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Roux-en-Y Gastric Bypass versus Sleeve Gastrectomy – a Meta-Analysis

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A research report submitted to the Department of Surgery, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree Master of Medicine in Surgery.

Johannesburg, 2013

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine in Surgery to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

Sarah Lena Nietz

day of 2013

PREFACE

My interest in bariatric surgery was sparked during an assignment to prepare a talk on bariatric procedures with specific emphasis on sleeve gastrectomy for a national registrar symposium. My exposure to this rapidly evolving field has been very limited as bariatric procedures are currently not performed in our provincial training hospitals. During my preparation I was given the opportunity to visit a private bariatric center. I was intrigued by the technically challenging laparoscopic procedures observed as well as the astounding postoperative effects I noticed on ward rounds. These were not limited to pure weight loss but included notable improvement in quality of life, early satiety and change in eating habits. However, foremost was the rapid improvement of comorbidities such as diabetes mellitus. How was it possible that insulin requirements markedly decreased within days following the procedure, long before any notable weight loss? This lead me to further research the intricate mechanisms that result in comorbidity resolution and weight loss following bariatric surgical procedures. I was able to understand the metabolic and neurohumoral changes that occur following complex procedures such as Roux-en-Y gastric bypass or biliopancreatic diversion but found myself at a loss understanding how a “simpler” procedure such as sleeve gastrectomy could achieve similar results. The sleeve gastrectomy is an emerging bariatric procedure and despite limited experience has rapidly gained popularity. Nevertheless, its relevancy appeared highly controversial in discussion with local experts and led me to ask *what is the evidence for sleeve gastrectomy in the treatment of morbid obesity?*

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My family and friends for their support and understanding during this time-consuming task.

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AGB	adjustable gastric banding
BAROS	Bariatric Analysis and Reporting Outcome System
BMI	body mass index
BOLD	Bariatric Outcomes Longitudinal Database
BPD	biliopancreatic diversion
BPD/DS	biliopancreatic diversion with duodenal switch
β-cells	Beta-cell (pancreas)
cm	centimeter
CRP	C-reactive protein
DVT	deep vein thrombosis
et al.	et alia
EWL	excess weight loss
FDA	Food and Drug Administration
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
GORD	gastro-oesophageal reflux disease
HbA1c	glycated haemoglobin
HDL	High-density lipoprotein
HOMA-IR	homeostasis model assessment for insulin resistance

kg/m^2	kilogram per square meter
LDL	Low-density lipoprotein
MD	mean difference
NIH	National Institutes of Health
NPY	neuropeptide Y
PE	pulmonary embolus
PYY	peptide YY
pg	page
PYY	peptide YY
RCT	randomized controlled trial
RYGB	Roux-en-Y gastric bypass
SG	sleeve gastrectomy
SOS	Swedish Obese Subjects
UKCRN	UK Clinical Research Network
USA	United States of America
VTE	venous thrombembolism
WHO	World Health Organization
$	United States Dollar

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ABSTRACT

Background

Morbid obesity is a growing pandemic and is a direct cause of diseases such as type 2 diabetes. Bariatric surgery is an effective long-term treatment modality. There are several procedures that have been described, however, sleeve gastrectomy (SG) has gained popularity despite a paucity of evidence for its use. In contrast, the Roux-en-Y gastric bypass (RYGB) has been validated and is considered the gold standard in bariatric surgery. Currently there is no evidence proving superiority of RYGB over SG.

Objectives

To determine whether SG is as effective as RYGB.

Methods

Randomized controlled trials (RCTs) comparing adults undergoing laparoscopic RYGB or SG for treatment of morbid obesity were compared in a fixed-effect model meta-analysis. Outcomes included measures of weight loss, improvement of comorbidities, procedure-related morbidity and mortality, and changes in gut hormone levels. Heterogeneity was assessed using the I^2 test, and all studies were assessed for bias.

Results

Eight RCTs were included in this review. No mortalities were reported. SG had lower rates of morbidity, re-operation and re-hospitalization, but this was not statistically significant. There was no significant difference between SG and RYGB for parameters of weight loss and diabetes resolution after 12 months follow-up. RYGB significantly improved dyslipidaemia with statistical differences in triglyceride and LDL reduction (MD=-0.17,

p=0.05 and MD=-0.43, p=0.002 respectively). SG lowered fasting ghrelin levels (MD=342.96, p=<0.00001), RYGB lowered leptin levels (MD= -6.96, p=0.02), and there was no difference in PYY levels.

Conclusions

SG and RYGB were equivalent in procedural morbidity and mortality, weight loss and parameters of diabetes resolution at 12 month follow-up. RYGB had a superior resolution of dyslipidaemia.

1. INTRODUCTION

1.1 Clinical Significance of Obesity

Obesity is a serious disease with significant complications that is rapidly developing into a pandemic (1). It has been recognized as a major threat to global health. The World Health Organization (WHO) estimated that globally more than 1.4 billion adults were overweight in 2008 (2). In South Africa, one in three men and one in two women are thought to be overweight or obese (3).

Body mass index (BMI) is considered to represent the most practical measure of a person's adiposity. Most expert groups endorse the recommended classifications for BMI adopted by the National Institute of Health (NIH) and WHO (2,4):

- 25-29.9 kg/m^2 is considered overweight
- 30 to 34.9 kg/m^2 is considered obese (class I obesity)
- 35 to 39.9 kg/m^2 is considered moderately obese (class II obesity)
- 40 to 49.9 kg/m^2 is considered severely or morbidly obese (class III obesity)

In response to the increasing and broad extent of obesity seen and varying risks and outcomes experienced, the surgical community has developed further categories for patients with higher BMIs and classifies patients with a BMI >50.0 kg/m^2 as “super obese”, >60 kg/m^2 as “super super“ or “supra super” obese and >70 kg/m^2 as “mega obese” (5-8).

Obesity is associated with an increased risk of death and carries a significant risk of life-threatening complications such as ischaemic heart disease, cardiac failure, diabetes and high blood pressure (9). The WHO comparative risk assessment estimates that in adults older than 30 years of age, increases in BMI above the theoretical optimum of 21 kg/m^2

are associated with an estimated 58% of type 2 diabetes mellitus, 39% of hypertensive disease, 32% of endometrial cancer, 23% of ischaemic stroke, 21% of ischaemic heart disease, 13% of osteoarthritis, 12% of colon cancer and 8% of postmenopausal breast cancer (10). A South African study revealed that the burden of disease attributable to excess body weight was 87% for type 2 diabetes, 68% for hypertensive disease, 61% for endometrial cancer, 45% for ischaemic stroke, 38% for ischaemic heart disease, 31% for kidney cancer, 24% for osteoarthritis, 17% for colon cancer and 13% for postmenopausal breast cancer (11).

The greatest association of comorbidity attributable to obesity is diabetes mellitus and prevalence of diabetes is increasing globally (12). In 2011, an estimated 366 million people had diabetes; a number that is predicted to increase to 522 million by 2030 (13). The combination of obesity and diabetes has been labelled diabesity (14); more than 60% of type 2 diabetics are obese and the incidence is virtually exponentially increased in severely obese subjects (15). Obesity appears to cause chronic low-grade inflammation which contributes to the development of metabolic syndrome (16). Metabolic syndrome describes a cluster of risk factors for cardiovascular disease and diabetes (17) including dysglycemia, dyslipidaemia, raised blood pressure and obesity. Metabolic syndrome is common and has a rising prevalence worldwide largely due to increasing obesity and sedentary lifestyles (18).

Besides the demonstrated expense of obesity regarding overall health impairment, the monetary cost of obesity related complications and their management is high. In the United States of America (USA), annual national aggregate direct medical cost of overweight and obesity has been estimated to be $113.9 billion; when limiting analysis to nationally representative studies only, the aggregate national cost of overweight and obesity amounts to $170.2 billion. This equals 7.1% of total healthcare spending in the

USA in 2008 (19). Health care workers, politicians and leaders in health must find ways of combating this potentially crippling disease for both the patients and the health economies.

1.2 Role of Bariatric Surgery in the Treatment of Obesity

Bariatric surgery has been shown to confer a survival benefit through a 25% mortality reduction after ten years compared to a matched, medically managed control population (20, 21).

1.2.1 Weight Loss

Medical weight reduction programs alone have not been able to produce long-term success when compared to surgical interventions, and bariatric surgery has been recognized as the only effective long-term treatment of morbid obesity (22,23). The Swedish Obese Subjects (SOS) group found that weight loss was still apparent ten years after surgery, demonstrating a 25% loss of total body weight in surgical patients compared to 1.5% loss in nonsurgical patients (24); however there is a gradual recurrence of weight gain, diabetes, dyslipidaemia, hypertension and metabolic syndrome following bariatric surgery.

1.2.2 Resolution of Comorbidities

The effect of bariatric surgery on diabetes was first recognized in 1986 (25). A systematic review of the consequences of bariatric surgery indicated that diabetes resolved or improved in 86.0%, obstructive sleep apnea in 83.6%, hypertension in 78.5% and dyslipidemia in 70% of patients (26). Bariatric procedures result in significant reductions of

clinical and biochemical manifestations of the metabolic syndrome (27); to such a degree that in 2009, the American Diabetes Association (ADA) included bariatric surgery as a treatment option for diabetes (28). Recent randomized controlled trials (RCT) have confirmed the value of bariatric procedures in reducing comorbidities associated with obesity, specifically diabetes, where surgery has proven to be superior in outcome compared to medical therapy (29,30).

1.2.3 Indications and Contra-indications

The indications for the surgical management of severe obesity were first outlined by the National Institutes of Health (NIH) Consensus Development Panel in 1991 (31). Potentially eligible patients should:

- Have severe obesity (BMI >40 kg/m^2) or
- Moderate obesity (BMI >35 kg/m^2) with a serious associated comorbidity
- Have acceptable risk for surgery
- Have failed previous nonsurgical weight loss
- Be well-informed and motivated

More recently indications have been extended to include patients with a BMI <35 kg/m^2; general consensus is that this applies only to patients with a BMI of 32-34 kg/m^2 with poorly controlled diabetes despite maximal medical therapy (23,32).

Contra-indications to bariatric surgery are few but include patients with untreated major psychiatric disorders, binge-eating disorders, current drug and alcohol abuse, severe comorbid disease with prohibitive anaesthetic risk, or inability to comply with follow-up and long-term requirements such as vitamin and mineral replacement (33,34). Bariatric surgery

in the elderly or very young (above 65 years old or less than 18 years old) is controversial, but may be considered in patients with severe comorbidities (32).

The success of a bariatric procedure should not be judged by weight loss alone but should include other outcomes as well. One of the outcome scoring systems available is the Bariatric Analysis and Reporting Outcome System (BAROS), which includes weight loss, evolution of comorbidities, quality of life and surgical complications (35).

1.2.4 Procedure-Related Morbidity and Mortality

Risk of death and adverse outcomes as a consequence of bariatric surgery has been shown to be low but varies between patient characteristics and type of procedure performed (36). In addition, mortality from bariatric surgery has decreased over the past decade (37). This is mainly due to the advent of laparoscopic approaches, improved anaesthesia and monitoring and a better understanding of the physiological changes in this patient group. Mortality rates are higher in patients with visceral obesity, BMI >50 kg/ m^2, redo-operations, patients with obstructive sleep apnoea and advanced age (38). Morbidity and mortality rates are increased if the operations are performed in low-volume centers (36,38). Recent results from the Bariatric Outcomes Longitudinal Database (BOLD) evaluated 57,918 patients after bariatric surgery and reported a 30-day mortality of 0.09% (39).

1.3 Bariatric Surgical Procedures

The number of bariatric surgical procedures being performed have increased dramatically over the past decade. In the USA bariatric procedures increased from 2.4 to 14.1 per 100,000 population between 1990 and 2000 and continues to increase (40). Globally

approximately 344.000 bariatric procedures are performed every year (41). Roux-en-Y gastric bypass (RYGB) is the most common procedure (47%), followed by adjustable gastric banding (AGB) (42%), sleeve gastrectomy (SG) (5%), and biliopancreatic diversion (BPD) with or without duodenal switch (BPD/DS) (2%) (41). Most of the bariatric procedures are performed laparoscopically with the exception of BPD/DS (39,41). Algorithms for procedure selection have been suggested but these have not been validated in clinical trials. Selection depends on the severity of obesity (BMI), comorbidities, age, gender, as well as patient preference and the surgeon's experience (42).

Bariatric operations have historically been categorized as either restrictive and/or malabsorptive procedures. Restrictive procedures such as AGB and SG cause restriction by reducing gastric capacity and thus limiting the amount of oral intake. Purely malabsorptive procedures such as the jejunoileal bypass result in an extreme alteration of flow of nutrients and digestive enzymes and have been banned due to unacceptably high morbidity and mortality rates (43). Benefits of both gastric restriction and intestinal malabsorption are combined in so called "hybrid" operations such as biliopancreatic diversion with or without duodenal switch and in the Roux-en-Y gastric bypass procedures.

1.3.1 Roux-en-Y Gastric Bypass

1.3.1.1 History

Mason and Ito developed a gastric bypass procedure for the treatment of morbid obesity in 1966 (44). They applied the observation of weight loss following partial gastrectomy for ulcer disease to obese patients with the aim of weight reduction. The procedure involved

horizontal transection of the stomach and reconstruction with a retrocolic jejenal loop for a gastrojejunostomy. The procedure was refined in terms of optimal calibration of the gastric pouch and diameter of the gastrojejunostomy (45). Griffen et al. (46) modified this early procedure by replacing the loop with a Roux-en–Y gastrojejunostomy. This reduced bile reflux and remains the accepted technique for reconstruction today. Torres et al. (47) introduced the use of a vertical gastric pouch along the lesser curvature resembling the prototype for the lesser curvature pouches currently used in modern gastric bypass surgery. A distal RYGB was also introduced with various lengths of the efferent and common limbs (48). A smaller gastric pouch size and longer length of the Roux limb appears to correlate with the degree of initial postoperative weight loss, especially in super obese patients (49,50).

1.3.1.2 Operative Technique

The first laparoscopic series was published in 1994 (51). No standardized operating technique has been described to date. Variations include passing the Roux limb in an ante- or retrocolic fashion, length of limbs and various techniques for creating the gastrojejunostomy. Generally, the procedure begins with formation of the Roux limb and jejunojejunostomy. The jejunum is divided 30 to 50 centimeter (cm) distal to the ligament of Treitz. The Roux limb is then measured distally to about 75 -150 cm. Once the appropriate length is measured, the biliopancreatic limb and the Roux limb are approximated side by side and a side-to-side functional end-to-side jejunojejunostomy is made. The omentum is divided to allow a tension-free passage of the Roux limb and the Roux limb is passed to an antecolic and antegastric position. Retrocolic antegastric or retrocolic retrogastric positions can be used if tension dictates but this is less common practice. The next step is creation of a 15-30ml vertically orientated gastric pouch with staple firings separating the pouch

from the gastric remnant following which the gastrojejunostomy is created. This is most commonly performed by circular-stapled technique described by Wittgrove et al. (51,52). Variations include the handsewn, linear-stapled, or transabdominal circular-stapled techniques. In all cases, a leak test should be performed either with insufflation or methylene blue. Liver biopsy is performed by some surgeons to document the degree of non-alcoholic steatohepatitis. Cholecystectomy is performed at the time of RYGB if the patient is found to have symptomatic cholelithiasis during preoperative workup (53).



Figure 1: Completed Roux-en-Y gastric bypass

1.3.1.3 Procedure-Related Morbidity and Mortality

The incidence of major postoperative complications following RYGB ranges between 8-15% (53,54). Mortality ranges from 0.3% in case series to 1% in controlled trials with an overall trend towards lower morbidity and mortality in more recent series (37, 39, 54).

Procedure-related morbidity can be divided into intra-operative, early or late complications. Intra-operative complications include trocar injuries, inadvertent injury to solid organs or

bowel and misconstruction. Early complications include venous thrombembolism (VTE), anastomotic leaks, bleeding and wound complications. Late complications include anastomotic strictures, marginal ulcers, bowel obstruction, dumping syndrome and nutritional deficiencies (55,56).

Early complications

Anastomotic leaks and VTE are the most common life threatening early postoperative complications (53).

VTE is an infrequent but potentially fatal complication and is the most common unexpected cause of death after bariatric surgery (57). The incidence of VTE post RYGB is 0.12% to 3.8% (58). The prevalence of asymptomatic deep vein thrombosis (DVT) following bariatric procedures is unknown but postmortem evaluation documented microscopic evidence of pulmonary embolus (PE) in 80% of patients who underwent gastric bypass (59). No Food and Drug Administration (FDA) approved protocol exists for VTE prophylaxis in patients undergoing bariatric surgery (57). Various modalities have been advocated to reduce the incidence of VTE in morbidly obese patients. These include various combinations of early ambulation, graded compression stockings, intermittent pneumatic compression devices, and chemoprophylaxis with subcutaneous or intravenous unfractionated heparin or low-molecular-weight heparins. Inferior vena cava filters are considered in patients with a history of recurrent DVTs while on appropriate anticoagulation, previously documented pulmonary embolus, and the presence of a hypercoagulable disorder (60).

Anastomotic leaks occur in up to 5.6% of cases and this rate does not differ significantly between laparoscopic or open RYGB (61). Leaks are the second leading cause of death following RYGB, and together with VTE account for more than 50% of the causes of death (62). They can occur at five different sites after RYGB and these include the

gastrojejunostomy, gastric pouch staple line, gastric remnant staple line, Roux limb staple line, and jejunojejunostomy (52,62). Management of the leak depends on the individual patient presentation and may be conservative or by laparoscopic or open re-exploration (63).

Gastrointestinal bleeding is estimated to occur in 1.1% to 4% of patients following RYGB (64). Most commonly the bleeding originates from one of the five staple lines and can be intra- or extraluminal. Other potential bleeding sites include port sites, liver or splenic injuries. Management depends on patient presentation, time of onset of bleeding and suspected site of bleeding; treatment options include conservative management with discontinuation of VTE chemoprophylaxis, endoscopic intervention and urgent re-exploration (62).

Wound complications are decreased in laparoscopic surgery compared to open surgery. Wound infection in less than 8% of procedures and port site herniation occurs in approximately 1% of patients (65). Infections are treated with antibiotics and drainage of collections, hernia repair is delayed until the patient's weight has stabilized unless the clinical situation demands urgent repair (incarceration etc.) (63).

Late complications:

Anastomotic strictures generally occur within one to three months of surgery and are reported in 5 to 27% of cases (66). They occur due to technical factors such as surgical technique, tension on the Roux limb or ischemia but also following recurrent marginal ulcers (62). Use of a 21 cm circular stapler is associated with higher stricture rates than other anastomotic techniques (67,68). Patients present with persistent or worsening postprandial vomiting with or without pain. Treatment is generally endoscopic with balloon dilatation (69).

Marginal ulcers occur at the gastrojejunostomy site in about 2-12% of patients (53,70). Most occur within the first few months after surgery but some may develop as late as ten years after surgery (71). They are associated with smoking, NSAID abuse, Helicobacter pylori infection, large pouch size and alcohol. Treatment is by elimination of risk factors and PPIs (53).

Bowel obstruction occurs in 3 to 4.5% of patients, most commonly due to an internal hernia (72,73). Rapid weight loss facilitates a larger mesenteric defect and the laparoscopic approach causes less adhesions which is postulated to lead to a greater tendency of herniation compared to open RYGB (72). The three potential spaces for internal herniation are the jejunojejunostomy defect, Petersen's space and the transverse mesocolic defect in cases using a retrocolic approach for the gastrojejunostomy (62). Another common cause of bowel obstruction post RYGB is obstruction at the jejunojejunostomy anastomosis. Less common causes include port site herniation, strictures, adhesive bands, bezoars, volvulus and jejunojejunostomy intussusception (62). CT scan may not be diagnostic and current recommendations are to return to theatre early for laparoscopic exploration should signs of bowel obstruction develop (53).

Dumping syndrome occurs in 70 to 76% of RYGB patients but generally settles with time. It can mostly be controlled by dietary modifications; octreotide may be added to decrease symptoms if dietary changes are ineffective (63).

Nutritional deficiencies following RYGB are common and should be screened for with routine laboratory tests. The most common deficiencies are iron, folate, Vitamin B12, Vitamin D and calcium and routine supplementation is recommended (53,74). Deficiencies occur more frequently following long Roux limb or distal gastric bypass procedures (63).

1.3.1.4 Outcomes

RYGB has proven to be more effective than medical therapy in terms of weight loss and resolution of comorbidities (24,75). Patients generally have an excess weight loss (EWL) of 60% to 70%, and an approximate 75% improvement of comorbidities (26,54). Long-term effectiveness has also been validated. Pories et al. (22) showed a mean EWL of 58% and 49%, and a mean BMI of 33.7 and 34.9 kg/m^2 at five and 14 years respectively. White et al. (76) reported a five year EWL of 70% and ten year EWL of 75%. Suter et al. (77) reported an EWL of 67.4, 62.7, and 58.1% at three, five and seven year intervals, however noted a small but significant weight regain over time; control of comorbidities and improvement in quality of life was maintained over five years. Overall, RYGB provides excellent weight loss in the majority of patients, and remains effective in the long-term, despite a small weight regain. Very poor results are uncommon, and essentially seen in super obese patients who may require revision to a BPD (77,78).

Compared to open techniques, the long-term results of laparoscopic approaches offer comparable weight loss, safety, cost effectiveness with decreased morbidity and mortality. The increased healthcare costs of RYGB are recovered within approximately three years of the surgery (79). Morbidity decreases further with increasing laparoscopic experience as there is a steep learning curve to perform these advanced laparoscopic procedures (52,80,81). Hand-assisted laparoscopic approaches, although technically less difficult, have not proven to have any benefit in outcome over open approaches (82).

1.3.2 Sleeve Gastrectomy

1.3.2.1 History

SG is an emerging bariatric procedure. It was originally performed as the restrictive component of a BPD-DS (83). Reduction of gastric capacity was intended to initiate short-term weight loss while the malabsorptive component of the operation in form of the BPD was expected to provide long-term weight loss. Early investigations showed that SG alone provided substantial weight loss and a staged risk management strategy for very large or high-risk patients who would not tolerate a longer or higher risk procedure was introduced (84). In the staged approach, the patient's medical condition was allowed to improve over one or two years following SG and patients would then be able to undergo a second-stage bypass procedure in the form of a gastric bypass or duodenal switch (85).

In recent years, SG has more commonly been used as a stand-alone procedure. It has gained rapid popularity and now accounts for more than 5-15% of all bariatric surgeries performed globally (41,86,87). An expert panel consensus statement was recently published (88). It addressed key technical aspects of the surgery, indications and contraindications, peri-operative management and prevention of complications. This is the first consensus guideline published in the field of bariatric surgery, with no other bariatric procedure having guidelines available and emphasizes the strong interest that SG has generated in the bariatric surgical community.

1.3.2.2 Operative Technique

Laparoscopic SG is a vertical gastrectomy creating a tubular stomach (87). The vascular attachments of the gastroepiploic arcade and short gastric vessels are divided. Dissection

commences along the greater curvature from the angle of His proximally ending three to four cm of the pylorus distally. Posterior attachments are divided to enable inspection of the posterior aspect of the stomach. Attachments between fundus and left crus are divided to ensure that no large pouch of fundus remains and the gastro-oesophageal junction can be identified and avoided during staple firing. After mobilization is completed, a first stapler is used tangentially across the antrum. A calibration tube is passed, either a bougie tube or a gastroscope. Care must be taken not to make the lumen too narrow at the incisura and further staplers are fired along the calibration tube towards the fundus. The final stapler is placed with care as not to impinge on to the gastro-oesphageal junction, but also not to leave a large fundal pouch. Approximately one cm of gastric serosa should be identified on the left of the stapler before firing. The staple lines are oversewn with a continuous imbricating suture; an alternative is to use a stapler with buttressing material. An endoscope is then used to perform a leak test and check for intraluminal haemostasis and patency. Alternatively, a methylene blue test is performed to check for leaks (87,88).

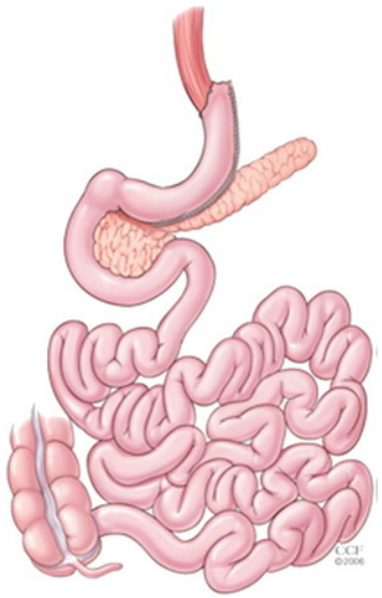


Figure 2: Completed sleeve gastrectomy (87)

1.3.2.3 Procedure-Related Morbidity and Mortality

The overall reported mortality for SG is 0.3% and published complication rates ranged from 0% to 29% (mean is 11.2%) (55). Intra-operative complications include trocar injuries and inadvertent injuries to adjacent solid organs or bowel. Early complications include early anastomotic leaks, bleeding, early strictures, wound complications and venous thrombembolism. Late complications include gastro-oesophageal reflux disease (GORD), late or chronic leaks or fistulae, late strictures and nutritional deficiencies.

Staple line leaks are the most serious complication following SG. They are classified into acute, early, late and chronic leaks and occur in approximately 2% of patients (87,88). The SG is susceptible to leaks due to the very long staple line and they most frequently occur near the angle of His or the gastro-oesophageal junction. Common causes are poor staple line placement and mid-sleeve stenosis along the long staple line. A high index of suspicion is critical and any clinical concern should prompt investigation for a possible leak. Management of the leak depends on the patient's status, the time of onset of the leak and whether the leak is contained or free. Treatment options include percutaneous drainage, endoluminal approaches such as clips, fibrin glue or stenting, laparoscopic or open re-exploration (87-90).

Strictures occur in less than 1% of cases and can either be early or late (91). The most common site is at the incisura and is more frequently due to kinking or angulation than a true mucosal stricture. Treatment depends on time of onset and patient status. Options are observation, endoscopic balloon dilatation, seromyotomy or conversion to gastric bypass in refractory cases (87,88).

Bleeding occurs in 3.57% of patients; management depends on patient status, time of onset and severity of bleeding as well as suspected site and may be conservative, endoscopic or by re-exploration (55,87).

Venous thrombembolism and *wound complications* are infrequent, occurring in approximately 1% and 2% of patients, respectively (55,88).

Gastro-oesophageal reflux disease occurs in approximately 20-30% of patients and is treated with PPIs. Refractory cases may require conversion to a RYGB (92,93).

Nutritional deficiencies may also occur post SG and require replacement (55,87).

Chronic gastrocutaneous fistula formation is an uncommon but challenging complication and treatment follows general management principles of enterocutaneous fistulae (87).

1.3.2.4 Outcomes

Early data suggest SG is efficacious in the management of obesity and may have an important role either as a staged or primary bariatric procedure (55). Weight loss following SG has varied in relation to the population studied. Initial reports of SG used this procedure to downstage high-risk or super obese patients before a second stage procedure and therefore follow-up was limited to one or two years (84,85,94). Later reports reflect a shift to the use of the SG as a stand-alone procedure and find it to be effective in patients with a lower BMI (95,96).

Brethauer et al. (97) conducted a systematic review of 36 studies evaluating weight loss after SG both as a primary and as a staged procedure. This demonstrated a reduction of mean BMI from 60.0 kg/m^2 to 44.9 kg/m^2 for the staged approach and 46.6 kg/m^2 to 32.2

kg/m^2 as a primary procedure. However, follow up in these studies was predominantly less than three years.

Shi et al. (29) analyzed 15 studies in a systematic review and reported an average EWL of 59.8% after one year, 64.7% after two years and 66.0% after three years following SG. Comorbidity resolution or improvement ranged from 45-95.3%; 77.2% for diabetes, 71.7% for hypertension and 61% for hyperlipidaemia. Follow-up ranged between 6 and 24 months.

A systematic review of 28 studies by Gill et al. (98) evaluated the rate of improvement in diabetes following SG. Complete diabetes remission was found in 66.2 % of patients while improvement or remission was found in 97%. Mean glycated haemoglobin (HbA1c) decreased from 7.9% to 6.2% in 11 studies that investigated this value. Improvements in metabolic syndrome, sleep apnoea, cardiovascular risk factors and oedema have also been reported (55,85,99).

Weiner et al. (100) investigated the effect of sleeve volume on initial and longer-term weight loss. Bougie size did not seem to have an impact on initial weight loss; however, sleeve dilatation and a consequent regain of weight occurred when larger bougies were used. Recently a consensus was reached that the optimal bougie size is 32-36 French gauge. Sleeve dilatation and “neo-fundus” formation may necessitate a resleeve procedure for “fundus regeneration” (101).

More recently, studies with longer-term follow up have been published and report a 52 to 61% EWL after five to six years of follow up (29,102,103). However, there appears to be significant weight regain between the third and sixth postoperative year. This is in keeping with findings of earlier studies evaluating restrictive procedures (104,105). Eid et al. (103)

evaluated EWL between the 6th and 8th postoperative year and reported EWL of 52%, 43% and 46% for the 6th, 7th and 8th year, respectively.

Weight regain may be managed by performing a subsequent BPD-DS, RYGB or re-sleeve (93,102,106). In a series of 26 patients, three patients required conversion to RYGB due to weight regain (11.5%) and one patient due to severe GORD symptoms (3.8%) (102). Himpens et al. (106) reported 11 (20.75%) patients that required conversion to BPD-DS for weight regain and two (3.7%) patients requiring a re-sleeve operation for sleeve dilatation. Limitations of the long-term studies are the use of telephonic follow-up leaving results self-reported and questionable (103,106); in addition Himpens et al. (106) included 11 patients that had undergone a second-stage BPD-DS in the analysis and weight regain may be higher than their results indicate. It is noteworthy that in Himpens et al. (106) weight regain coincided with the interruption of the office visits after three years and this emphasizes that loss of continuous support and control is likely to play an important role in weight regain.

Overall, longer-term data remains scant and sustainable weight loss and comorbidity control questionable.

1.4 Mechanisms of Weight Loss and Endocrine Effects

Although the simple concepts of restriction and malabsorption provide a framework for categorizing bariatric operations, they do not fully explain the complex physiology and metabolic effects of bariatric surgery (107). The complexity of these effects are subject to ongoing research. I will discuss the most recognised hypotheses.

1.4.1 Entero-encephalic and Entero-insulinar Axes

Following RYGB, endocrine effects with neurohumoral and gut hormone changes appear to be the primary reason for the procedure's effectiveness (108,109). Two main axes have been identified through which the gut facilitates changes in central regulatory centers of the brain and in the endocrine pancreas, the entero-encephalic axis and the entero-insulinar axis. The entero-encephalic axis is believed to be vital to the physiologic regulation of appetite, nutrient intake and energy homeostasis (109). Hormonal peptides involved are ghrelin, neuropeptide Y (NPY), peptide YY (PYY) and leptin. The entero-insulinar axis includes the incretins glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), which are involved in the synthesis, secretion, and regulation of insulin (109).

1.4.2 Foregut and Hindgut Hypotheses

A study on rodents suggested that specific gastrointestinal procedures can have direct, weight-independent effect on diabetes (103) and initiated the proposal of two hypotheses regarding the alteration of gut continuity and flow to explain the changes in gut hormones following RYGB: the foregut and hindgut hypotheses (110). The foregut hypothesis postulates that exclusion of the duodenum from nutrients leads to a weight-reducing and antidiabetic effect via exclusion of a signal that promotes insulin resistance (110). The foregut hypothesis is largely based on the release mechanism of GIP which is an incretin that is produced by the K-cells in the mucosa of the duodenum and jejunum in response to nutrient contact. GIP is part of the entero-insulinar axis and physiological roles include regulation of pancreatic β-cells, control of glucose-dependent insulin and postprandial glucagon levels, and fatty acid metabolism (111). After RYBG, exclusion of the duodenum

causes loss of K-cell stimulation and a reduction in GIP levels with consequent decrease in β-cell stimulation and insulin release. Most human studies have shown a decrease in GIP following RYGB (111).

The hindgut hypothesis relates to rapid nutrient delivery to the distal intestine with changes in gut hormones altering satiety and glucose metabolism; these appear to include an increased GLP-1 and PYY which are released by L-cells in the distal gastrointestinal tract (108,112). Both GLP-1 and PYY postprandial profiles have been shown to start rising as early as two days following RYGB (113). GLP-1 is an incretin and has many functions as part of the entero-insulinar axis, including the stimulation of insulin secretion by the pancreas, increase in insulin sensitivity of pancreatic cells, inhibition of hepatic gluconeogenesis, and reduction of hunger and food intake through anorexigenic effects through the entero-encephalic axis (114,115). PYY is an enterokine with a central anorexigenic effect on NPY receptors as part of the entero-encephalic axis. It also slows nutrient flow through the gastrointestinal tract, which is referred to as the ileal brake, a negative-feedback mechanism that is thought to be responsible for a suppression of appetite (116).

1.4.3 Further Hormonal Mediators

NPY is a potent appetite stimulator and is released by the hypothalamus. It is stimulated by orexigenic signals such as ghrelin and inhibited by anorexigenic signals such as PYY and leptin (109). Despite the known orexigenic effects, bariatric surgery has not proven to alter NPY levels significantly (109,117).

Ghrelin is an orexigenic peptide and is also called the “hunger hormone”. It is produced in the fundus and stimulates hypothalamic release of NPY and growth hormone. Ghrelin has been shown to be reduced following RYGB (118,119) or unchanged (120).

Leptin is categorized as an adipokine and is released predominantly by adipose tissues. It is a marker of adiposity, which reflects the total fat mass and acts as an adipostat by inhibiting NPY (109,121). In the obese patient leptin levels are increased but ineffective due to the development of so-called “leptin resistance” (122). Leptin levels are reduced after bariatric procedures and directly correlate with the percent of weight loss and resolution of leptin resistance (118).

1.4.4 Mechanism of Sleeve Gastrectomy

SG was initially thought to be a purely restrictive procedure but early evidence suggests that SG may have metabolic effects beyond weight loss. In view of its relatively minor gastric restriction with no intestinal bypass, the impressive effects of SG remain uncertain (123). Ghrelin levels have been reduced following SG as a consequence of resection of the fundus, which may explain early satiety and thus increased weight loss.

PYY and the incretin GLP-1 have been significantly increased after RYGB secondary to rapid nutrient delivery to secreting areas such as the ileum and colon. Rapid nutrient transit may also occur after SG secondary to faster gastric emptying and L- cell stimulation with increase of gut hormones such as PYY and GLP-1 and subsequent improvement in glucose metabolism (71,108,124,125).

However, SG remains a restrictive operation (91). Weight loss is greatest in the first months after operation and subsequently rapid improvements in diabetes are observed.

Diabetes resolution may be related more to a decrease of insulin resistance because of caloric restriction and weight loss rather than to an increase of insulin secretion (126). The exact mechanisms of SG are not known.

1.5 Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy

SG has attracted interest because it does not require an intestinal anastomosis or intestinal bypass and is considered to be less technically challenging than a RYGB (55). Besides technical ease, laparoscopic SG may offer advantages such as shorter operating and hospitalization time, lower morbidity, normal intestinal absorption, normal gut continuity and postoperative access to the distal stomach and bile ducts, no risk of internal hernias, and pylorus preservation, which prevents dumping syndrome (55,87). In addition, SG is considered by some to be the most appropriate option in extremely obese high-risk patients (85).

A significant shortcoming of research involving SG is that medium-term data is limited, and currently there is no long-term data (more than ten years follow-up). In contrast to this, the RYGB has proven long-term efficacy (22,76,77).

Data comparing SG and RYGB is limited. Hutter et al. (127) analyzed data from the American College of Surgeons – Bariatric Surgery Center Network accreditation program which included 28,616 patients. SG's morbidity and effectiveness in terms of BMI reduction and obesity-related comorbidities lies between that of the AGB and RYBG at one year follow-up.

Choulliard et al. (128) investigated weight loss, resolution of comorbidities, and complications for both SG and RYGB using a case-control study design with an 18 month

follow-up. Morbidity was significantly greater in the RYGB group (20.5%) compared to the SG group (6.5%; $P<0.05$). EWL was not statistically significant after one year,with 58% reduction for the SG and 64% reduction for RYGB. Diabetes control was significantly better in the RYGB group compared to SG. 86% of patients with diabetes in the RYGB group were medication free compared to 62% of previously diabetic patients in the SG group ($P<0.05$). The resolution of other comorbidities such as hypertension and sleep apnea were not statistically different between the groups.

Another study (129) reported a shorter operative time (82 minutes) for SG compared to RYGB (98 minutes), major complication rate of 4.7% for SG and 9.3% for RYGB, EWL after one year of 78.8% for SG and 86% for RYGB. Resolution of comorbidities was seen in 40% for SG and 64.7% of RYGB. None of the results were statistically significant and the study concluded that in the short-term, both procedures are equivalent in terms of safety and effectiveness .

Shi et al. (55) assessed operating time, hospital stay and cost among nine patients undergoing SG and nine undergoing RYGB at their institution. Mean operating time was 110 min for SG and 135 min RYGB, average hospital stay was 2.7 days for SG and 2.9 days for RYGB. Overall cost for a SG was $10,317 and $11,666 for RYGB. This suggests that SG may be cost effective as a primary procedure.

In general the results of comparative effectiveness studies have demonstrated a lower complication rate, but also less EWL and less resolution of comorbidities for SG compared to RYGB (37).

1.6 Why Do This Meta-Analysis?

A Cochrane review (75) and more recent meta-analysis (130) included only one RCT that compared SG to RYGB. In this trial (N=32), BMI and weight loss after 12 months follow-up were similar between RYGB and SG (71).

The most recent review (131) comparing SG, RYGB and adjustable gastric banding included two RCTs comparing RYGB to SG (71,108). A meta-analysis was not performed as the sample sizes were too small in both studies resulting in too low a power to detect statistical differences.

More recently, further RCTs have been published, including the STAMPEDE trial which is regarded as the landmark study (29). It was designed to compare intensive medical and surgical treatment in improving glycaemic control in obese patients with type 2 diabetes. This is the only randomized controlled trial comparing SG and RYGB with intensive medical therapy. Patients treated surgically were significantly more likely to achieve glycaemic control, with a significant reduction in diabetes medication and a greater loss of weight and reduction of BMI. Weight loss in the RYGB group and SG group was 29.4±9.0 kg and 25.1±8.5 kg, respectively. In addition, incidence of metabolic syndrome, rates of hyperinsulinaemia and C-reactive protein (CRP) levels were significantly reduced in both surgical groups. High-density lipoprotein (HDL) was increased and use of cardiovascular medication decreased in the surgical group. Most differences between SG and RYGB were statistically not significant but somewhat more favorable in the RYGB group. Adverse events were more common in the RYGB than in the SG. However, this study used a 12 month follow-up period and thus provides no long-term comparison between SG and RYGB.

Overall, data comparing SG and RYGB is lacking. No meta-analysis to date has focused on specifically comparing SG to RYGB.

In view of the paucity of evidence and newly published RCTs a meta-analysis evaluating SG versus RYGB may provide evidence for the role of SG in bariatric surgery.

1.7 Hypothesis

SG results in improved weight loss and comorbidity resolution compared to RYGB.

1.8 Objectives

To evaluate the benefits and risks of a SG versus RYGB in bariatric surgery by means of a meta-analysis; to come to an evidence based conclusion of which procedure is safer, and results in more effective weight loss and comorbidity resolution in morbidly obese patients.

1.9 Aims

To provide evidence for improved, safer patient care through rational procedure selection between two surgical procedures for bariatric surgery following the results of this meta-analysis, together with recommendations for future practice and research.

2. METHODS OF INVESTIGATION

2.1 Meta-Analysis

The meta-analysis was performed in adherence to the principles of a Cochrane review (132). Review Manager 5 software (133) was used for data collection and analysis. Two investigators (Martin Brand [MAB] and myself [SAN]) reviewed the search results and collected data from the included studies independently. I performed the data analysis and interpretation thereof under the guidance of MAB.

2.1.1 Outcome Measures

Primary outcome measures

- Weight loss (changes in BMI, EWL)
- Improvement of comorbidities (changes in fasting glucose, insulin, homeostasis model assessment for insulin resistance (HOMA-IR) and lipid profile)

Secondary outcome measures

- Procedure-related mortality
- Procedure-related morbidity
- Hormone changes (GLP-1, PYY, ghrelin and leptin)

2.1.2 Search Methods for Identification of Studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (October 2012) in the Cochrane Library, MEDLINE (1974 to October 2012), EMBASE (1980 to October 2012), LILACS (1982 to October 2012), Science and Social Sciences Citation Index Expanded (1974 to October 2012) and PscINFO (to October 2012). Search strategies are supplied in Appendix 1.

Conference proceedings

- The Society of American Gastrointestinal and Endoscopic Surgeons annual meeting (2000 to 2012)
- American Society for Metabolic and Bariatric Surgery annual meeting (1983 to 2012)
- International Federation for the Surgery of Obesity and Metabolic Disorders annual meeting (2007 to 2012)
- International Consensus Summit for Sleeve Gastrectomy annual meeting (2008 to 2012)
- European Association for Endoscopic Surgery annual meeting (1992 to 2012)

Ongoing trials

- National Research Register
- UKCRN (UK Clinical Research Network)
- Clinicaltrials.gov
- Controlled Clinical Trials
- Australia NZ Clinical Trial Register

Reference Lists

Reference lists of all studies identified by the above methods were searched for further trials.

2.1.3 Criteria for Considering Studies for this Review

Types of studies

Only randomized clinical trials with interventions of RYGB and SG were included. Inclusion was irrespective of blinding, language, or publication status.

Types of participants

Adults undergoing laparoscopic RYGB or laparoscopic SG for treatment of obesity were included.

Types of interventions

Patients undergoing laparoscopic RYGB were compared to patients undergoing laparoscopic SG.

2.1.4 Selection of Studies and Data Extraction

SAN and MAB independently selected trials for inclusion using the criteria specified above and reviewed the references of these studies for further relevant trials. Data concerning details of the study population, intervention and outcomes were extracted by SAN and checked by SAN and MAB using a data extraction form. This form included the following information:

- Year and language of publication
- Year of study
- Inclusion and exclusion criteria
- Outcomes
- Sample size
- Duration of follow-up
- Methodological Quality
- Indicators of weight loss
- Adverse events (mortality and morbidity related to the procedure)
- Indicators of comorbidity resolution
- Changes in gut hormones

Differences in data extraction were resolved by referring back to the original study and discussing the differences.

Where cohorts were reported in more than one publication, data was extracted from the most recent article. The earlier articles were referred to for methodological details, baseline characteristics or further outcomes as indicated.

Bias risk was independently assessed for each trial.

Where necessary the corresponding authors of the trials were contacted to clarify missing or unclear information.

2.1.5 Assessment of the Risk of Bias of Included Trials

Generation of the allocation sequence

- Yes, adequate, sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Unclear, the trial was described as randomized but the method of sequence generation was not specified.
- No, inadequate, the sequence generation method is not, or may not be, random. Quasi-randomized studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Yes, adequate, allocation was controlled by a central and independent randomization unit, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrollment.
- Unclear, the trial was described as randomized but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrollment.

- No, inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomized. Quasi-randomized studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Yes, adequate, the trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Unclear, the trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trail.
- No, not performed, the trial was not double blind, so that the allocation was known during the trail.

Incomplete outcome data

- Yes, adequate, the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- No, inadequate, the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Yes, adequate, pre-defined, or clinically relevant and reasonably expected outcomes are reported on.

- Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- No, inadequate, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Any other bias

- Yes, adequate, the trial appears to be free of other components that could put it at risk of bias.
- Unclear, the trial may or may not be free of other components that could put it at risk of bias.
- No, inadequate, there are other factors in the trial that could put it at risk of bias, eg, no sample size calculation made, early stopping, industry involvement, or an extreme baseline imbalance.

Trials with adequate generation of allocation sequence, adequate allocation concealment, adequate blinding, adequate handling of incomplete outcome data, no selective outcome reporting, and without other bias risks were considered low-bias risk trials. Trials with one or more unclear or inadequate quality component were considered high-bias risk trials. However, we are aware that in a large number of reviews, such optimal division of trials may not be possible.

2.1.6 Measurement of Treatment Effect

Dichotomous data were analyzed for relative risk ratio (RR), and the absolute effects were measured with the risk differences. Continuous data were analyzed for mean difference

(MD). 95% confidence intervals were calculated for these measures. Treatment effect was considered by intention-to treat analysis, using available case analysis and analysis by imputation. The Mantel-Haenszel method using the fixed effect model was used for the meta-analysis (134). Results were presented on a forest plot graphic.

2.1.7 Heterogeneity and Subgroup Analysis

Statistical heterogeneity was tested using the I^2 test (135) and chi-squared test. A p-value less than 0.05 represented statistical significance. If heterogeneity was identified, subgroup analysis was performed. The subgroups used included BMI, EWL, fasting insulin, fasting glucose, HOMA-IR, total cholesterol, low-density lipoprotein (LDL), HDL, triglycerides, morbidity and mortality, ghrelin, PYY, GLP-1 and leptin.

2.1.8 Sensitivity Analysis

A sensitivity analysis was performed at the end of the review by examining the trial inclusion criteria, reassessing excluded studies, re-analyzing data imputing, and re-analyzing data using the DerSimonian and Laird method (136).

2.1.9 Funnel Plot

A funnel plot was used to explore small study bias. A linear regression approach described by Egger et al. was used to determine the funnel plot asymmetry (137).

3. RESULTS

3.1 Description of Included Studies

The electronic search strategy revealed 92 articles; two additional articles were identified through other search strategies (Appendix 1). Of the 92 studies, 17 abstract articles were reviewed further; of these four were previous review articles or commentations, one article explained the rationale behind a study included in this meta-analysis and two studies compared other interventions. Hence ten potentially eligible studies were identified (17,29,71,92,108,121,138-141). On review of the full text of these studies, two studies (140,141) were excluded as they used a mini-GB and not a RYGB as comparison resulting in eight studies included into the meta-analysis (17,29,71,92,108,121,138,139) (Figure 3). These included 520 patients, 259 patients allocated to RYGB and 261 patients allocated to SG. Description of operative techniques and demographics of included studies are shown in table 1 and 2.

Helmiö et al. (139) conducted their multi-center trial in three tertiary referral hospitals in Finland. This study is part of the ongoing SLEEVEPASS trial.

Inclusion criteria were a BMI >40 kg/m^2, or BMI >35 kg/m^2 with significant comorbidity, age between 18 and 60 years and a previously successfully instituted and supervised but failed adequate diet and exercise program.

Exclusion criteria were a BMI >60 kg/m^2, psychiatric disorder, eating disorder, alcohol or substance abuse, active gastric ulcer disease, difficult gastro-oesophageal reflux disease with large hiatus hernia; and previous bariatric surgery. Two patients from the RYGB group were excluded from the study after randomization due to liver cirrhosis in one case, and

the patient being unfit for general anaesthesia in the other; one patient was converted to SG intra-operatively due to technical difficulty. 117 patients remained in the RYGB group according to intention-to-treat analysis and 121 patients in the SG group.

Primary endpoints of the study are weight loss and resolution of associated comorbidities, secondary endpoint are improvement in quality of life and morbidity and mortality of the procedures. Follow-up duration was 30 days thus far and the current publication reports on 30-day morbidity and mortality.

Karamanakos et al. (71) compared weight loss, appetite suppression and changes in ghrelin and PYY levels following RYGB and SG. The trial took place in Greece in a single center. Patients were followed up for a duration of 12 months. Morbidity and mortality was not reported.

Inclusion criteria were not listed. Exclusion criteria were chronic medical or psychiatric illness, substance abuse and previous gastrointestinal surgery.

Kehagias et al. (92) compared mid-term outcomes in non-superobese patients undergoing RYGB and SG. The trial took place in Greece in a single-center. Duration of follow-up was three years.

Inclusion criteria were not listed. Exclusion criteria included chronic medical or psychiatric illness, substance abuse and previous gastrointestinal surgery. Primary outcome was weight loss and secondary outcomes were morbidity and mortality, improvement of comorbidities and nutritional deficiencies. However, resolution of comorbidity was not defined.

Peterli et al. (17) conducted their study in Switzerland on a cohort of 23 non-diabetic patients as a subgroup analysis of the SM-BOSS trial which stopped recruiting patients in late 2011. This parallel group trial focused on investigation of weight change, glycaemic control and changes in gut hormones in non-diabetics. Patients were followed up for a duration of 12 months. The study was not blinded and all operations were performed by the same surgeon. Morbidity and mortality rates were not reported.

Inclusion criteria were age of 18-60 years, health insurance covering, BMI >40 kg/m^2 and a two year unsuccessful medical treatment program.

Exclusion criteria of this study were diabetes mellitus, large hiatal hernia and previous extensive abdominal surgery.

Peterli et al. (108) also published an earlier study which was also done under the SM-BOSS trial on a different study subgroup to the current study. This study included a follow-up period of three months. The aim of this subgroup analysis was to compare the effects of RYGB and SG on glycaemic control.

Woelnerhannsen et al. (121) also published a parallel group trial of the SM-BOSS trial and focused on the relationship of weight, adipokines, lipid profiles and insulin sensitivity following RYGB and SG. However, on review of results and cohort it appeared that the study group was in fact the same as published by Peterli et al. (17) in 2012 with one study reporting results as mean and standard deviation and the second as mean and standard error of mean. Correspondence with the author revealed that both trials were on the same study population, consequently this publication was only used for outcomes that were not reported in the latest publication.

Ramón et al. (138) performed their study in a single-center study in Spain. They recruited 30 patients of which five were males, four patients had a BMI >50 kg/m^2 and six refused participation in the study leaving 15 included patients. The study focused on the investigation of changes in glucose and gut hormones following RYGB and SG. Follow-up duration was 12 months. Although computer-generated randomization took place, methods of allocation concealment and blinding were not stated. Morbidity and mortality rates were not reported.

Inclusion criteria were an age of 18-60 and a BMI >40 kg/m^2 or BMI >35 kg/m^2 with at least one severe comorbidity.

Exclusion criteria were a BMI >50 kg/m^2, male gender, patients deemed not suitable for bariatric laparoscopic surgery and revisional surgery.

Schauer et al. (29) performed their randomized, single-center, non-blinded trial at the Cleveland Clinic and compared intensive medical therapy alone with medical therapy and RYGB or SG. Duration of follow-up was 12 months.

Inclusion criteria were age of 20 to 60 years, a diagnosis of type 2 diabetes (HbA1c >7.0%) and a BMI of 27 to 43.

Exclusion criteria were previous bariatric surgery or other complex abdominal surgery and poorly controlled medical or psychiatric disorders.

218 patients were screened of which 33 had a low HbA1c, 16 declined participation, 17 did not pass screening evaluation, one patient had a low BMI and one was excluded due to a fear of needles. 150 eligible patients were assigned by block-randomization to RYGB (n=50), SG (n=50) or intensive medical therapy (n=50). After randomization, one patient

withdrew consent for SG (n=49), seven patients withdrew from the study and two patients were lost to follow-up in the medical group (n=41).

Primary outcome was the proportion of patients with a HbA1c of 6% or less (with or without diabetes medications) 12 months after randomization.

Secondary outcomes were levels of fasting plasma glucose, fasting insulin, lipids, and high-sensitivity CRP, HOMA-IR index, weight loss, blood pressure, adverse events, coexisting illnesses and changes in medications.

3.2 Risk of Bias of Included Studies

All included trials were randomized controlled trials. Seven trials had adequate sequence generation (17,29,71,92,108,121,138) and six had adequate allocation concealment (17,71,92,108,121,139). Two trials were adequately blinded (71,92). None of the trials showed attrition or reporting bias. Three publications were performed as subgroup analyses under the swiss SM-BOSS trial (17,108,121). One trial (108) appears to include a different study population and subgroup than the later studies. The later two studies (17,121) were reviewed. The results and cohorts appeared to be the same with one article reporting results as mean and standard deviation and the other as mean and standard error of mean. Correspondence with the author revealed that both trials included the same study population. Consequently the earlier publication (121) was only used for outcomes that were not reported in the more recent publication (17). The designation of ‘other bias’ was allocated to all three trials for duplicate publication bias (17,108,121). Risk of bias is illustrated in figure 4 and figure 5.

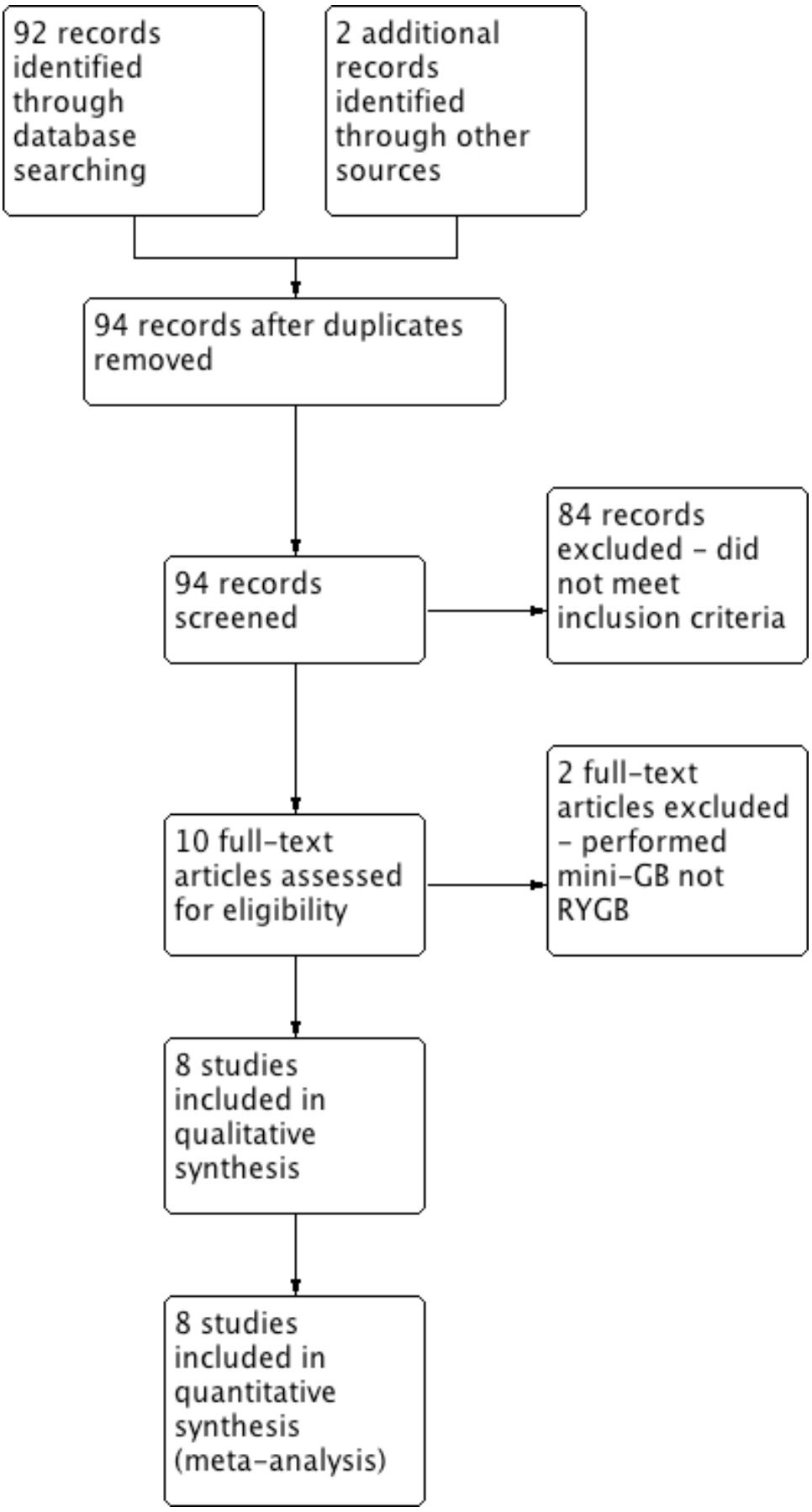


Figure 3: Flow diagram of literature search and inclusion of studies

	RYGB			SG	
Study	**Gastric pouch**	**Roux limb**	**Biliopancreatic limb**	**Bougie size**	**Gastric volume**
Helmiö (139)	20-40 ml	150 cm	50-80 cm	33-35 French	not reported
Karamanakos (71)	15-20 ml	150 cm	not reported	33 French	85% reduction 40-60 ml
Kehagias (92)	15-20 ml	150 cm	not reported	33 French	50-60 ml
Peterli (17)	small (not quantified)	150 cm	50 cm	35 French	not reported
Peterli (108)	not reported	150 cm	50 cm	35 French	not reported
Ramón (138)	15-30 ml	150 cm	50 cm	36 French	not reported
Schauer (29)	15-20 ml	150 cm	50 cm	30 French	75-80% reduction
Woelnerhannsen (121)	not reported	150 cm	50 cm	35 French	not reported

Table 1: Operative technique described by included studies

Study	Recruited N	Randomized N	RYGB N	SG N	RYGB Age	SG Age	Cohort Age	RYGB F:M	SG F:M
Helmiö (139)	NR	240	119 (*)	121	NR	NR	49 (23-67)	NR	NR
Karamanakos (6)	NR	32	16	16	37±8.25	30.6±7.8		12:4	15:1
Kehagias (92)	60	60	30	30	36±8.4	33.7±9.9		22:8	22:8
Peterli (17)	NR	23	12	11	41.4±10.1	35.2±10.7		9:3	8:3
Peterli (108)	NR	27	13	14	41.8±10.4	37.8±10.4		NR	NR
Ramón (138)	30	15	7	8	NR	NR	48.1 ±8.8	7:0	8:0
Schauer (29)	218	150	50	50 (**)	48.3±8.4	47.9±8.0		29:21	39:11
Woelnerhannsen (121)	NR	23	12	11	41.4±10.1	35.2±10.7		9:3	8:3

Table 2: Demographics of included studies

NR=not reported, *= 2 excluded, 1 converted to SG, **=1 withdrew consent

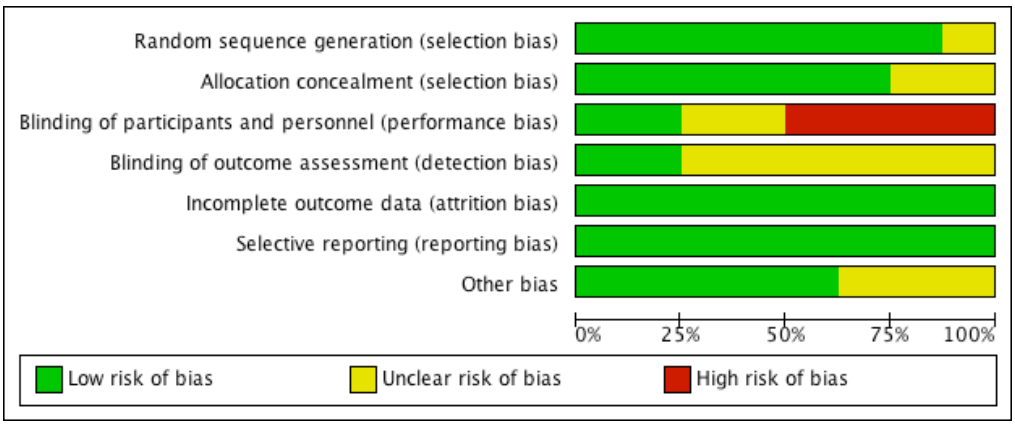


Figure 4: Methodological quality graph

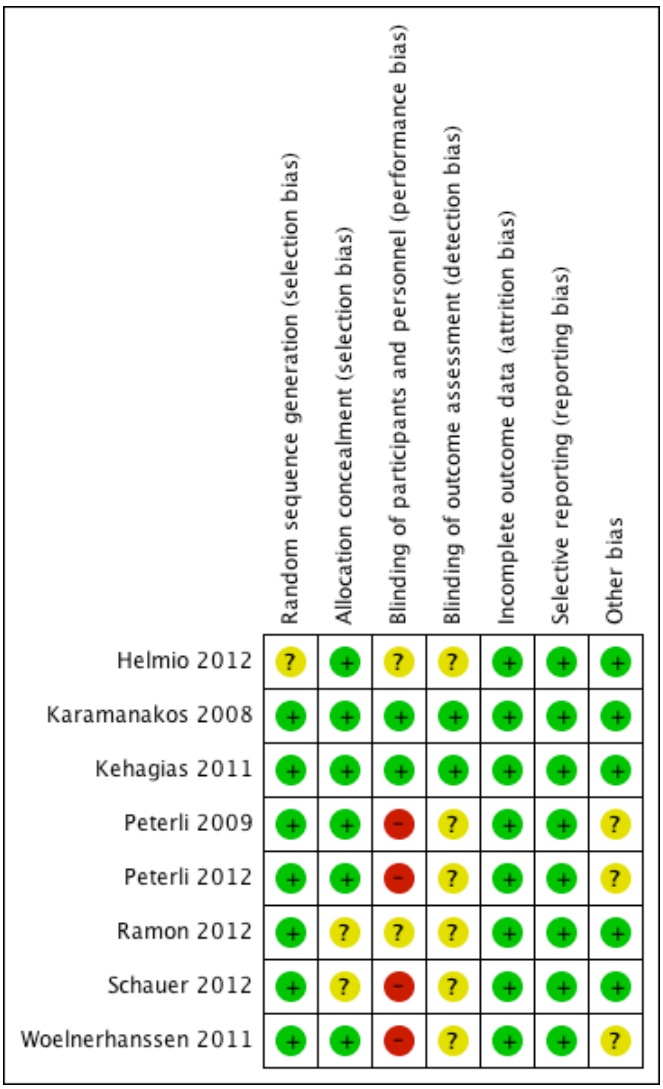


Figure 5: Methodological quality summary

3.3 Effects of Interventions

3.3.1 Primary Outcome Measures

3.3.1.1 Weight loss

Six trials reported preoperative *BMI* (17,29,71,92,108,138). One trial (108) reported three month follow-up and one trial (92) reported BMI after three year follow-up. All others reported 12 month follow-up BMI. A total of 256 patients were included in the preoperative BMI analysis. Results are shown in Figure 6. Five studies were analyzed for three month follow-up BMI (29,71,108,138), which included 196 patients. MD was 0.31 (-0.75-1.36), I^2=1%, p=0.57. Four trials reported 12 month follow-up BMI (17,29,71,138). Results are shown in figure 7, but there was significant statistical heterogeneity (I^2=65%). Karamanakos et al. (71) was identified as the trial which was responsible for most of the heterogeneity, and excluding it from the analysis resulted in a non-significant heterogeneity (I^2=15%) (figure 8).

EWL was reported in five studies (17,29,71,92,108). One trial (108) reported three month follow-up results and four trials reported 12 month follow-up results. One trial (92) reported mean EWL with no standard deviation and could therefore not be used in the analysis. EWL was analyzed for three trials after three month follow-up (17,71,108) and include 82 patients. MD was 0.62 (-2.79-4.03), I^2=26%, p=0.72. EWL was analyzed for three trials after 12 month follow-up and included 154 patients (Figure 9) (17,29,71). There was significant statistical heterogeneity (I^2=75%). Karamanakos et al. (71) was identified as the trial that caused the increased heterogeneity, and following exclusion of this trial from analysis there was no heterogeneity (I^2=0%) (Figure 10).

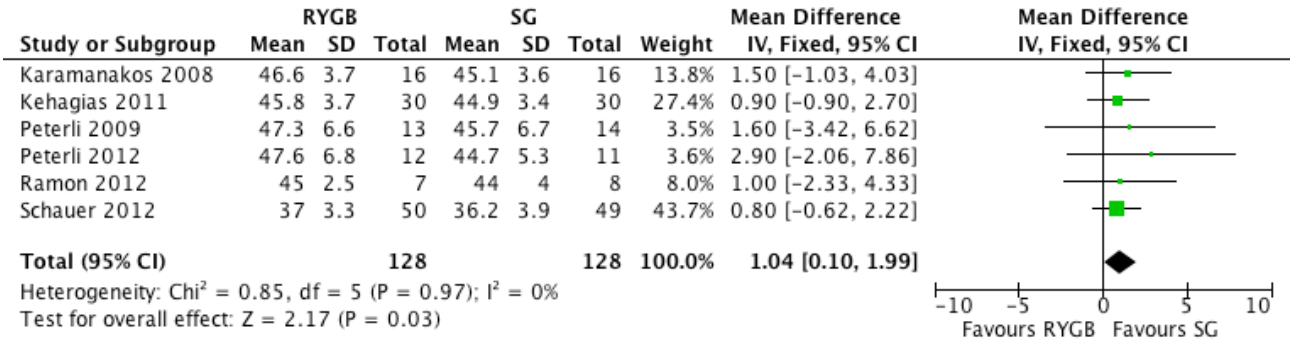


Figure 6: Forest plot, preoperative BMI

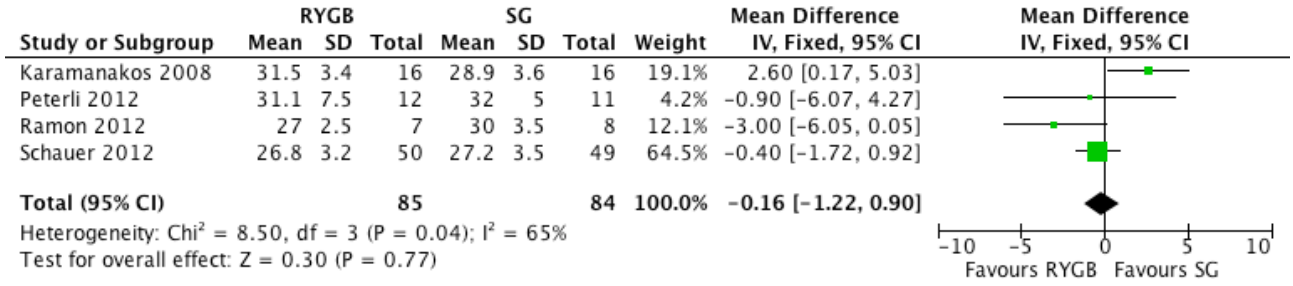


Figure 7: Forest plot, BMI after 12 month follow-up

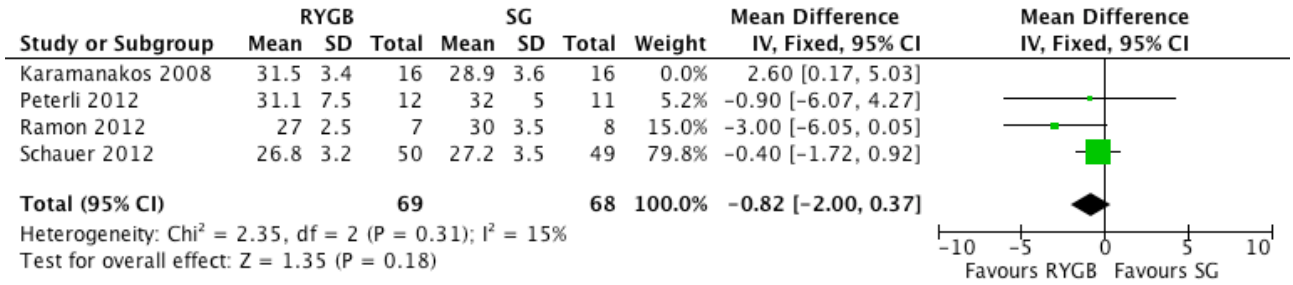


Figure 8: Forest plot, BMI after 12 month follow-up excluding Karamanakos et al. (71)

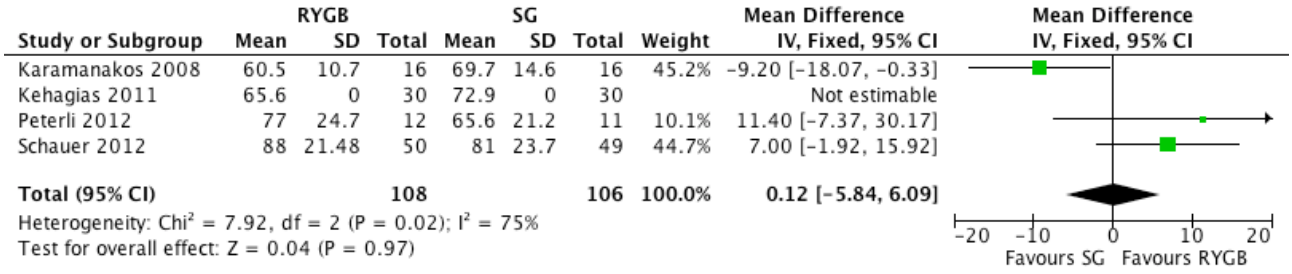


Figure 9: Forest plot, EWL after 12 month follow-up

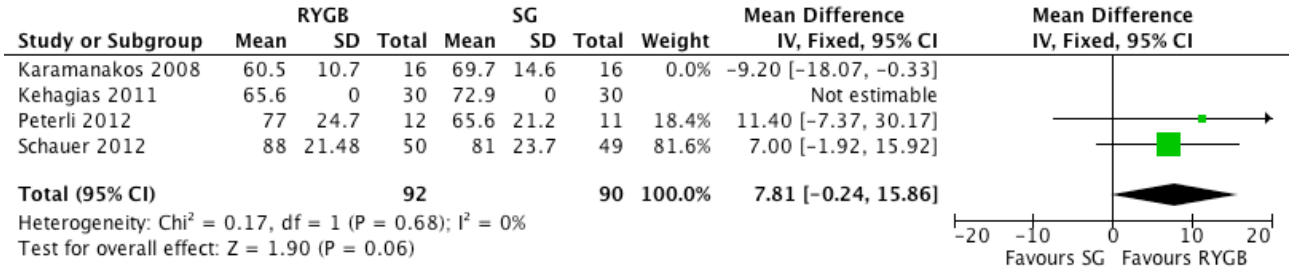


Figure 10: Forest plot, EWL after 12 month follow-up excluding Karamanakos et al. (71)

3.3.1.2 Improvement of Comorbidities

Glucose was measured in five trials (29,71,108,121,138). All five trials provided preoperative values for a total of 196 patients. MD was 0.14 (-0.22-0.49), I^2=35% and p=0.45. Two studies (108,138), provided results after three month follow-up. These included 42 patients. MD was -0.14 (-0.65-0.37), I^2=11%, p=0.59. Four studies (29,71,121,138) were analyzed after 12 month follow-up and included 169 patients. Results are shown in figure 11, however there was significant statistical heterogeneity (I^2=85%). Woelnerhannsen et al. (121) was identified as the study causing this heterogeneity; excluding this trial from the analysis resulted in no heterogeneity (I^2=0%) (Figure 12).

Insulin was measured in four trials (29,108,121,138). Preoperative fasting insulin was analyzed for a total of 164 patients; MD=1.65 (-0.96-4.27), I^2=71%, p=0.22. Two trials reported fasting insulin after three month follow-up (108,138). Results are shown in Figure 13. Fasting insulin after 12 month follow-up was reported in three trials (29,121,138) which included 137 patients. Results are shown in Figure 14.

HOMA-IR was reported in four trials (29,108,121,138). Preoperative HOMA-IR included 164 patients. MD was 0.60 (-0.17-1.37), p=0.13, I^2=65%. One trial (108) reported three month follow-up and one trial (138) provided graphs from which means and standard deviation were calculated. Three trials reported evaluation at three months (108,121,138) which included 65 patients. Results are shown in Figure 15. Three trials (29,121,138) reported 12 month follow-up including 137 patients. Results are shown in Figure 16.

Lipid profile was evaluated by three trials and included 154 patients (29,71,121)). All three trials measured preoperative and 12 month follow-up values for total cholesterol, HDL, LDL and triglycerides.

Total cholesterol was analyzed for baseline values and results were MD=0.06 (-0.28-0.39), I^2=53%, p=0.74. After 12 month follow-up, analysis is shown in Figure 17.

Analysis of preoperative *HDL* was MD=0.05 (-0.04-0.15), I^2=0%, p=0.25; analysis after 12 month follow-up is shown in Figure 18.

Preoperative *LDL* analysis showed MD=-0.05 (-0.32-0.22) and p=0.72 with significant statistical heterogeneity (I^2=78%). Karamanakos et al. (71) was identified as the trial that caused the increased heterogeneity. After excluding this trial the results were MD=-0.29 (-0.60-0.03), p=0.07 with no heterogeneity (I^2=0%). LDL was analyzed after 12 month follow-up and showed again significant statistical heterogeneity (I^2=48%), with MD=-0.29 (-0.52 - -0.06) and p=0.01. Following exclusion of Karamanakos et al. (71), there was no heterogeneity and results are shown in Figure 19.

Preoperative *triglyceride* analysis revealed MD=0.14 (-0.13-0.42), I^2=31% and p=0.31. Triglycerides were analyzed after 12 month follow-up. MD was -0.09 (-0.25-0.06) and p=0.23 with a significant statistical heterogeneity (I^2=67%). Karamanakos et al. (71) was again identified as the trial that caused the increased heterogeneity. After excluding this trial the results were MD=-0.17 and p=0.05 with no heterogeneity (I^2=0%) (Figure 20).

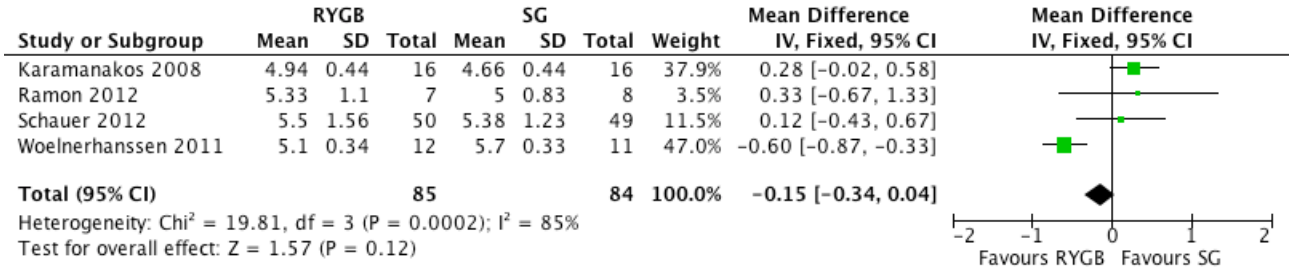


Figure 11: Forest plot, fasting plasma glucose after 12 month follow-up

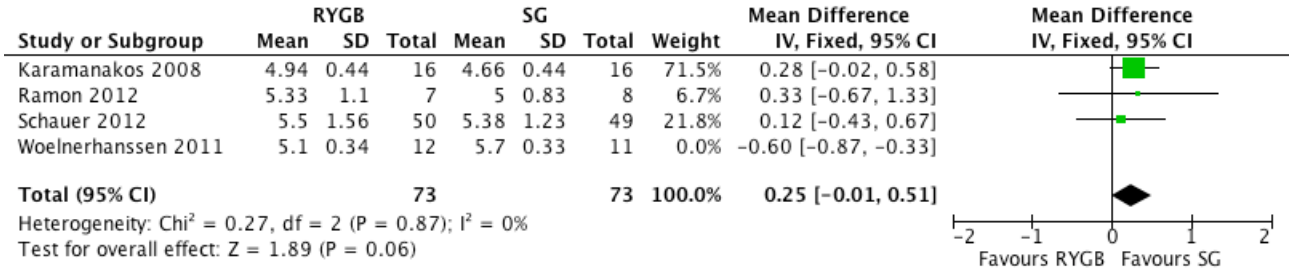


Figure 12: Forest plot, fasting plasma glucose after 12 month follow-up excluding Woelnerhannsen et al. (121)

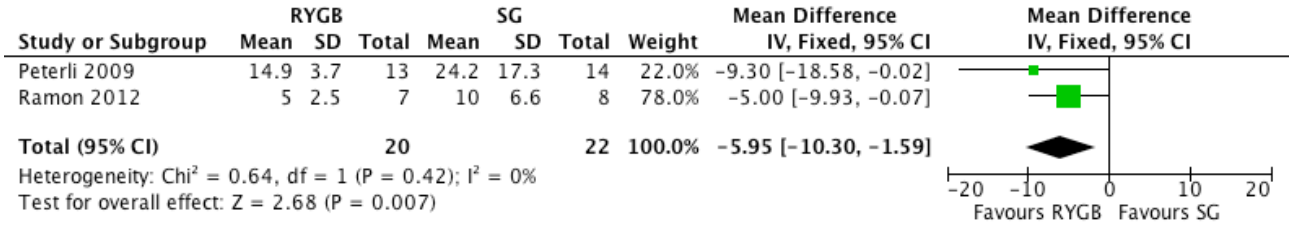


Figure 13: Forest plot, fasting insulin after three month follow-up

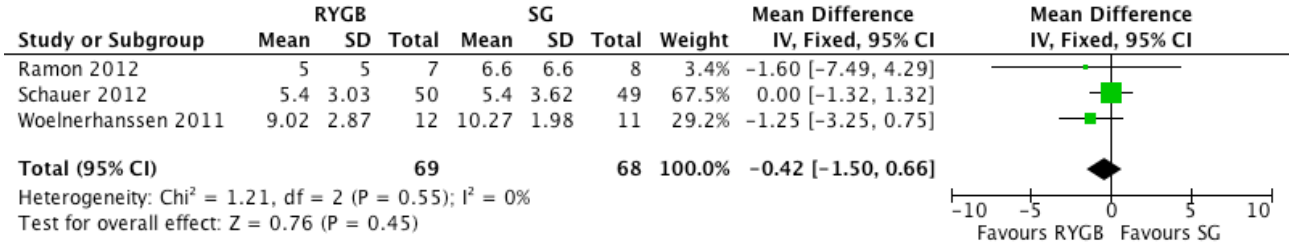


Figure 14: Forest plot, fasting insulin after 12 month follow-up

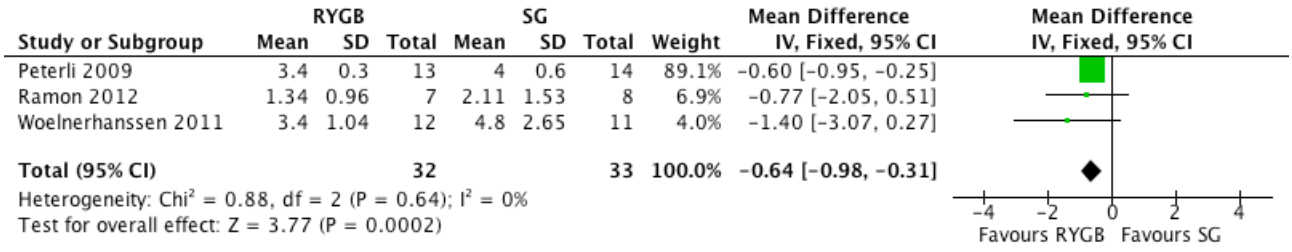


Figure 15: Forest plot, HOMA-IR after three month follow-up

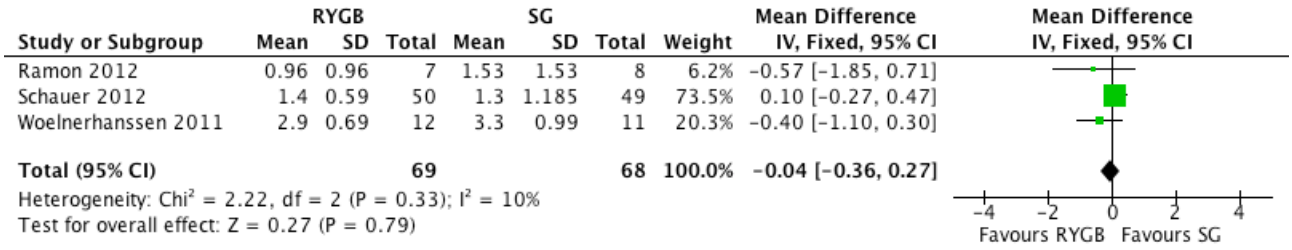


Figure 16: Forest plot, HOMA-IR after 12 month follow-up

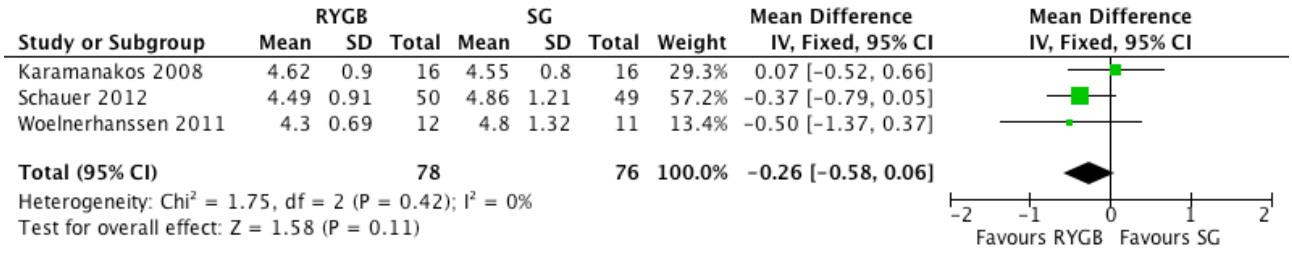


Figure 17: Forest plot, cholesterol after 12 month follow-up

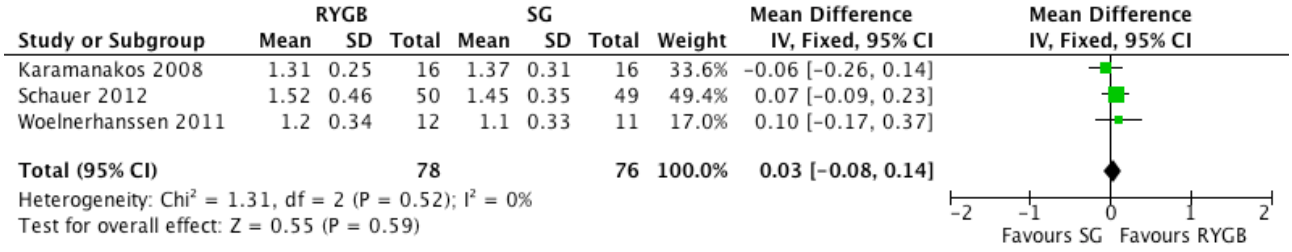


Figure 18: Forest plot, HDL after 12 month follow-up

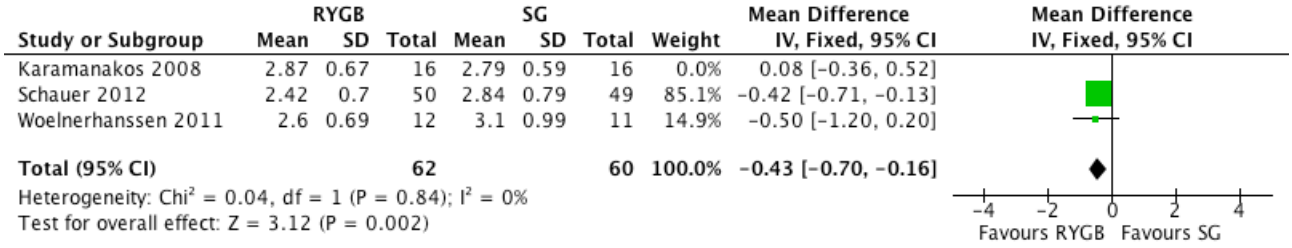


Figure 19: Forest plot, LDL after 12 month follow-up excluding Karamanakos et al. (71)

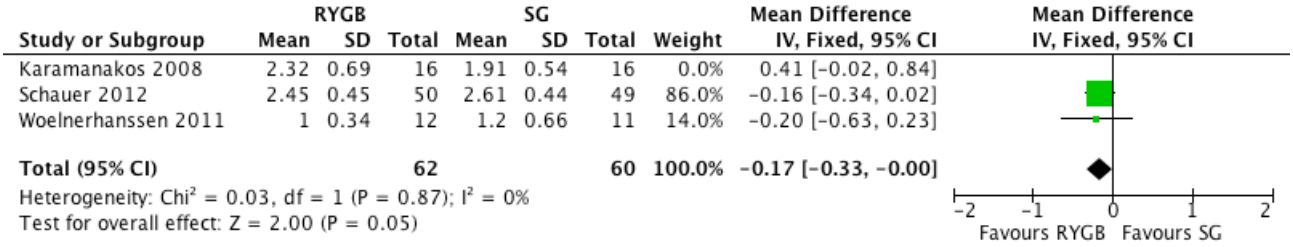


Figure 20: Forest plot, triglycerides after 12 month follow-up excluding Karamanakos et al. (71)

3.3.2 Secondary Outcome Measures

3.3.2.1 Procedure-Related Mortality

Three trials included mortality as an outcome (29,92,139); there were no mortalities out of 397 patients.

3.3.2.2 Procedure-Related Morbidity

Three trials included procedure-related morbidity as an outcome (29,92,139).

Helmiö et al. (139) reported on 30-day morbidity and classified complications as minor or major. Morbidity resulting in death or re-operation, a hospital stay exceeding seven days or a need for blood transfusion of four or more units were classified as major complications; all others were classified as minor complications. The RYGB group had a total of 20 (17.1%) minor complications and 11 (9.4%) major complications; the SG group nine (7.4%) minor and seven (5.8%) major complications. The difference between minor complications was statistically significant (p=0.023) and the difference between major complications was not significant (p=0.292). The RYGB group required six re-operations on four different patients; the SG group four re-operations on three patients. 30-day readmission rate was 3.3% (n=4) after SG and 6.8% (n=8) after RYGB.

Kehagias et al. (92) reported major early (within 30 days) and major late complications. These were similar for both groups with two major early, one major late complication in each group but two re-operations in the RYGB group compared to one re-operation in the SG group. They reported approximately 20% of patients following SG had symptoms of

gastro-oesophageal reflux but did not list and detail other minor complications in either group.

Schauer et al. (29) listed adverse events that occurred up to one year after surgery or initiation of medical therapy and reported these as either serious adverse events or other adverse events. In total, 11 out of 50 (22%) patients in the RYGB group required hospitalization compared to 4 out of 49 (8%) patients in the SG group. A total number of 16 other serious events were listed in the RYGB group and 11 in SG group. Re-operations were performed in three patients from the RYGB group and one patient from the SG group. Under other adverse events, a total of 40 events were reported for the RYGB group and a total of 47 for the SG group. The number of hypoglycaemic episodes was 28 (56%) for RYGB versus 39 for the SG (80%).

Total *major complications* are shown in Figure 21.

Total *minor complications* were analyzed but showed significant statistical heterogeneity with Schauer et al. (29) reporting more complications in the SG group and Helmiö et al. (139) in the RYGB group. RR was 1.06 (0.87-1.31), p=0.55, I^2=93%. The reason for the heterogeneity could not be accounted for.

Re-operation rate was analyzed for the three trials and a total of nine patients requiring re-operation were recorded for RYGB and five for SG. RR was 1.82 (0.62-5.35) with a p=0.28 and no heterogeneity (I^2=0%).

Re-admission rate was reported in two trials (29,139). Analysis showed 17 total events in RYGB group versus eight in the SG group. RR was 2.12 (0.95-4.75), p=0.07 with no heterogeneity (I^2=0%).

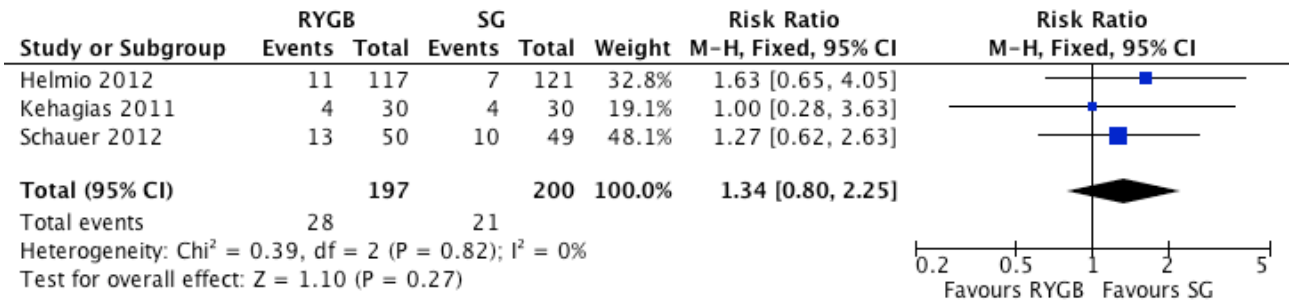


Figure 21: Forest plot, major complications

3.3.2.3 Hormone Changes

Fasting ghrelin was investigated in four trials (17,71,108,138) with Peterli et al. providing a follow-up of three months (108). Preoperative analysis showed significant heterogeneity (I^2=54%) and is shown in Figure 22. Peterli et al. was identified as causing the increased heterogeneity (17) and after exclusion of this trial there was no heterogeneity (Figure 23). Ghrelin levels were analyzed after 12 month follow-up. MD was 232.31 (206.92-257.69), p=<0.00001 with a significant statistical heterogeneity (I^2=67%). After excluding the same trial (17) there was no heterogeneity (I^2=0%). Results are shown in figure 24.

Fasting PYY was investigated by the same trials (17,71,108),133). One trial (108) provided a follow-up to three months. Preoperatively, a total of 97 patients were included in the four trials and analysis showed a significantly higher PYY level for the RYGB group preoperatively (Figure 25). Exclusion of Peterli et al. (17) resulted in a non-significant difference of preoperative PYY (p=0.74) with no heterogeneity (I^2=0%) (Figure 26). After three month follow-up the results were MD=31.65 (20.31-42.99) and a significant difference (p=<0.00001) with significant statistical heterogeneity (I^2=36%). Peterli et al. (17) was again identified as the trial that caused the increased heterogeneity. Exclusion of this trial resulted in a statistically significant difference (p=0.0003) with no heterogeneity (Figure 27). PYY after 12 months follow-up showed a MD=23.01 and p=0.003 with significant statistical heterogeneity (I^2=69%). Peterli et al. (17) was identified as the cause of increased heterogeneity and results after exclusion are shown in Figure 28.

Fasting *GLP-1* was investigated by three trials (17,108,138) with one trial reporting a three month follow-up (108). The trial of Peterli et al. (17) was identified as causing increased statistical heterogeneity throughout GLP-1 analysis. Preoperative fasting GLP-1 resulted in MD=0.92 (0.42-1.42), p=0.0003 and significant heterogeneity (I^2=20%). After exclusion of

the trial results were MD=-1.00 (-3.52-1.51) and p=0.43 with no heterogeneity (I^2=0%). Analysis of GLP-1 after three months follow-up resulted increased heterogeneity (I^2=92%) when including Peterli et al. (17); excluding this trial there was no heterogeneity (I^2=0%) (Figure 29). Analysis including the forementioned trial after 12 month follow-up showed a significant statistical heterogeneity (I^2=93%). Only two trials reported a 12 month follow-up and as a result 12 month analysis of GLP-1 could not be performed.

Leptin was assessed in two trials (121,138). Preoperative MD was -1.95 (-10.37-6.47) and p=0.65 with significant statistical heterogeneity (I^2=64%). Leptin was analyzed after 12 month follow-up and is shown in Figure 30.

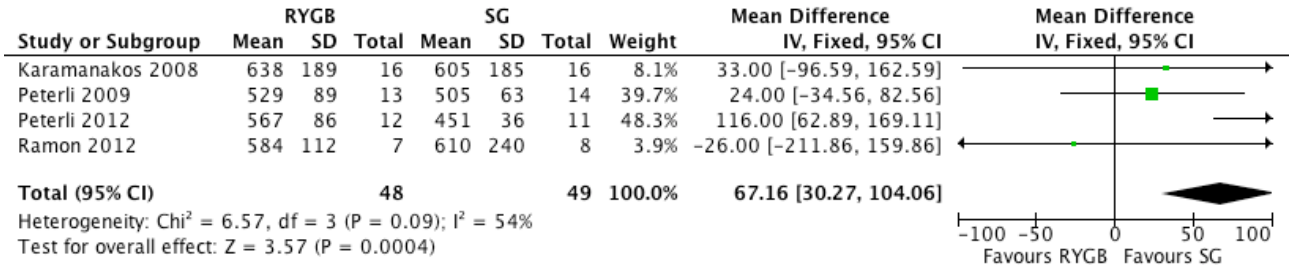


Figure 22: Forest plot, preoperative fasting ghrelin

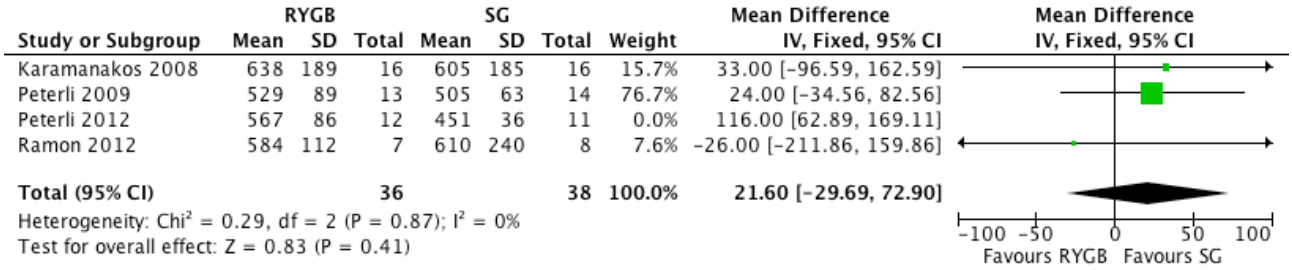


Figure 23: Forest plot, preoperative fasting ghrelin excluding Peterli et al. (17)

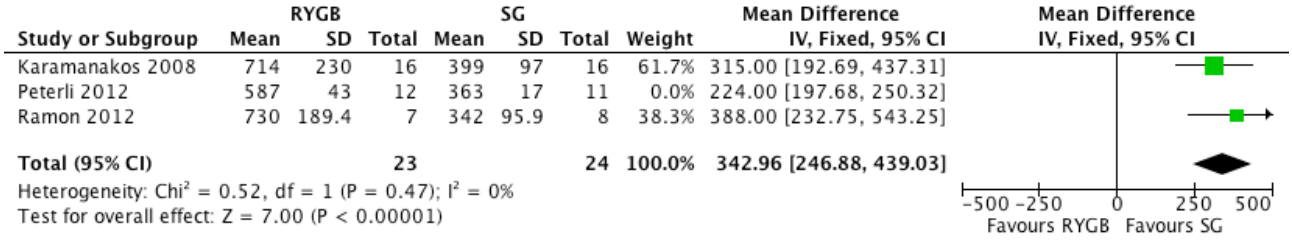


Figure 24: Forest plot, fasting ghrelin after 12 month follow-up excluding Peterli et al. (17)

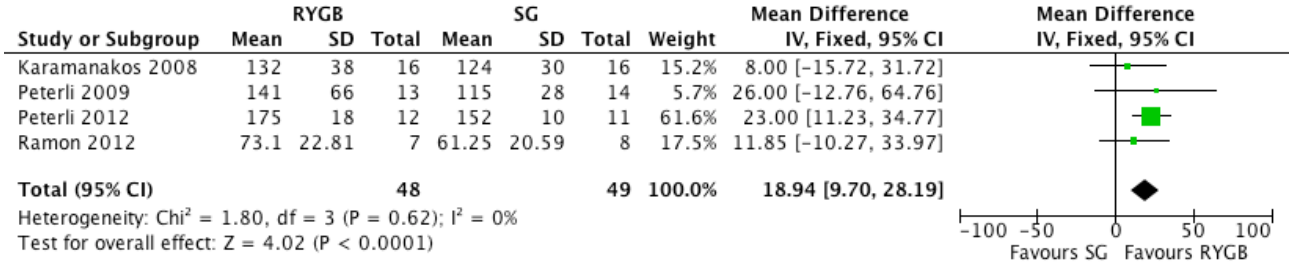


Figure 25: Forest plot, preoperative fasting PYY

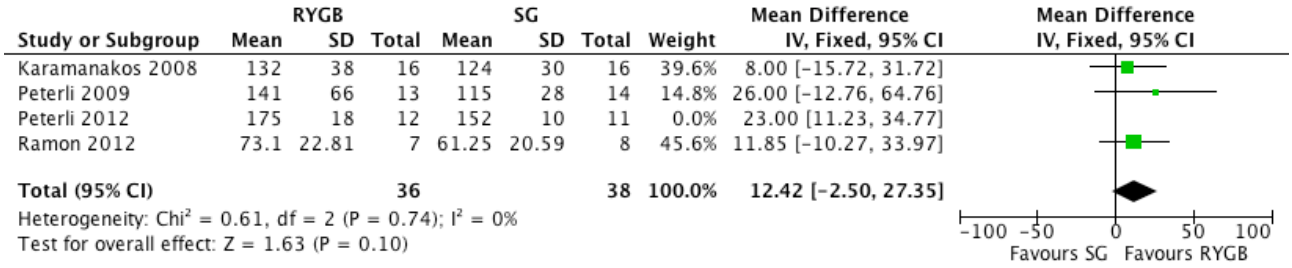


Figure 26: Forest plot, preoperative fasting PYY excluding Peterli et al. (17)

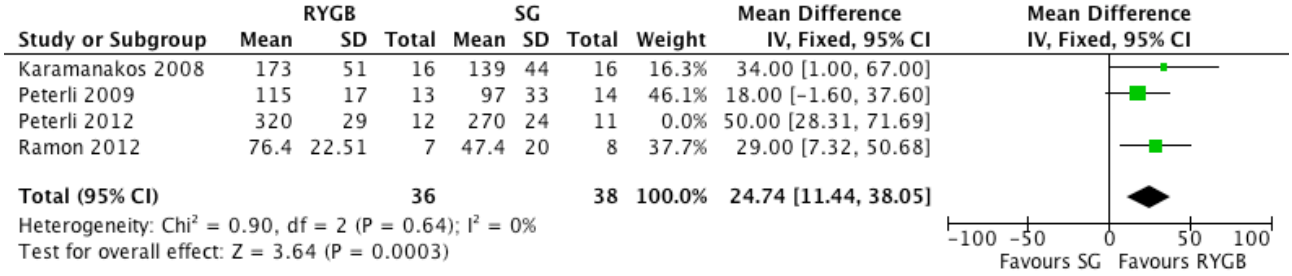


Figure 27: Forest plot, fasting PYY after three month follow-up excluding Peterli et al. (17)

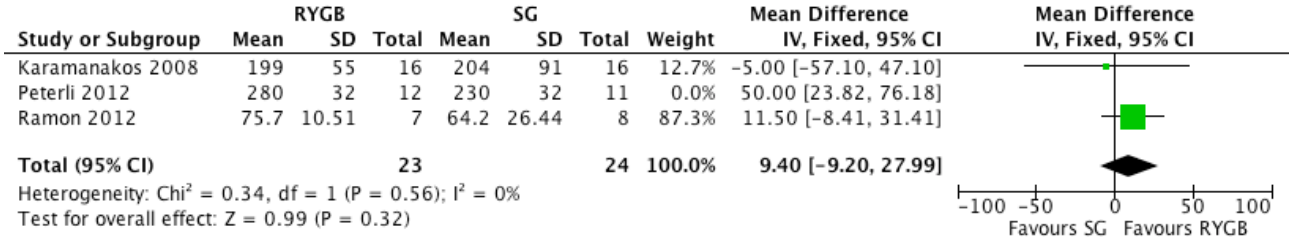


Figure 28: Forest plot, fasting PYY after 12 month follow-up excluding Peterli et al. (17)

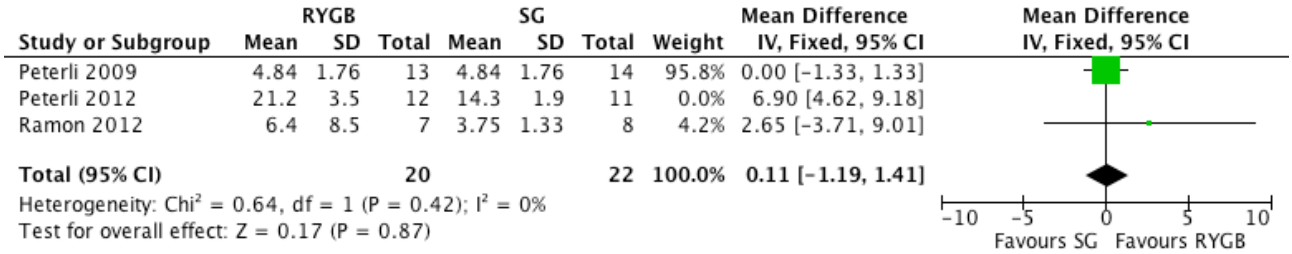


Figure 29: Forest plot, fasting GLP-1 after three month follow-up excluding Peterli et al. (17)

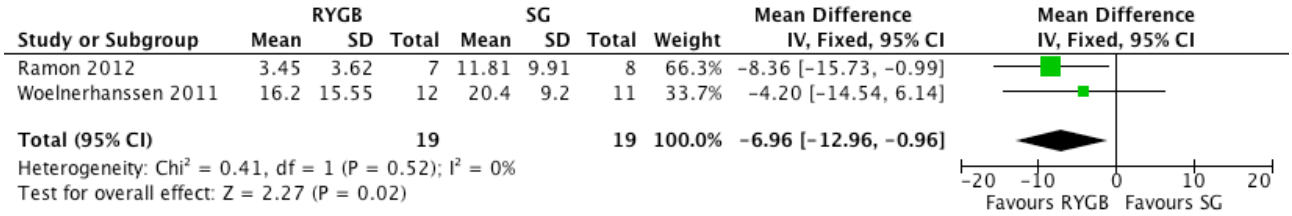


Figure 30: Forest plot, leptin after 12 month follow-up

4. DISCUSSION

4.1 Primary Outcomes

Although each study claimed no statistically significant difference between the RYGB and SG groups in baseline BMI, meta-analysis demonstrated a significantly lower BMI for the SG compared to RYGB with a p-value of 0.03 and no heterogeneity. This raises the question of whether bias in randomization and allocation occurred in the included studies; it would appear that lower BMI patients were more likely to be allocated to SG. After 12 month follow-up BMI was reduced in both groups. With the exception of Karamanakos et al. (71), the authors uniformly report a lower BMI in the RYGB group. Analysis of the four eligible trials resulted in significant heterogeneity, which reduced following exclusion of Karamanakos et al. (71). MD was -0.82 favouring RYGB but this was not statistically significant (p=0.18). Analysis of EWL after 12 month follow-up again showed significant statistical heterogeneity (I^2=75%) when including Karamanakos et al. (71); this was reduced to I^2=15% on exclusion and resulted in a MD of 0.12 favouring RYGB and a p-value 0.06, tending to, but not achieving statistical significance.

Kehagias et al. (92) could not be included in the analysis of 12-month BMI or EWL as the authors did not provide BMI loss after 12 months but after three year follow-up. EWL was reported as mean without SD. Interestingly, they also reported a higher EWL for SG compared to RYGB at one, two and three year follow-up (72.9%, 73.2%, 68.5% vs 65.6%, 65.3% and 62.1%, respectively) and the trial was performed at the same institution as Karamanakos et al. (71). This poses the question how they achieved different results and whether they were performing the surgeries differently or providing a different postoperative care plan. No differences could be detected on surgical technique (Table 1)

and no details were provided by the authors regarding a specialized dietary plan or other postoperative measures that would distinguish them from other trials.

In conclusion, in view of the somewhat more favourable overall results of the RYGB and the background of a significantly higher baseline BMI compared to the SG group, the RYGB may be better than SG in terms of 12 month BMI and EWL outcome. No statistically significant differences on outcomes of weight could be detected.

All studies reporting on biochemical parameters reflecting glycaemic control and resolution of type 2 diabetes showed decreases of fasting insulin, glucose and the HOMA-IR following both RYGB and SG. No statistically significant differences were detected in this meta-analysis for these outcome parameters during preoperative or 12 month postoperative evaluation.

After three month follow-up, two trials offered analysis of 42 patients but Insulin and HOMA-IR were significantly lower following RYGB compared to SG (Figure 13 and 15). This may point out that resolution of diabetes is more rapid after RYGB and follows a more weight-independent mechanism than SG.

One trial reported on HbA1c (29) and therefore this could not be included as an outcome in this analysis. Schauer et al. (29) reported a significant reduction in HbA1c in both the RYGB and SG group after 12 months compared to the intensive medical therapy group. Furthermore they reported on the proportion of patients reaching the target HbA1c of <6% with or without use of diabetic medication. Both RYGB and SG had significantly more patients in these groups compared to intensive medical therapy. Differences between RYGB and SG were statistically non-significant but somewhat more favourable in the RYGB group. It would appear plausible to encourage use of HbA1c in the investigation and follow-up of future trials. Besides offering a further solid biochemical parameter for

objective assessment, HbA1c may offer more comprehensive evaluation of diabetes resolution or improvement as its value reflects long-term glycaemic control rather than once off short-term parameters such as fasting glucose and insulin which are more variable.

Schauer et al. (29) also reported on the use of anti-diabetic medications and presented results regarding the average number of diabetes medications used and the percentage of patients reaching targeted HbA1c <6% with or without diabetes medications. The average number of diabetes medications was significantly reduced following both RYGB and SG after 12 month follow-up. Patients were using an average of 2.6 and 2.4 medications at baseline versus 0.3 and 0.9 one year after RYGB and SG, respectively. 42% of RYGB patients reached a HbA1c of <6% without any use of diabetes medications compared to 36.7% of SG patients but this was not statistically different. Schauer et al. (29) also pointed out that reduction of diabetes medications occurred before maximum weight loss supporting the concept that mechanisms independent of weight loss contribute to diabetes resolution. Documenting the use of medications as an outcome appears rational and provides good feedback on the progress of patients following bariatric procedures. This also provides actual evidence in categorizing patients into having complete resolution or improvement of diabetes and should be included in future trials.

One concern in this part of the meta-analysis is that trials investigated different study populations; one trial only included diabetic patients, some of them with advanced long-standing diabetes and documented target organ damage (29), one trial investigated non-diabetic patients (121) and two trials investigated a mixed group (108,133). However, all trials documented increased glucose, insulin and evidence of insulin resistance with an elevated HOMA-IR at baseline and an improvement after 12 months for both surgical procedures.

In terms of overall assessment of metabolic syndrome, Schauer et al. (29) was the only trial quantifying resolution by evaluation of CRP as an indicator of low-grade chronic inflammation. They noted that both RYGB and SG had a significantly greater reduction in CRP than the intensive medical therapy group; an indication of attenuation of chronic inflammation and a possible link to improvement of insulin sensitivity. Future trials should include CRP for complete evaluation and evidence of resolution of metabolic syndrome.

Changes in lipid profile were investigated in three trials that were included in this meta-analysis. These reported significant decreases in triglycerides following both procedures with no statistical significance between them; one trial reported a triglyceride decrease only after RYGB but not after SG (29). Total cholesterol was analyzed preoperatively and after 12 months with no significant difference between the two study groups. Heterogeneity was significant in the preoperative analysis and Karamanakos et al. (71) was identified as the trial causing the increased heterogeneity. The total cholesterol was overall higher than in the other study populations, and higher in the SG than in the RYGB at baseline; their reported p-value was 0.07. During analysis of LDL, the same trial was identified as causing high heterogeneity; LDL overall was again higher than in other study populations and on review of the trial's preoperative LDL it was significantly higher in the RYGB compared to SG (p=0.03) (71). Following exclusion of this trial the 12-month analysis of LDL showed a significantly lower LDL in the RYGB group compared to SG with a p-value of 0.002 (Figure 19).

Triglyceride analysis again showed heterogeneity caused by Karamanakos et al. (71); following exclusion the triglycerides were significantly lower in the RYGB compared to the SG after 12 months with p=0.05 and no heterogeneity (I^2=0%) (Figure 20).

HDL increased in all included studies after 12 month follow-up and the meta-analysis revealed no statistical difference between RYGB and SG.

Schauer et al. (29) reported on the use of lipid lowering agents and found a reduction of these from 86% and 78% preoperative use to 27% and 39% after 12 months for RYGB and SG, respectively. Documentation of the use of lipid-lowering agents should be included in future research.

Overall, RYGB appears superior in resolution of dyslipidaemia over a 12-month period with statistical differences noted in triglyceride ($p=0.05$) and LDL ($p=0.002$) reduction. In combination with the fact that RYGB appears to facilitate more rapid resolution of diabetes, RYGB may be the more appropriate procedure for patients with severe associated comorbidities.

Kehagias et al. (92) reported comorbidity resolution but did not quantify the resolution and could not be included in the analysis of comorbidity improvement. This emphasizes the necessity to use biochemical or other objective parameters to assess and quantify comorbidity resolution. This is in contrast to Schauer et al. (29) where comorbidity resolution was investigated and documented in detail and included a wide array of objective parameters to objectively assess comorbidity improvement and resolution. Future research should include these objective parameters in their assessment and reporting of comorbidity resolution.

4.2 Secondary Outcomes

Three trials reported procedure-related morbidity and mortality. These included a total of 397 patients undergoing either RYGB or SG. None of the trials reported any mortality. This emphasizes the improved safety and decrease in mortality rates observed in the field of bariatric surgery when procedures are performed for the appropriate indications and in the appropriate setting (26).

Meta-analysis of morbidity was limited as the classification of morbidity varied strongly among trials. For example, Schauer et al. (29) included any transfusion as a serious event whereas Helmiö et al. (139) defined a transfusion requirement of four or more units as a major complication.

When considering all events classified as serious by the individual trials, the meta-analysis showed 28 total events in the RYGB group and 21 in the SG group; results favoured SG with less major morbidity but this was not statistically significant (p=0.27).

Reoperation rates were higher in the RYGB group with nine events compared to five events in the SG group. However, this was not significant (p=0.28). The same applied to readmissions where rates following SG were lower but the difference was not significant (p=0.07).

Minor complication rates were analyzed according to the different definitions of a minor event by the trial authors. Results showed high heterogeneity (I^2=93%) with more complications reported by Schauer et al. (29) in the SG group and more by Helmiö et al . (139) in the RYGB group and no statistical significance between the two groups. Kehagias et al. (92) reported GORD symptoms in approximately 20% of patients following SG but did not provide any other details with regard to minor morbidity. Notably, Schauer et al.

(29) described self-reported hypoglycaemic episodes in 80% of patients after SG versus 56% of patients after RYGB reporting at least one episode.

Overall, results from the trials and this meta-analysis indicate that both RYGB and SG appear to be safe procedures with acceptable major morbidity rates and no mortality reported. No significant difference between the procedures was revealed but SG had somewhat lower major morbidity. Minor morbidity appears underreported and variable among authors. A consensus on reporting morbidity according to a specific classification would be beneficial for future research and allow meaningful comparison between different bariatric surgical procedures.

All hormone analyses were performed on fasting results and this meta-analysis did not include data on postprandial responses. The trial by Peterli et al. (17) was identified as the cause of significant statistical heterogeneity for ghrelin, PYY and GLP-1 analyses. Review of the trial revealed that the author presented maximum concentration values in response to a test meal. Fasting levels were only presented in graphs and no actual data including mean or SD were provided for fasting results. Therefore, the trial had to be excluded from the analysis.

Analysis of preoperative fasting ghrelin showed a significantly lower ghrelin level in the SG group with high heterogeneity (I^2=54%, p=0.0004). Peterli et al (17) was identified as the trial that caused the increased heterogenity and exclusion of this trial resulted in resolution of heterogeneity and a non-significant p-value. The analysis of ghrelin after 12 month follow-up revealed a significantly lower ghrelin in the SG group with a mean difference of 342.96 with a significant p-value of <0.00001 and no heterogeneity. Analysis of ghrelin levels after 3 months showed similar results indicating that SG reduces ghrelin levels early and sustains this effect over 12 months. Because the gastric fundus is the main location of

ghrelin synthesis, reduction of ghrelin after SG with resection of the fundus is not unexpected. No reduction of ghrelin was observed in the RYGB group after 12 months. RYGB results indicate that ghrelin levels had decreased three months postoperatively but were regained 12 months postoperatively. This is in contrast to previous studies that reported ghrelin reduction following RYGB (119). Karamanakos et al. (71) evaluated appetite and noted a partial appetite recovery after RYGB but not after SG; this may be due to the difference in ghrelin levels observed. Physiological ghrelin levels in the non-obese are characterized by a rise during fasting periods and a postprandial fall. Diet-induced weight loss will increase ghrelin levels (119). The usual suppression of ghrelin following food intake is not observed in the obese (142). Interestingly, the trials reported that although ghrelin levels did not decrease 12 months after RYGB, the postprandial suppression after meals was regained; this was not observed for SG, in which ghrelin levels remained low with no major suppression noted following meal intake (17,138). These findings indicate that appetite suppression may be more consistent after SG but response to a meal after RYGB in terms of meal satisfaction may be similar or even greater. This requires further research to investigate appetite suppression and postprandial satisfaction following RYGB and SG.

PYY analysis, excluding Peterli et al. (17), showed a non-significant higher fasting PYY level for RYGB patients in the preoperative phase (p=0.10). After three months, there was a statistically significant increase in the RYGB group compared to SG with a mean difference of 24.74, no heterogeneity and a p-value of 0.0003. After 12 months there was still a somewhat higher fasting PYY in the RYGB group but this was not significant (p=0.32). We did not analyze postprandial response in this meta-analysis, which limits insight in to the physiological changes of PYY following RYGB and SG. In obese patients, PYY levels are reduced and also have a lower response contributing to an increased

appetite and impaired glucose tolerance (143). Before surgery PYY levels did not significantly increase after meals thus suggesting an attenuated PYY response (17,138). Postoperatively, the authors described an exaggerated PYY response to a test meal for both RYGB and SG. However, PYY response to meal ingestion gradually decreased after six months possibly due to physiologic adaptation. Following the hindgut theory, the response of PYY was expected for RYGB (110). SG does not alter small bowel nutrient passage but still developed a similar response of PYY. This may be due to accelerated gastric emptying (125) or a difference in nutrient digestion and delivery with the foregut mediating a PYY response through other humoral mechanisms (17). This requires further research to fully understand the mechanisms involved in PYY response following SG.

Analysis of GLP-1 was inconclusive. Excluding Peterli et al. (17), only two trials reported on GLP-1 with one trial providing a three month follow-up (108). Meta-analysis after three months showed no statistical difference between RYGB and SG. 12-month analysis could not be performed as only one trial provided results (138). A limitation of this meta-analysis is that only fasting results were investigated and GLP-1 is mainly increased as a postprandial response. Ramón et al. reported a significantly greater GLP-1 postprandial response for RYGB than for SG (138); Peterli et al. (17) also observed a less prominent response pattern for the SG group. An attenuated response to meals was observed in preoperative patients. Although described as a lower response in the SG group compared to RYGB, marked improvement of postprandial response was noted and may indicate similar potential mechanisms for GLP-1 increase as for PYY (17).

Leptin was evaluated by two included trials (121, 138). Meta-analysis after 12 months showed a significant difference between RYGB and SG with a p-value of 0.02 and no heterogeneity. Leptin was significantly lower in the RYGB group. Only 38 patients were compared in the meta-analysis and interpretation of this result should be with caution.

Woelnerhannsen et al. (121) reported a decrease in leptin as early as one week after surgery and noted that the reflection of leptin of the total fat mass may only apply to steady-state conditions but not during rapid weight changes as seen after bariatric surgery (121). Leptin was significantly reduced after both procedures; the meta-analysis revealed a significantly lower leptin following RYGB ($p=0.02$).

Further research is needed to completely understand the effects of RYGB and SG on gut hormones, satiety and glucose homeostasis.

In conclusion, after 12 month follow-up no statistically significant difference was demonstrated between SG and RYGB for weight loss and diabetes resolution but RYGB was superior in resolution of dylipidaemia. Both procedures appear to be safe procedures when performed in an appropriate setting.

4.3 Limitations

- Follow-up time in trials comparing SG to RYGB is limited to 12 months. Non-RCTs have demonstrated a gradual decline in effectiveness following SG; weight regain was observed after the third postoperative year and resulted in some patients requiring conversion to RYGB and BPD-DS (102,103,106). Partial long-term loss of effectiveness has also been noted for RYGB (77,78) but these long-term results to date have not been compared in RCTs to date.

- A subset of the included studies had very small cohort sizes and even combined in the meta-analysis the sample size may not be powered to detect moderate differences between the two procedures.

- The methodological quality of included studies is a further limitation as only two trials were adequately blinded.

- We could not utilize all trials for all outcomes as the various trials investigated different outcomes which reduced sample size and power to detect differences. Variations among included trials in the definition of minor morbidity outcome limited comparison. In addition, some of the outcomes had insufficient or inadequate reporting in the primary trials.

- Fasting hormones but no postprandial hormone responses were investigated which may limit insight into response profiles following SG and RYGB.

- There were no data available to assess the differences in operating and hospitalization time, as well as overall costs and this could not be evaluated in this meta-analysis.

5. CONCLUSIONS

5.1 Implications for Practice

- There is no statistically significant difference between SG and RYGB in weight loss after 12 months of follow-up.
- There is no statistically significant difference in the parameters of diabetes resolution after 12 month follow-up. However, HOMA-IR and insulin levels were significantly lower three months after RYGB, indicating a more rapid resolution of diabetes following RYGB.
- RYGB appears to be superior in the resolution of dyslipidaemia over a 12-month period with statistical difference noted in triglyceride and LDL reduction.
- Both SG and RYGB appear to be safe procedures when performed in the appropriate setting. No statistically significant difference between the two procedures could be proven with regards to procedure-related morbidity and mortality.

In other words, SG is as safe as RYGB and equivalent to RYGB in all outcome parameters after 12 month follow-up except for triglyceride and LDL reduction where RYGB is better. However there are no long-term outcome studies enabling comparison of SG to RYGB.

5.2 Implications for Research

- Larger RCTs comparing SG to RYGB are needed to enable adequate power to detect moderate differences between the procedures.
- RCTs are required with long-term follow-up to assess and compare effectiveness of each procedure.
- Comorbidity improvement requires objective evaluation and future research should include biochemical parameters or other objective measures to quantify improvement of comorbidity; parameters that have been underutilized to date are HbA1c and CRP and should be recognized as important measurement tools. All parameter outcomes should be reported in a standardized manner.
- Investigation of medication use should be encouraged to assess procedure response and to distinguish between resolution and improvement of comorbidities.
- Consensus should be reached on a standardized classification and reporting system of procedure-related morbidity specific to bariatric surgery, and these should be used in future RCT's.
- When investigating hormones, future research should investigate fasting and postprandial hormone levels to capture the gastrointestinal hormone response profile and include an assessment of appetite suppression and satiety.
- Subgroup parallel-trials and publications during ongoing trials should be avoided. Cohort overlaps in publications should be clearly stated.

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7. APPENDIX

Search Engine	Date	Search Strategy
MEDLINE (Ovid SP)	1950-October 2012	1. laparoscopic (83255) 2. sleeve gastrectomy (835) 3. Roux-en-Y gastric bypass (6929) 4. 2 or 3 (7430) 5. 1 and 4 (2636) 6. randomized control trial (116469) 7. 5 and 6 (92)

Appendix 1: Electronic search strategy