for a maximum of 12 months with studies demonstrating a significant improvement in weight and HbA1c, however results >1 year are limited and the device does not at present have approval for use (56).

MECHANISMS OF ACTION IN BARIATRIC SURGERY

Although the development of the set point theory would support that for the majority of adults, there appears to be a pre-determined inherent weight around which most will not significantly deviate from in the long term, there appear to be profound changes following bariatric surgery which contribute to weight loss which is maintained. Irrespective of the procedure performed, people tend to demonstrate a similar weight loss pattern following surgery with an initial period of rapid weight loss for the first 18 months followed by a period of weight stability and a subsequent very gradual weight regain. In spite of the recognized weight regain, what is key is that overall, following surgery, there seems to be a new, lower set point and the adoption of a similar weight gain trajectory as to what is seen in the general population.

Early views of bariatric surgery saw procedures characterized according to the mechanism by which they were thought to act with sleeve gastrectomy (SG) described as a volume reducing surgery, biliopancreatic diversion (BPD) seen as a hypoabsorptive procedure and Roux en Y gastric bypass (RYGB) as both. Subsequent mechanistic and behavioral studies have since produced greater insights in to the mechanisms of weight regulation, alterations in appetite and satiety and neurohormonal changes as well as bile acid metabolism which are now recognized as key regulators resulting in weight loss an improvement in metabolic dysfunction (41, 57, 58).

Neurohormonal Changes

The key to understanding many of the effects of bariatric surgery is an appreciation of the complex interaction between gut hormones and higher cortical centers which regulate appetite and satiety. Mechanistic studies following bariatric surgery have provided important insights on how these neurohormones mediate their effects as well as how these pathways may be modulated surgically and pharmacologically to produce sustained weight loss as well as improvements in metabolic dysfunction associated with obesity.

Central regulation of appetite and hunger occurs primarily within several nuclei located within the hypothalamus including the arcuate nucleus (ARC) which is one of the most well defined and characterized. Within the ARC, there are distinct neuronal subtypes which respond to signals from the brain stem as well as from within the circulation to potentiate their effects on appetite and hunger. Hunger stimulating neurons found within the medial ARC express neuropeptide Y (NPY) and agouti-related peptide (AgRP) which are recognized as the primary orexigenic neurons. Animal studies have contributed to characterizing the effects of these neurons with pharmacological activation of the NPY/AgRP neurons producing a rapid increase in food intake and fat stores while decreasing energy expenditure (59). The orexigenic effects of these neurons are counterbalanced by those within the lateral ARC, including pro-opiomelanocortin (POMC) and cocaine-and-amphetamine-related transcript (CART) neurons which decrease hunger and appetite α-melanocyte stimulating hormone (α-MSH) as it is one of the primary agonists of the anorectic melanocortin-4 receptor (MCR4) (60). The importance of the melanocortin pathway has been clearly illustrated by the effects of MCR4 deficiency in humans which has been identified as the most common cause of monogenic obesity. In these individuals, there is dysregulation of eating behaviors resulting in hyperphagia and obesity (61).

In addition, further peripheral feedback via gastrointestinal neurohormones plays an important role in modulating appetite and satiety. Although gut hormones have long been recognized to have essential roles within the gastrointestinal tract, regulating the release of insulin and exocrine secretions as well as altering motility, their central effects in regulating metabolism and energy balance

via the gut brain axis are becoming increasingly well recognized and characterized.

The adipocyte derived hormone, leptin, has been identified as an important mediator in the regulation of body weight, serving as a marker of nutritional status and overall fat mass. Although leptin has a bidirectional effect and may affect both anorectic and orexigenic pathways, it appears to be predominantly related to the preservation of body weight. Falling leptin levels secondary to decreased fat mass appear to stimulate orexigenic NPY neurons in the ARC of the hypothalamus, mediating increased appetite and food intake (62, 63). Although initially considered as a potential therapeutic target for those with obesity given its effects on appetite and food intake, studies have demonstrated that those with obesity have high circulating levels of leptin and may be resistant to its effects (64). Studies have shown that in people with obesity, the administration of exogenous leptin does not significantly impact food intake, nor does it result in a reduction in body weight aside from very rare cases of congenital leptin deficiency (65).

Ghrelin is the only characterized peripherally derived orexigenic neuropeptide, mediating its effects on appetite centrally within the ARC of the hypothalamus by activating NPY/AgRP neurons (66). Ghrelin is primarily produced peripherally by the stomach and centrally within the pituitary gland and the two sources have been seen to have differing means of signaling. Pituitary derived ghrelin mediates its effect directly via the hypothalamus whereas ghrelin produced from within the stomach is believed to act via vagal afferents as its effects have been shown to be diminished following vagotomy (67). In addition to mediating central changes in appetite, ghrelin also produces important changes in glucose homeostasis with ghrelin being shown to inhibit glucose-stimulated insulin secretion and impairs glucose tolerance (68). The primary regulator of plasma ghrelin levels appears to be overall caloric intake with levels rising and falling in line with food intake and fasting although the exact mechanisms by which ghrelin secretion is controlled have still not been elucidated. The importance of ghrelin in long-term weight regulation in those with obesity has been supported by studies which have demonstrated increased levels of ghrelin following diet induced weight loss, a change which was not seen in those with surgically mediated weight loss following bariatric surgery (69). Furthermore in people living with obesity, the normal physiological reduction in ghrelin levels in the post-prandial period is attenuated which suggests a potential role for ghrelin in the development of obesity (70).

Glucagon-like peptide-1 (GLP-1) is one of the best characterized neurohormones involved in the physiological and metabolic changes mediated by bariatric surgery, acting both through central and peripheral receptors to mediate its effects. GLP-1 is an incretin hormone which is secreted by the enteroendocrine L cells primarily located within the terminal ileum and colon in response to luminal nutrient exposure, particularly fats and carbohydrates (71). Within the gastrointestinal tract, GLP-1 has an important role in regulating gastric emptying and has been demonstrated to decrease the rate of gastric emptying and increasing post prandial satiety and fullness, an effect which is thought to be mediated via the vagus nerve (72). Studies in rodent models following vagotomy have demonstrated a lack of GLP-1 secretion following ingestion of high fat test meals, supporting the importance of the vagus nerve as a mediator of this response (73). The delay in gastric emptying has also been demonstrated to have an effect on glucose absorption rates and glycemia. In those given the GLP-1 antagonist there was an increased glycemic response following a carbohydrate test meal (72). The predominant effects of GLP-1 on altering glucose metabolism occur via its action as an incretin hormone. Within the pancreas, GLP-1 binds to β-cells stimulating insulin secretion in a glucose dependent manner. In addition, GLP-1 improves glucose sensitivity in glucose resistant β-cells, allowing previously resistant β-cells to sense and respond to glucose and hyperglycemia (74). The use of GLP-1 receptor agonists have also been shown in

rodents to increase β-cell proliferation while inhibiting apoptosis to increase overall β-cell mass (75). Further augmenting its effect on improving post prandial glycemia, GLP-1 also stimulates somatostatin by binding to GLP-1 receptors on pancreatic β-cells while inhibiting pancreatic glucagon secretion in a glucose dependent manner (76). Within the liver, GLP-1 inhibits hepatic glucose production while stimulating glucose uptake by muscle and adipose tissue. Centrally, GLP-1 is also produced within the nucleus of the solitary tract in the brainstem which projects to the hypothalamic paraventricular nucleus which expresses GLP-1 receptors (77). The small molecular size of GLP-1 allows it to cross the blood-brain-barrier thus GLP-1 receptor agonists given peripherally are thought to mediate central effects via receptors in the hypothalamus to promote satiety and reduce energy intake, contributing to weight loss.

Similar to GLP-1, peptide YY (PYY) is primarily secreted by the endocrine L cells within the terminal ileum in the postprandial period and has overlapping effects to GLP-1. Following its release, PYY results in delayed gastric emptying and decreased gastric secretion. Centrally, PYY acts within the arcuate nucleus of the hypothalamus by binding to the anorectic POMC neurons to inhibit feeding (78). Vagotomy results in an attenuated anorectic response to PYY, suggesting the potential role of the vagus in this pathway (79). In addition to its anorectic effects, PYY plays a role in weight maintenance via its effects on energy expenditure. In humans, peripheral infusion of PYY has been shown to increase energy expenditure as well as raising fat oxidation rates (80). Further establishing the role of PYY in body weight regulation was a study that demonstrated a negative correlation between fasting PYY levels and levels of adiposity and resting metabolic rate (81). In people living with obesity, there is a lower postprandial PYY level compared to normal body weight individuals in response to a test meal, which was associated with decreased satiety and relatively increased food intake (82). Peripheral administration of PYY produces a similar reduction in food intake in those with obesity as in those of a normal body weight, suggesting that PYY resistance is not likely contributing to the development of obesity (83).

Bile Acid Metabolism

In addition to the critical role neurohormones are thought to play in long-term weight regulation, changes in bile acid (BA) metabolism have been recognized as a potential key mediator, which may contribute to long term weight loss following bariatric surgery. Studies in both human and rodent models have demonstrated increased plasma bile acids following Roux en Y gastric bypass (RYGB), sleeve gastrectomy (SG), and biliopancreatic diversion (BPD) in both human and rodent models. The farnesoid X receptor (FXR) is a nuclear BA receptor and is an important regulator of genes which are involved in BA synthesis and transport in addition to its role in lipid and glucose metabolism (84). There is growing interest that changes in BA metabolism via FXR are a key link between the alterations in BA composition following bariatric surgery and the improvements in glucose homeostasis and remission of T2DM. Studies in rodent models have supported the potential relationship between alterations in BA metabolism mediated by the FXR with weight loss and improvements in glycemic control. In mice with diet induced obesity undergoing SG and FXR receptor genetic disruption, there was a clear decrease in weight loss and improvements in glycemia compared to wild type littermates also undergoing SG, establishing the importance of a functional FXR to mediate some of the metabolic improvements following surgery (85). It is thought that the increase in plasma bile acids results in FXR activation which in turn produces an increase in FGF19 which has effects mimicking the actions of insulin, increasing glycogen synthesis while decreasing gluconeogenesis (86).

Increased plasma BA are also thought to induce metabolic changes following bariatric surgery by binding to the G protein coupled receptor, TRG5, which is expressed in the distal ileum. Found within

the enteroendocrine L cells, BA are thought to activate TGR5, which is a key element in the signaling pathway responsible for increasing GLP-1 production (86). In addition to the changes in glucose metabolism mediated by TGR5 activation, it is thought that this receptor may play a role in contributing to an overall shift towards a negative energy balance in the postoperative period, resulting in increased oxygen consumption and energy expenditure.

Table 1. Possible Mechanisms of Bariatric Surgical Effect.
Induce satiety, reduce appetite, control hunger
Change of taste preference - less sweet foods; lower fat content
Reduce caloric Intake
Diversion from proximal duodenum
Malabsorption of macronutrients
Increased energy expenditure; Increased diet-induced thermogenesis
Changes in the normal homeostatic adaptations to weight loss
Changes in the gut microbiome
Changes in plasma bile acid levels
Changes in gut hormones: candidates include the incretins (GLP-1; GIP), ghrelin, CCK, Peptide YY
Central mechanisms: Modify hedonics; central appetite control; altered food preferences

OUTCOMES AFTER BARIATRIC SURGERY

Mortality And Adverse Events

PERIOPERATIVE MORTALITY

Although there is often a perception that bariatric surgery should be reserved as treatment of last resort when all other approaches have not been effective, this is not supported by current data. Early data on morbidity following bariatric surgery was significantly higher but has remarkably decreased in part owing to the near universal adoption of the minimally invasive approach and advances in surgical techniques.

UK registry data looking at all primary bariatric operations from 2009-2016 demonstrated a 30-day mortality rate of 0.08% after discharge with an overall downward trend in mortality over the study period. Similarly, a population based study comparing 30 day, 90 day, and 1 year mortality rates demonstrated that bariatric surgery had the lowest mortality rate over all time periods compared to other common elective procedures including cholecystectomy, hysterectomy, and hip and knee arthroplasty (87, 88).

Early Adverse Events (<30 days)

Overall, the incidence of adverse events in the early postoperative period is low, with similar rates seen in randomized controlled trials comparing different procedures. In a review of more than 100,000 cases, the most common early adverse events were not directly related to the procedure, rather they were myocardial infarction and pulmonary embolus which were seen in 1.15 and 1.17% of cases respectively (89). These two complications were also associated with the highest mortality rate amongst those experiencing early postoperative complications (89). Bleeding in the early postoperative period although potentially serious and requiring a return to operation room is uncommon with rates cited between 0.5% for SG and 1% following RYGB (90).

Looking specifically at procedure related complications, staple line leak following SG although uncommon remains a concern as it can be challenging

to treat. A systematic review of 148 studies including more than 40,000 individuals found an overall leak rate of 1.5% (91). Several techniques have been identified to help reduce the risk of leaks including reinforcement and buttressing, however, no consensus exists as to the ideal approach. Although RYGB is seen as a technically challenging procedure due to the formation of two anastomoses, the risk of anastomotic leak is approximately 1% and an overall complication rate of 4.4% (92, 93). Similar rates of anastomotic leak have been reported following OAGB (94).

Late Adverse Events

Depending on the specific procedure several long-term medical problems can occur and include micronutrient deficiencies, dumping syndrome, hypoglycemia, cholelithiasis, nephrolithiasis, and osteoporosis and fractures. These medical problems are discussed in detail in the Endotext chapter entitled Medical Management of the Postoperative Bariatric Surgery Patient (95).

RYBG is the procedure with the greatest amount of data to support its long-term safety and efficacy. However, there are several well characterized long-term complications which may arise. Internal herniation, although rare, occurs in approximately 2-3% following RYGB, presenting with symptoms of small bowel obstruction, most commonly severe abdominal pain (96). It is important to have a high index of suspicion with these symptoms as definitive diagnosis based on imaging alone is unreliable and diagnostic laparoscopy should be considered (97). It is also worth noting that studies have found that up to 10% of individuals report chronic abdominal pain following RYGB which can be difficult to treat and may impact negatively on quality of life (98, 99).

One of the primary concerns in the long-term for patients undergoing SG is the possibility of developing de novo reflux or the worsening of pre-existing symptoms which can be difficult to treat (100). A RCT with 5-year follow-up demonstrated that 16% of patients following SG developed de novo reflux vs 4% undergoing RYGB (46). The SM-BOSS study also found a reflux remission rate of 60.4% compared to 25.0% following SG (101). In patients with severe reflux following SG, conversion to RYGB has been found to be effective in improving or treating symptoms (102). Given the concerns regarding the long-term risk of reflux and the development of Barrett's esophagus, IFSO has issued guidance to recommend surveillance endoscopy one year postoperatively and then every 2-3 years thereafter (39).

Although there is more limited long-term data for patients undergoing OAGB, studies have shown that up to 41% of patients at 5 years reported gastro-esophageal reflux compared to 18% of those undergoing RYGB (103). Given the anatomical configuration, bile acid reflux and esophagitis has also been found endoscopically and although the long-term implications are unknown, it does raise concerns regarding future cancer risk (104).

Considering the nature of bariatric surgery, a commitment to long-term follow up, particularly focusing on nutritional supplementation and monitoring, is an essential element in the decision to proceed with an operation. However, the specific requirements are largely procedure specific and determined by the anatomical changes involved. Although relatively rarely performed DS is noteworthy not only for the weight loss and improvement in metabolic dysfunction it can result in relatively high-risk nutritional deficiencies compared to other procedures.

Weight Loss Outcomes

The ability to produce not only profound weight loss but weight loss which is sustained in the long term is

essential to the success of bariatric as a treatment for obesity, which is recognized as a chronic and progressive disease. As such, the importance of studies can in some ways be categorized according to the length of their follow-up period when considering their clinical relevance or impact although clearly the soundness of the overall methodology is the primary determinant. Short-term studies (1 - 3 years) are plentiful but simply suggest potential effectiveness. Medium term studies (3 -10 years) are far fewer but are more assuring of real effectiveness. There is also now mounting longer term data emerging which further adds to the more than 25-year follow up of the landmark Swedish Obese Subjects (SOS) study.

SHORT AND MEDIUM-TERM OUTCOMES

In recent years, there have been a number of RCTs with 5-year follow up periods which have emerged comparing weight loss between different procedures. The SM-BOSS study was a multi-center RCT comparing SG to RYGB with a primary end point comparing weight loss (101). At 5 years, the study did not show a statistically significant difference in excess BMI loss with -61.1% seen following SG compared to -68.3% following RYGB. Similarly, the SLEEVEPASS study also sought to compare SG to RYGB with the primary end point of weight loss measured as % excess weight loss (EWL) (105). The %EWL at 5 years was 49% after SG and 57% following RYGB, however, this difference was not statistically significant. The individual participant data of both studies were merged with the results supporting a greater percentage BMI loss and resolution of hypertension with RYGB compared to SG but no difference in T2DM remission or quality of life at 5 years (106).

While none of the published data at present clearly supports the superiority of one procedure over another, there are two ongoing RCTs, ByBandSleeve and Bypass Sleeve Equipoise Trial (BEST) which may change this (107, 108).

LONG-TERM (>10 YEAR) OUTCOMES

The prospective Swedish Obese Subjects (SOS) study was a key step in establishing the effect of bariatric surgery in people with obesity compared to usual care and now has more than 25 years of follow-up data. Follow-up data which was measured at 2, 10, 15, and 20 years demonstrated -23%, -17%, -16% and -18% mean changes in body weight in the surgery group compared to between 1% and -1% in the standard care group at these same time points (6). It is worth noting that this study included several procedures such as gastric banding and vertical banded gastroplasty which are no longer commonly performed.

Looking specifically at RYGB, there is mounting data to support the long-term weight loss produced by the procedure. A prospective study looking at 1156 participants undergoing RYGB over a 12 year follow up period found a -26.9% mean percent weight loss (45). The mean percent weight loss at 6 years was similar at -28% suggesting that weight remained relatively stable after the initial period of weight loss in the first year. These results were similar to a retrospective cohort analysis of 10-year weight loss outcomes following RYGB which showed a mean weight change of -28.6% (109).

Data looking at >10-year outcomes for SG is more limited, however, the 10-year observational follow up study of the SLEEVEPASS study showed a mean excess weight loss (EWL) of 43.5% (110). Similarly, high quality studies evaluating the >10-year weight loss outcomes are limited for OAGB given the relative recent adoption of the procedure. However, a retrospective single-center analysis of 385 participants showed a mean % total weight loss (TWL) of 33.4% (111). Although infrequently performed due to the high complication and reoperation rate, BPD/DS remains the procedure which produces the most substantial weight loss with studies showing a 10 year TWL of 40.7% (50).

Overall, it would appear that the effect of bariatric surgery, irrespective of the procedure performed, is a period of rapid weight loss followed by prolonged weight stability which is essential to improving long-term morbidity and mortality.

Type 2 Diabetes and Bariatric Surgery

Type 2 diabetes and obesity are inherently linked diseases and improvements in glycemic control has become one of the earliest indicators that surgical modification of the gastrointestinal tract could result in profound metabolic changes and indeed could help modify the underlying disease process. Early studies looking at jejuno-ileal bypass demonstrated a rapid normalization of blood glucose in the early postoperative period, prior to any weight loss, which first raised the possibility that these operations could produce changes in a weight loss independent manner. The 1995 observational study which showed a normalization of glycemia in more than 600 people with obesity and T2DM undergoing RYGB was one of the first to create widespread interest in the possibility of employing surgery as a treatment for T2DM (112). Having recognized this effect, the metabolic effects of bariatric surgery and its implications for T2DM have become one of the main focuses of research. RCTs comparing bariatric surgery to medical management alone have consistently demonstrated that it is more effective in improving glycemia and cardiovascular risk factors, irrespective of the procedure performed. As such, it is now endorsed by governing bodies world-wide as a central element of the treatment algorithm for people with T2DM and obesity (113).

The STAMPEDE trial was a RCT comparing the use of bariatric surgery, either SG or RYGB in conjunction to intensive medical therapy (IMT) compared to IMT alone (8). Over a 5 year follow up period, only 5% of the participants in the IMT group reached an HbA1c of <6% vs 23% undergoing SG and 29% following RYGB. A further study involving three arms compared RYGB to BPD and medication. Over a ten year follow up period, T2DM remission rates were 25% for RYGB, 50% for BPD, and 5.5% for those treated with medication, however, that includes one participant who crossed over from the medical therapy group to surgery (7). Although the study showed that the remission rates decreased in both surgical groups between the 5 and 10-year follow up period and was lower particularly within the RYGB group, even in those who did relapse, glycemic control remained very good (HbA1c<7% or <53mmol/mol). The ARMSS-T2DM study a pooled analysis of four RCTs is currently the largest analysis with the longest follow up comparing bariatric surgery with medical treatment/lifestyle modification for T2DM (114). At 12 years, the between group difference in HbA1c levels was -1.1% with none of the patients in the medical group in remission compared to 12.7% in remission in the bariatric surgery group. The patients in the bariatric surgery group were also using fewer anti-diabetes medications.

REMISSION RATES IN RCTs

As of April 2024, there were 12 randomized controlled trials which irrespective of the type of surgery have consistently demonstrated the greater improvements in glycemic control and disease remission with bariatric surgery compared to medical therapy (8, 10-16, 18, 115-117) All studies have compared one or more bariatric procedures with a group having non-surgical treatment (NST). The difficulty in drawing firm conclusions is in part due to the studies not being directly comparable due to extensive heterogeneity, including different criteria for patient selection, treatment durations, and the use of various definitions of remission of diabetes, particularly the cut-off values for HbA1c. Nevertheless, they serve to provide key comparisons with NST, the current offering to more than 99% of people with diabetes.

The first of the studies was performed the Centre for Obesity Research and Education (CORE) in Melbourne (115). 60 patients were randomized to LAGB or NST. They were required to have a BMI between 30-40kg/m^2 and to have been known to have

T2DM duration < 2 years. At 2-year follow up, 73% of patients were in remission (defined as a HbA1c < 6.2%) following LAGB vs 13% in the NST group.

The STAMPEDE study randomized 150 patients to either intensive medical therapy (IMT) alone or IMT plus SG or RYGB. Remission was defined as an HbA1c <6.0%. At 5 years, remission rates were 5% in the IMT group vs 23% following SG and 29% following RYGB.

Mingrone et al report the longest follow up having completed a 10 year follow up of 60 patients to NST, BPD, or RYGB (7). They used criteria of HbA1c <6.5% and fasting glycemia <5.55mmol/L without medication for one year to define remission. Of all the patients who initially went into remission in the surgical group, 37.5% remained in remission at 10 years with 25% for RYGB and 50% for BPD. 20 of the 34 patients in the surgical group who were in remission at 2 years subsequently relapsed by 10 years, however, all maintained good glycemic control with a mean HbA1c of 6.7%. There were two patients within the medical group at 10 years who were in remission included in the intention to treat analysis. However, these were both patients who had surgery during the follow up period.

Ikamuddin et al (118), carried out a multicenter RCT with 120 patients undergoing either RYGB or having NST. The defined remission as HbA1c <6% at consecutive annual visits without the use of medications. None of the participants in the medical therapy group were in remission at any point during the study while 16% of the participants who underwent RYGB were in remission at year two and 7% at year five.

Courcoulas et al randomized 69 patients into 3 groups – NST, RYGB, and LAGB (13). They defined remission as HbA1c< 6.5% and FBG <125mg/dL. At five years, the reported remission rates were 30% for the RYGB group and 19% for LAGB while none of the patients in the medical group were considered to be in remission.

A Summary of the RCTs to date comparing the long-term efficacy of metabolic surgery compared to medication or lifestyle modification for T2DM can be seen in Table 2 (Adapted from Courcoulas et al (114)).

Table 2. RCTs Comparing Long-Term Efficacy of Metabolic Surgery vs. Medication or Lifestyle

Study	No of participants	Follow-up (months)	Study design	Remission criteria	Remission* (%)	P value
Parikh (8)	57	6	RYGB/LAGB/SG *v* control	HbA_{1c}<6.5%	65 *v* 0	0.001
Liang (9)	101	12	RYGB *v* control	HbA_{1c}<6.5%	90 *v* 0	<0.001
Halperin (10)	38	12	RYGB *v* control	HbA_{1c}<6.5%	58 *v* 16	0.03
Ding (11)	45	12	LAGB *v* control	HbA_{1c}<6.5%	33 *v* 23	0.46
Cummings (12)	43	12	RYGB *v* control	HbA_{1c}<6.0%	60 *v* 5.9	0.002
Dixon (13)	60	24	LAGB *v* control	HbA_{1c}<6.2%	73 *v* 13	<0.001
Wentworth (14)	51	24	LAGB *v* control	FBG <7.0 mmol/L	52 *v* 8	0.001
Simonson (15)	45	36	LAGB *v* control	HbA_{1c}<6.5% and FBG <126 mg/dL	13 *v* 5	0.60
Kirwan (16)	316	36	RYGB/LAGB/SG *v* control	HbA_{1c}≤6.5%	37.5 *v* 2.6	<0.001
Schauer (17)	150	60	RYGB *v* SG *v* control	HbA_{1c}≤6.0%	22 *v* 15 *v* 0	<0.05

Ikramuddin (18)	120	60	RYGB *v* control	HbA_{1c}<6.0%	7 *v* 0	0.01
Courcoulas (19)	69	60	RYGB *v* LAGB *v* control	HbA_{1c}<6.5% and FBG <125 mg/dL	30 *v* 19 *v* 0	0.02
Mingrone (20)	60	120	RYGB *v* BPD *v* control	HbA_{1c}<6.5% and FBG <100 mg/dL	25 *v* 50 *v* 5.5	0.008

V= versus

DURABILITY OF REMISSION

As long-term evidence from RCTs has emerged, it would support that some of the metabolic effects appear to diminish over time, which perhaps in part reflects the underlying nature of diabetes, which is understood as both chronic and progressive. The SAMPEDE study found a three-year remission rate following RYGB of 38% which fell to 22% at five-years (8, 119). The suggestion that the metabolic effects of RYGB are attenuated with time were supported by the RCT with the longest follow up which found the remission rate fell from 75% at 2 years to 37% at 5 years and 25% at 10 years (7).

The effects of SG were examined in the STAMPEDE study which showed a reduction in remission rates from 37% to 24% between years 1-3 and 15% at 5 years (8). The initial remission rates as well as long-term remission have been demonstrated to be highest following BPD with 63% in remission at 5 years and 50% at 10 years (7).

MACROVASCULAR AND MICROVASCULAR COMPLICATIONS

The durability of remission and the reduction of complications has been demonstrated at a fifteen year follow up in the SOS study, a prospective matched cohort study (120). They reported that the remission rate for the surgical group, predominantly gastroplasty, at two years was 72% and at 15 years was 31%. This remission rate, though reduced with time, was significantly better than the 6.5% in the control group, indicating an important long-term benefit. Furthermore, and arguably more important than the remission rate, they found the number macrovascular and microvascular complications of diabetes were fewer at 15 years in the surgical group than in the controls.

OTHER HEALTH OUTCOMES AFTER BARIATRIC SURGERY

Cancer

Obesity has been demonstrated to not only be a risk factor for the development of certain types of cancer but may also increase the risk of mortality associated with cancer. The SOS study was the first interventional trial which demonstrated a decreased incidence of cancer, amongst patients undergoing bariatric surgery compared to matched controls (121). Since then, there has been increased recognition of the possibility that weight loss mediated by bariatric surgery may reduce both the incidence of cancers as well as improving long term outcomes. A subsequent matched cohort study, the SPLENDID study demonstrated reduced cumulative incidence of mortality related to 13 types of cancer in patients undergoing bariatric surgery compared to the non-surgical group with an adjusted HR of 0.52 (122). Further studies examining the effect of bariatric surgery specifically on the incidence of non-hormonal cancers demonstrated a nearly 50% reduction in patients undergoing bariatric surgery compared to matched controls (123).

Cardiovascular Disease

Obesity is one of the most important modifiable risk factors in the prevention of cardiovascular disease. However, until the publication of several critical studies, what was not clear was whether or not weight loss achieved through surgical means could modify individual cardiovascular risk factors and produce a resultant improvement in mortality. There are now more than 30 observational studies which have examined primary prevention of cardiovascular disease, demonstrating reduced morbidity and mortality in patients with obesity undergoing surgery compared to usual care. The SOS study which has more than 30 years of follow up data has demonstrated the long-term benefits of bariatric surgery on reducing cardiovascular risk, demonstrating a 30% reduction in death from cardiovascular disease (6). One of the largest observational studies to date including nearly 14,000 patients found a 62% reduction in new onset heart failure, 31% reduction in myocardial infarction rates, 33% reduction in stroke, and a 22% reduction in atrial fibrillation (124).

Liver

The term metabolic dysfunction-associated steatotic liver disease (MASLD) is a broad categorization of a spectrum of liver diseases ranging from hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH, which can progress to cirrhosis and end-stage liver disease. MASLD is now the most common cause of chronic liver disease globally; however, its implications have up until recently been largely underappreciated due to the fact that many patients are asymptomatic. In patients with obesity, the incidence of disease is far higher, and the entire spectrum of disease is seen, with up to 80% having steatosis, 37% MASH, 23% fibrosis, and 5.8% cirrhosis (125).

The majority of patients with MASLD are asymptomatic and a significant proportion will also be biochemically normal; thus, a diagnosis of MASLD can only be made on the basis of imaging studies. It is difficult to monitor the progression of MASLD, particularly in those with normal liver enzymes; however, one-third of patients with early-stage MASH will progress to fibrosis within five to ten years of diagnosis (126). Given the growing number of individuals affected by obesity and MASLD, it is anticipated that MASH will become the leading indication for liver transplantation (127). An increasing body of evidence supports the consideration of MASH and fibrosis as a significant obesity-related complication and recommend its inclusion as an indication for bariatric/metabolic surgery, given their potential reversibility with substantial weight loss mediated by surgery.

A meta-analysis of 21 studies, including over 2000 patients undergoing bariatric/metabolic procedures, found a resolution of steatosis or steatohepatitis and biochemical normalization in most patients (128). The critical finding was that in those with severe disease and established fibrosis there was a reversal of these changes in 30% of patients.

Dyslipidemia of Obesity

Increased fasting triglyceride and decreased high-density lipoprotein (HDL)-cholesterol concentrations characterize the dyslipidemia of obesity and insulin resistance (129). This dyslipidemia pattern is highly atherogenic and a common pattern associated with coronary artery disease (130). Bariatric surgery produces substantial decreases in fasting triglyceride levels, a normalization of HDL, and an improved total cholesterol–to–HDL-cholesterol ratio (131-133). Although elevation of total cholesterol is not purely obesity-driven, evidence would support that procedures such as OAGB and RYGB (134) can produce significant improvements in total cholesterol levels(135).

Hypertension

There is evidence of a reduction in both systolic and diastolic blood pressure (BP) following weight loss in association with bariatric surgery (136). The GATEWAY study examined the long-term effects of bariatric surgery on hypertension (HTN) control and remission. The RCT involved 100 participants comparing 5-year outcomes in people with HTN on medical therapy alone vs RYBG and medical therapy. RYBG was associated with HTN remission in 46.9% of participants compared to 2.4% of those in the medical therapy group. The number of medications required to maintain BP<140/90mmHg was reduced by 80.7% following RYGB (137).

Asthma

There is a positive relationship between asthma and obesity with a possible dose-response effect (138, 139). The Nurses' Health study identified a five-fold increase in the relative risk of asthma with a weight gain of 25kg from age 18 when compared to a weight stable group (140). In patients with obesity, outcomes from asthma are worse with more patients with poor control despite maximal therapy, more frequent exacerbations, and poorer quality of life (141). Given the link between sustained weight loss and improvements in asthma, there has been significant interest in the possible role of surgery in the management of patients with obesity and asthma. A systematic review of studies involving SG, LAGB, RYGB and BPD described a consistent improvement in pulmonary function tests following bariatric surgery as well as quality of life (142).

Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by recurrent episodes of upper airway obstruction and hypoxia during sleep due to abnormal airway collapsibility. Excess weight is the strongest independent risk factor in the development of obstructive sleep apnea, with a 10% change in body weight associated with a 30% worsening in the apnea-hypopnea index (AHI), one of the primary indexes for measuring severity (143). A systematic review of 69 studies found that irrespective of the procedure performed, bariatric surgery resulted in a significant improvement in most patients. These findings were supported by a further meta-analysis which found 83.6% of patients reporting resolution or improvement of symptoms (144). Although there is evidence demonstrating significant improvements with regard to the AHI, it is essential to note that despite this, most patients following treatment remain within the moderate to severe range. Bariatric surgery should not be undertaken with the goal of cure in mind, but rather to control or reduce disease severity.

IMPROVEMENT IN QUALITY OF LIFE (QOL)

Several studies clearly demonstrate major QOL improvements following bariatric procedures (145-149). A large prospective study of QOL after bariatric surgery employed the Medical Outcomes Trust Short Form-36 (SF-36). The SF-36 is a reliable, broadly used instrument that has been validated in people living with obesity. In this study, 459 participants with complex obesity were found to have lower scores compared with a control population for all 8 aspects of QOL measured, particularly the physical health scores. Weight loss provided a dramatic and sustained improvement in all measures of the SF-36. Improvement was greater in those with more preoperative disability, however, the extent of weight loss was not a good predictor of improved QOL. Even for patients who required revisional surgery during the follow-up period, they found a similar improvement in measures of QOL. Similar improvements in QOL have been demonstrated in patients having LAGB for previously failed gastric stapling (150).

IMPROVEMENT IN SURVIVAL

The ultimate test of effectiveness of a treatment is the reduction of mortality. There is a growing body of evidence on long-term mortality of people who have undergone bariatric surgery compared to people with obesity who have not had surgery which shows improved survival. The SOS study demonstrated that over a median follow up period of 24 years that there was a lower risk of mortality in the people who had undergone surgery compared to the matched controls which resulted in a median increase in life expectancy by 2.4 years (6). The risk of death from both cardiovascular risk but also cancer was lower in the patients who had undergone surgery. In spite of these improvements, the group of patients who had undergone surgery still had an 8-year shorter life expectancy relative to the general population with the leading cause of death being cardiovascular disease.

A systematic review and meta-analysis of 16 matched cohort studies and one prospective controlled trial found that there is a median improvement in life expectancy of 6.1 years in patients who had undergone bariatric surgery compared to usual care. Although both participants with and without T2DM demonstrated an increased overall survival, the treatment effect was considerably larger for those with T2DM with an increased life expectancy of 9.3 years compared to the non-surgical group. The number needed to treat to prevent one additional death in 10 years was 8.4 for people with T2DM compared to 29.8 for those without (151).

FUTURE DIRECTIONS COMBINING MEDICATIONS WITH SURGERY

There has long been a focus on comparing outcomes for the treatments of obesity and related diseases, particularly T2DM looking at the use of either surgery or medical therapy. Although studies have consistently demonstrated the efficacy of surgery in achieving long-term reductions in weight and improvements in diabetes, it is clear from our understanding of the disease process itself that obesity is a chronic and progressive disease which will over time require treatment intensification. Looking to the management of other diseases, including cancer, surgery is often viewed as a means of establishing disease control with adjunctive medical therapies to sustain this effect in the long-term (152, 153).

The concept of utilizing medication with bariatric surgery has been demonstrated to be both safe and effective as demonstrated by the STAMPEDE trial in which both RYGB and SG were combined with IMT. Impressive advances in pharmacotherapy initially developed as anti-diabetes medications but equally recognized for its efficacy in producing weight loss in people without diabetes has made the potential for employing multi-modal care even more promising, improving long term disease control and remission.

WHO SHOULD BE CONSIDERED FOR BARIATRIC SURGERY?

For many years, the criteria for bariatric surgery were largely based on the National Institutes of Health (NIH) guidelines issued more than 30 years ago in 1991 (154). These guidelines were highly constrained by BMI cut offs and based on surgical outcomes from the era of open surgery. Having recognized the significant advances in surgery, safety outcomes as well as our greater understanding of the disease process, related disease, and mechanisms of action of surgery, IFSO and ASMBS jointly released updated guidelines in 2022 (1).

Major changes to the previous guidelines include:

- Metabolic and bariatric surgery (MBS) is recommended for individuals with BMI>35kg/m^2 regardless of the presence of obesity related disease.
- MBS should be considered for individuals with a BMI 30-34.9kg/m^2 with metabolic disease.
- BMI thresholds should be adjusted in the Asian population such that a BMI>25kg/m^2 suggests

clinical obesity and individuals with a BMI>27.5kg/m^2 are offered MBS.
- Appropriately selected children and adolescents should be considered for MBS.

NEEDS AND CHALLENGES

Bariatric surgery should be viewed as a process of care that begins with a careful initial clinical evaluation and detailed patient education, continuing beyond the operative procedure through a permanent follow-up. The increasing number of safe and effective bariatric procedures should be seen as part of a growing number of treatments for obesity which may need to be combined in a stepwise and progressive approach to achieve long-term disease control. Improving care for people with obesity undergoing bariatric surgery is an evolving process as our understanding of the disease itself and its implications for people living with obesity deepens. Future areas which remain to be improved include

- A better understanding of the mechanisms of action of each procedure is required to enable optimum surgery and follow up.
- Accurate and comprehensive data management. Bariatric surgical procedures should be incorporated into national clinical registries to enable objective assessment of the risks and benefits across the community.
- More randomized controlled trials to improve our understanding of the long-term outcomes of different procedures and their implications for control of obesity related co-morbidity
- Improved evidence-based decision-making pathways to help determine who would benefit most from bariatric surgery.
- High quality clinical trials looking at the use of multimodal care, combining bariatric surgery with pharmacotherapy to improve long-term disease remission and control.
- Definition of safe and efficient pathways for assessment, surgery. and post-surgery care.
- Greater focus on understanding the implications of obesity stigma, how it affects patient care and what clinicians can do to address these inequalities.

Bariatric surgery has the potential to be one of the most important and powerful treatment approaches in medicine. High quality clinical care, good science, and comprehensive data management will allow optimal application of this approach to be realized.

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