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Research Article

Effects of Bariatric Surgery on Glucose Control, Weight Reduction and Disease Remission among Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Background: Bariatric procedures aim to reduce weight and appear to have independent metabolic benefits such as blood glucose control.

Objective: To determine the effectiveness of Bariatric Surgery versus conventional medical therapy on glucose control, weight reduction and disease remission among patients with type 2 diabetes mellitus.

Conduct of Study: Published English-written RCTs from Jan 1, 1990 - June 30, 2012 were included. Participants were type 2 diabetic patients treated with any conventional bariatric procedure, controls were managed medically, and outcomes were quantitatively measured biochemical parameters for blood glucose control. Values of Hba1c, body weight and remission rate were obtained. Heterogeneity was evaluated statistically. Sensitivity and subgroup analyses were performed appropriately.

Results: Among 16 articles retrieved, 3 studies met the inclusion criteria. A total of 170 patients underwent bariatric surgery. There is lower HbA1c levels among patients who underwent bariatric surgery compared to those who were given medical therapy alone (p value = 0.03). Likewise, statistically significant lower post-treatment weight is seen among patients who underwent surgery (p value = 0.01). Higher remission rate was also achieved after Bariatric Surgery ($p < 0.00001$), however there is significant heterogeneity ($Chi^2 = 3.02$; $I^2 = 0\%$).

Conclusion: Among participants, better glycemic control and significantly lower body weight were achieved after Bariatric surgery compared to medical therapy alone. These beneficial effects were seen and sustained for 1 to 2 years following the procedure. A substantial number of patients also achieved disease remission. However, there is high incidence of adverse effects mainly nutrition-related complications and hypoglycemia.

Keywords: *Bariatric Surgery; Glucose; Disease Remission; Diabetes Mellitus*

Introduction

The significant increase in the prevalence of obesity and diabetes in recent years is a public health policy issue of major importance. Nearly half the adults in Europe and 64.5% of American adults are overweight or obese, and the epidemic is spreading around the world as Western lifestyles are increasingly adapted. According to the World Health Statistics 2012, in every region in the world, obesity doubled between 1990 and 2008. Today, half a billion people (12% of the world's population) are considered obese [1].

Obesity and type 2 diabetes are linked in several ways. Obesity is involved in the pathologic process that culminates in the development of frank type 2 diabetes [2,3], and is a severely aggravating factor in the disease itself, as well as a serious risk factor for the cardiovascular disorders that frequently affect persons with diabetes [4]. Epidemiologic evidence for this study is robust. According to a survey by the Centers for Disease Control and Prevention, the prevalence of obesity among persons diagnosed with diabetes was 53% in men and 58% in women. Even higher percentages were classified as overweight - 86.3% in men and 84.2% in women.

In a short term observation period, it was found out that the modest weight loss achieved by overweight or obese type 2 DM patients using lifestyle modification and medical management were associated with improvements in glycemic control, hypertension and dyslipidemia [5]. However, there is also strong evidence that significant weight loss achieved by particularly severely obese patients is only rarely sustained. With the role of obesity in the development of Type 2 DM along with its complications, recent guidelines suggest that achieving weight loss and sustaining a normal weight is the most logical and cost-effective means of controlling type 2 diabetes mellitus [6].

Medical therapeutic options targeting primarily glucose control are all ideally added to, and not exchanged for, lifestyle change. Unfortunately, such strategies have very limited success in controlling blood glucose levels amongst the severely obese, with many of these patients not achieving targets. A number of these medications used for treating type 2 diabetes, including insulin, themselves can result in weight gain.

A major challenge in the management of type 2 diabetes mellitus is the need for continuous monitoring and intensification of therapies which is done by adding new agents in increasing doses over time. Guidelines such as the National Institute of Health and Clinical Excellence (NICE) support more vigorous intensification of hypoglycemic therapies in early stages of diabetes [7]. For instance, NICE recommends stepping up from monotherapy to dual therapy once values of HbA1c ≥ 6.5%, and increasing to triple therapies once HbA1c ≥ 7%. In one trial that randomized patients with type 2 diabetes and co-existing cardiovascular disease into intensive (targeting HbA1c < 6.5%) and non-intensive treatment arms, mortality was higher in the intensive group. Results were driven by deaths in those people who failed to achieve target HbA1c because treatment was intensified [8]. This should not be applied to patients with early type 2 diabetes. They should be treated less vigorously as the legacy effect of early intervention is considerable.

One concern that has been raised is the frequency by which health care providers escalate therapies. Approaches which rely only on intensifying lifestyle or other time-consuming measures have set clinicians up for failure to achieve targets [9]. It is possible to achieve more benefits, in terms of complication prevention and even slowed disease progression, if treatments are started and intensified early. There have even been suggestions of starting polypharmacy at diagnosis [10,11], but there is limited current evidence to demonstrate the efficacy of this [8].

Apart from the side effect profiles and suboptimal deployment of existing therapies, there also remain issues on patient engagement in various aspects of life. Very few clinical services routinely provide psychological support to encourage life-long engagement in self-care.

The continuing morbidity and mortality in persons with diabetes is a sign that the answer as to the best management for type 2 diabetes in terms of maximizing metabolic control is still elusive. Given this scenario, the option of bariatric intervention needs to be considered in appropriately selected patients. Bariatric procedures aim to reduce weight and maintain weight loss through altering energy balance primarily by reducing food intake and modifying the physiological changes that drive weight regain. There also appear to be independent metabolic benefits, associated with effects of incretins and possibly other hormonal or neural changes after some surgical procedures [12], in addition to weight loss.

A 2009 Cochrane review including patients with and without diabetes concluded that bariatric surgery resulted in greater weight loss than conventional treatment in obese class I (BMI > 30) as well as severe obesity, accompanied by improvements in comorbidities such as type 2 diabetes, hypertension and improvements in health-related quality of life [13].

A number of guidelines exist on the use of bariatric surgery for the treatment of severe obesity in general, and for the treatment of type 2 diabetes in particular. A recent Diabetes Surgery Summit of 50 international experts recommends that conventional GI surgery

Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LAGB), or bilio-pancreatic diversion (BPD) should be considered for the treatment of type 2 diabetes in acceptable surgical candidates with BMI > 35 kg/m^2 who are inadequately controlled by lifestyle and medical therapy. Further trial evidence was deemed necessary for inadequately controlled type 2 diabetes in candidates suitable for surgery with mild-to-moderate obesity (BMI 30 - 35 kg/m^2) [14].

Research Question

Among patients with Type 2 Diabetes Mellitus, how effective is Bariatric Surgery in compared to conventional medical therapy in achieving glucose control, weight reduction and disease remission?

Objectives

General Objective: To determine the effectiveness of Bariatric Surgery versus conventional medical therapy for the management of Type 2 Diabetes Mellitus.

Specific Objectives

1. To determine the effectiveness of Bariatric Surgery compared to conventional medical therapy in improving glucose control among patients with type 2 diabetes mellitus.
2. To determine the effectiveness of Bariatric Surgery compared to conventional medical therapy in reducing weight among patients with type 2 diabetes mellitus.
3. To determine the effectiveness of Bariatric Surgery compared to conventional medical therapy in inducing disease remission among patients with type 2 diabetes mellitus.
4. To identify and evaluate the safety and adverse effects of Bariatric Surgery compared to conventional medical therapy among patients with type 2 diabetes mellitus.

Review or Related Studies and Literature

Bariatric surgery, known as metabolic surgery, is a form of gastrointestinal operation that was designed to achieve substantial weight loss in severely obese patients. Moreover, it was seen to have effectively treated hyperglycemia and other obesity-related conditions (hyperlipidemia, blood pressure, obstructive sleep apnea and quality of life) in those patients who were successfully operated on [15,16]. There are various types of bariatric surgeries that have been conventionally performed worldwide.

Adjustable Gastric Banding (AGB) is a restrictive procedure that employs a band-like, saline-filled adjustable tube wrapped around the superior portion of the stomach, just distal to the gastroesophageal junction. This is the most flexible procedure since the band may be adjusted according to individual body weight requirements. Available data showed successful weight reduction by 20 - 30%. Weight reduction in successfully treated patients was shown to have been achieved gradually, usually observed at maximum of 2 - 3 years. Usual complications and adverse events include band erosions, leaks, gastric pouch dilatation and development of anemia and other nutritional deficiencies (e.g. Iron, Vitamin B12, Folate) [17,18].

Roux-en-Y Gastric Bypass (RYGB) involves the creation of small and vertically oriented gastric pouch. The upper pouch is completely separated from the gastric remnant and is anastomosed to the adjacent jejunum. Continuity of bowel segments is restored via creating an entero-entero anastomosis between the excluded biliopancreatic limb and the alimentary limb. Weight reduction by 25 - 35% is achieved by successfully operated patients. This is achieved rapidly at a maximum of 1 - 2 years. However, weight regain may occur after 3 - 5 years post-surgery. Similarly, anemia and nutritional deficiencies including essential vitamins and minerals (e.g. Vitamin 12, copper, zinc, calcium) have often been associated with these patients. Leaks, gastric ulcers and GI obstruction were observed as well in some cases.

Biliopancreatic Diversion (BPD) consists of a distal, horizontal gastrectomy that creates a functional remnant upper stomach approximately 200 - 500 ml in size. Desirable size of remnant stomach is based on individual patient characteristics. The remnant stomach is then anastomosed to the distal 250 cm of small intestine (alimentary limb). The excluded small intestine carries bile and pancreatic secretions. The 50-cm -common limb is the only bowel segment where digestive enzymes and food mix. Also, in this short common limb, fat and carbohydrates are being absorbed.

A variant known as BPD with Duodenal Switch is a complex procedure as well but was found to have less complication. A sleeve vertical gastrectomy is performed followed by closure at 2 cm distance from pylorus distally. Thereafter, a duodeno-ileal anastomosis (duodenal switch) is done. The gastric fundus is almost entirely resected sparing the antrum and pylorus. A very short segment of duodenum is also preserved, along with the vagus nerve. Both BPD and its Duodenal Switch variant are considered malabsorptive procedures. Compared to AGB and RYGB, BPD has a high incidence of developing anemia and nutritional deficiencies (e.g. calcium, vitamin D, copper, zinc and fat-soluble vitamins). Percentage of mean weight loss averages 30 - 40% and the effect has been observed at a rapid rate, maximum at 1-2 years [17,18].

Choice of surgical procedure depends on several factors including familiarity with different surgical techniques, regional expertise, and adherence to post-surgical bundles of care. Other concerns include safety and reversibility of the procedure [18]. Bariatric Surgery is a challenging therapeutic option for Type 2 Diabetes Mellitus. The birth of this idea dates back in the year 1991. Early existing guidelines have recommended Bariatric Surgery as treatment for severe obesity. Initially, this has not been widely accepted due to issues of safety, complexity and cost-effectiveness. Through advancements of surgical equipments and introduction of new techniques, use of bariatric surgery has increased worldwide to address problems of obesity and metabolism [19].

In 1985, the National Institute of Health had established the health implications of obesity. The risk for morbidity and mortality accompanying obesity was emphasized to be proportional to the degree of overweight, pointing out that patients with severe obesity are the potential candidates for treatment by surgical procedures. A 1978 NIH consensus conference on surgery for obesity considered primarily intestinal (jejunoileal) bypass, which exerts its weight-loss effects through malabsorption, decreased food intake, and possibly other mechanisms. However, the conference highlighted the undesirable side effects of this operation [19]. Newer procedures for weight loss include both food aversion and malabsorption. Refinements in such procedures have led to reports of results superior to those seen with the earlier operation. Nonsurgical treatment of clinically severe obesity was also stated in the 1991 NIH Consensus Conference. It aims to create a caloric deficit sufficient to result in both permanent weight loss and reduction of weight-related risk factors or comorbidity. The specific amount of targeted weight loss is defined on a case-by-case basis and does not necessarily require reduction to ideal body weight. Patient selection according to the Consensus Conference requires assessing risk-benefit ratio in each case. Those patients judged by experienced clinicians to have a low probability of success with nonsurgical measures, as demonstrated for example by failures in established weight control programs or reluctance by the patient to enter such a program, may be considered for surgery.

The National Institute for Clinical Excellence has also issued recommendations to the NHS on the use of gastric surgery for the treatment of morbid obesity. Bariatric surgery is recommended as a treatment option for adults with obesity if patients have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease that could be improved if they lost weight, or if all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months [20].Bariatric surgery is also recommended as a first-line option (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m2 in whom surgical intervention is considered appropriate.

In 2009, the American Diabetes Association guidelines included the consideration of bariatric surgery as part of the strategy for patients to gain control of their high blood sugars. Bariatric surgery has been shown to stabilize glycemia in approximately 55% to 95% of patients with diabetes, depending on the surgical procedure (gastric banding or bypassing or transposing or resecting sections of the small intestines) [21].

Ideal candidates for bariatric surgery are those patients with type 2 diabetes whose body mass index (BMI) is > 35 kg/m^2, especially if diabetes is not controlled with lifestyle and pharmacologic therapy. Although small trials have shown glycemic benefit in patients with diabetes whose BMI is 30 - 35 kg/m^2, the American Diabetes Association guidelines do not recommend bariatric surgery outside of research protocol in those with BMI < 35 kg/m^2 [22].

Scottish Intercollegiate Guidelines Network 2010 stated that Bariatric surgery should be included as part of an overall clinical pathway for adult weight management. Bariatric surgery should be considered on an individual case basis following assessment of risk/benefit in patients with a BMI ≥35 kg/m^2, presence of one or more severe comorbidities which are expected to improve significantly with weight reduction (e.g. severe mobility problems, arthritis, type 2 diabetes) [22]. Indications for Bariatric Surgery, according to the Bariatric Scientific Collaborative Group, include patients in age groups from 18 to 60 years old with BMI > 40 kg/m^2, with BMI 35 - 40 kg/m^2 with existing co-morbidity in which surgically induced weight loss is expected to improve the disorder (such as metabolic disorders, cardiorespiratory disease, severe joint disease, obesity related severe psychological problems) [23].

The latest international guideline, International Diabetes Federation (2011), has stated a recommendation for surgery to be prioritized to DM patients with BMI > 40 kg/m^2 or BMI > 35 kg/m^2 when diabetes and other co-morbidities not controlled by optimum medical treatment [2,3].

The guidelines aforementioned have generally followed the 1991 National Institutes of Health, and have focused on Body Mass Index (BMI) and presence of comorbidities. Each guideline have presented similar stipulations: failure from previous weight loss attempts, no specific contraindication to surgery, and patient's commitment to long-term follow up and aftercare. There is an increasing interest in the use of Bariatric Surgery in people who are Class I Obese (BMI 30 - 35 kg/m^2). It can also be noted that all guidelines were focused more on decreasing the prevalence of obesity and associated morbidity rather than remission of Type 2 Diabetes. There is lacking substantial evidence on the specific use of bariatric surgery for Type 2 DM patients whether they are obese or not. Hence, recommendations were raised to conduct quality studies to justify previous claims and position statements.

In the *Review of Hormonal and Metabolic Mechanisms of Diabetes Remission after Gastrointestinal Surgery by Joshua P. Thaler and David E. Cummings*, several hypotheses were presented that can explain the rapid, weight-independent hypoglycemic effects of bariatric surgery (particularly the RYGB).

Starvation-followed-by-weight-loss hypothesis: This is one important hypothesis that has been conceptualized. It states that there is marked improvement of glycemic control due to restricted oral food intake greatly observed in the immediate postoperative period. After the surgery, patients were initially put on *nothing per orem*. The residual β-cells are stimulated minimally. In this model, by the time patients return to his optimum diet, the insulin-sensitizing effects of weight reduction from the bariatric operation takes place. In most general surgery, especially involving the GI tract, patients are subjected to perioperative caloric restriction. Notably, rapid remission of Type 2 DM is not observed in these settings; more so, glycemic control is worsened after a major surgery due to disturbances of counterregulatory stress hormones (e.g. cortisol and catecholamines). This remarkable phenomenon is unique to RYGB and certain bariatric procedures involving intestinal bypasses, such as BPD. Although well-thought, this hypothesis fails to explain the marked glycemic control achieved after RYGB in comparison with equivalent weight loss from dieting or restrictive bariatric operations. Hence, this hypothesis clearly cannot account for the full antidiabetic impact of RYGB [24].

Ghrelin hypothesis: Ghrelin is a 28-amino-acid peptide growth hormone secretagouge that is produced primarily by stomach and duodenal cells. This hormone has been implicated in the stimulation of fat storage and food intake. The hypothesis states that there is disturbance of ghrelin regulation after RYGB. The compromised secretion of ghrelin in post RYGB was suggested to contribute to the anorexic and antidiabetic effects of the said procedure [25]. Besides contributing to the decrease appetite and oral intake of post-RYGB, compromised ghrelin secretion might also improve glucose tolerance. Ghrelin also can stimulate insulin counterregulatory hormones, suppress the insulin-sensitizing hormone adiponectin, block hepatic insulin signaling at the level of phosphatidylinositol-3-kinase, and inhibit insulin secretion [26]. All of these actions acutely elevate blood glucose levels.

Lower intestinal hypothesis: Another mechanism for improved glucose homeostasis after bariatric operations involves the accelerated passage of ingested nutrients to the distal gut because of intestinal bypass. The unabsorbed nutrients in the distal gut intensify the secretion of GLP-1, thereby improving glucose homeostasis. GLP-1 is an incretin peptide that increases glucose tolerance by enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, increasing β-cell mass and possibly improving insulin sensitivity [26]. The peptide, along with peptide YY (PYY) and oxyntomodulin, is produced primarily in the ileum and colon by nutrient-stimulated L cells. All three of these peptides can cause food intake reduction and are possible contributing the anorectic effects of some bariatric operations. After BPD, which transport food from the stomach directly to the ileum, postprandial GLP-1 are markedly increased. In RYGB, it is less obvious because its intestinal bypass is far less extensive. Moreover, GLP-1 secretion is stimulated not only by direct nutrient contact with distal intestinal L cells but also by proximal nutrient-related signals that are transmitted from the duodenum to the distal bowel by neural pathways [27]. Because RYGB diverts nutrients away from the duodenum, the procedure might theoretically lower the postprandial GLP-1 levels [28,29].

Upper intestinal hypothesis: This theory postulates that elimination of a short segment of proximal small intestine, primarily the duodenum, from contact with ingested nutrients employs direct anti-diabetes effect. Presumably, this anti-diabetes effect can be caused by one or more unidentified duodenal factors or processes that influence glucose homeostasis. The obvious principle of the procedure is re-routing the flow of food in the GI tract after meals. This exerts beneficial effects on glycemia that persist between meals [30,31].

Methods

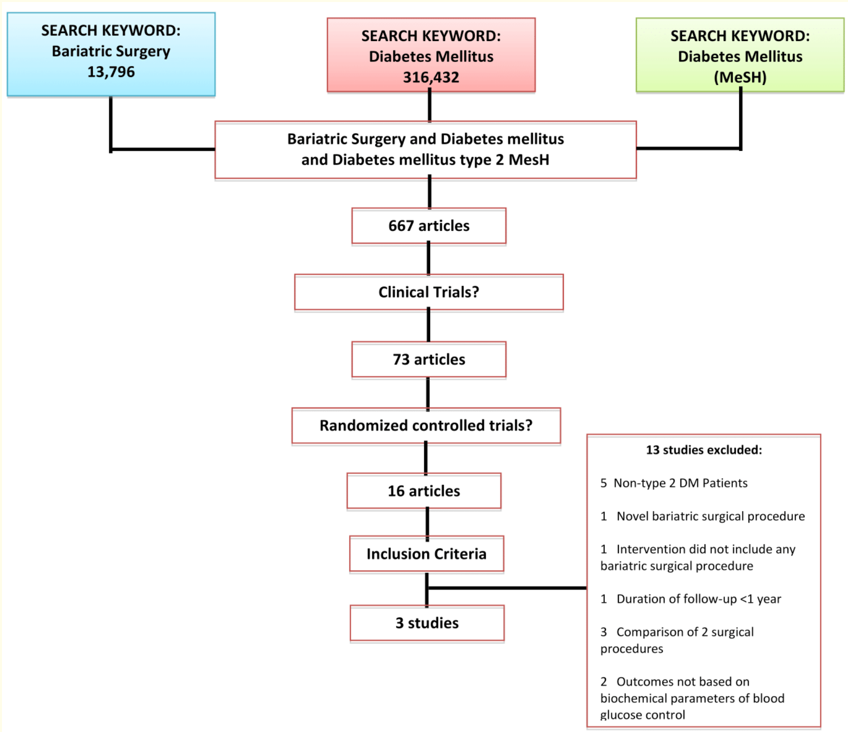
Search Strategy and Study Inclusion Criteria

A broad electronic search of published English-language literatures using PUBMED search engine from year 1990 to 2012 (cut off June 30, 2012) was conducted. The following search terms used were -Bariatric Surgery and -Type 2 Diabetes Mellitus A total of 16 articles were retrieved.

For inclusion in this systematic review and meta-analysis, studies needed to include type 2 diabetic participants who were treated with any conventional bariatric procedure, controls should be non-surgically treated, and outcomes should be quantitatively measured and based on biochemical parameters of blood glucose control. Studies which are non-RCTs and whose inclusion criteria indicated bariatric surgery for non-Type 2 DM patients were excluded. To supplement the electronic search, manual reference checks were performed in the identified studies.

	Inclusion	Exclusion
Participant	Adult Type 2 DM Patients	Non-type 2 DM Patients Patients who have previously undergone Bariatric Surgery
Intervention	Bariatric Surgery VS Conventional Medical Therapy Note: Study should employ any of the following conventional bariatric surgical procedures: -Roux-en-Y Gastric Bypass (RYGB) -Laparoscopic Adjustable Gastric Band (LAGB) -Biliopancreatic Diversion (BPD) -Sleeve Gastrectomy (SG) Duration of follow-up should be ≥ 1 year	Novel bariatric surgical procedure Duration of follow-up < 1 year
Outcome	Quantitatively measured outcomes: - Improvement on Hba1c -Weight Change -Remission	Outcomes not based on clinically important biochemical parameters of blood glucose control
Method	Randomized Controlled Trials	Non-Randomized Controlled Trials
Quality	Quality Scale A and B	Quality Scale C

Table 1: *Inclusion and Exclusion Criteria.*



Flow Chart 1: *Search Strategy.*

Data Collection and Reporting

Study authors, years of publication, surgical procedures, and study designs were summarized. Baseline characteristics of study groups and outcomes measured equally in each article were recorded as well. Diabetes-related clinical outcomes were collected, calculated and reported as remission rates, percent changes and mean ± standard deviation.

Risks of bias for each included study were assessed using the-Quality Scale For Meta-Analytic Reviews. Specific type of bias were scored respectively using raw scores of A to C, with the score of A indicating highest quality of study.

Obtained values for remission rates, post-treatment Hba1c and body weight were entered in the RevMan 5 software, thereafter creating a forest plot. Heterogeneity among included studies was assessed as depicted graphically in the forest plot. If calculated confidence intervals or results of each individual studies have poor overlap, presence of statistical heterogeneity is considered. Heterogeneity were statistically analyzed (Tau2, Chi2, I2). Measures for treatment effects were conducted using either Fixed Effects Model or Random Effects Model where significant heterogeneity was expected. We also did subgroup analysis for the different surgical procedures. For outcomes showing substantial heterogeneity, sensitivity analysis were likewise performed.

Results and Discussion

Among the 16 articles retrieved by literature search and manual reference checks, 3 studies met the selection criteria. Thirteen studies were excluded based on various reasons which are as follows (See Table 2 below): Non-type2 DM Patients (5), Novel bariatric surgical procedure (1), Intervention did not include any bariatric surgical procedure (1), Duration of follow-up < 1 year (1), Compared two different surgical procedures (3), Outcomes not based on biochemical parameters of blood glucose control (2).

Excluded Articles	Reason for Exclusion
Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. Dunn et al, Diabetes Care. 2012	Short duration of Study Follow-Up (eg. 1 month follow-up period)
Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. Lee et al, Surg Obes Relat Dis. 2011	Participants were non-type 2 DM Patients
Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Lee et al, Arch Surg. 2011	Two surgical procedures were compared
Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. Goodpaster et al, JAMA. 2010	Intervention did not include any bariatric surgical procedure
Aerobic endurance training improves weight loss, body composition, and co-morbidities in patients after laparoscopic Roux-en-Y gastric bypass. Shang et al, Surg Obes Relat Dis. 2010	Not all participants have type 2 DM Patients Intervention did not include any bariatric surgical procedure
Acute effect of roux-en-y gastric bypass on whole-body insulin sensitivity: a study with the euglycemic-hyperinsulinemic clamp. Lima *et al*, Clin Endocrinol Metab. 2010	Not all participants have type 2 DM Patients
Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. Fabbrini *et al*, Gastroenterology. 2010	Not all participants have type 2 DM Patients Intervention did not include any bariatric surgical procedure
A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. Schouten *et al*, Ann Surg. 2010	Not all participants have type 2 DM Patients Novel bariatric surgical procedure
Cost-efficacy of surgically induced weight loss for the management of type 2 diabetes: a randomized controlled trial. Keating et al, Diabetes Care. 2009	Outcomes are not based on clinically important biochemical parameters of blood glucose control Primary outcome of interest is cost-efficacy
Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. Tarnoff *et al*, Surg Endosc. 2009	Not all participants have type 2 DM Patients
Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. Pinheiro *et al*, Surg Obes Relat Dis. 2008	Two surgical procedures were compared
Twenty-four hour insulin secretion and beta cell NEFA oxidation in type 2 diabetic, morbidly obese patients before and after bariatric surgery. Salinari *et al*, Diabetologia 2008	Outcomes not based on clinically important biochemical parameters of blood glucose control

Table 2: *Excluded Articles and Reasons for Exclusion.*

Study Characteristics

All 3 included studies were randomized controlled trials. The studies were conducted in different countries: USA [32], Rome [33] and Australia [34]. Surgical procedures performed in this paper are Laparoscopic Adjustable Gastric Band (LAGB), Roux-en-Y Gastric Bypass (RYGB), Biliopancreatic Division (BPD) and Sleeve Gastrectomy (SG). Of the 3 studies identified, 2 of them, particularly Mingrone., *et al.* and Schauer., *et al*. involved two different types of surgical intervention. We decided to analyze each surgical procedure and plot their respective results separately. The follow-up period ranged from 1-2 years. Only one study [32] reported results of a 1 year follow-up. Summary of data is presented in table 2.

Patient Characteristics

Of the 340 participants included in the analysis, half (170) underwent bariatric surgery. All studies reported gender, and 60% of the total study population were females. The mean age of the patients ranges from 43 to 48 years. The duration of diabetes prior to surgery ranged from 2-8 years. Mean BMI is between 37- 45.2 kg/m^2. Data are summarized in table 3.

	Dixon., *et al.* 2008	**Mingrone., *et al.* 2012**	**Schauer., *et al.* 2012**
Type of Study	RCT	RCT	RCT
Participants Mean Age Type II DM Mean BMI (kg/m^2) Female/Male ratio Sample Size in each Treatment Arm	46.8 Yes (<2 yrs) 37.05 (>30 and <40) 8 : 7 (32/28) n = 30	43.37 Yes (≥5 yrs) 45.2 (≥35) 8 : 7 (32/28) n = 20	48.63 Yes (8 yrs) 36.67 (≥27 and ≤43) 33 : 17 (99/51)
Interventions Bariatric Procedure I VS Control Bariatric Procedure II VS Control	LAGB* VS Conventional Medical Therapy ---	BPD** VS Conventional Medical Therapy RYGB*** VS Conventional Medical Therapy	RYGB*** VS Conventional Medical Therapy SG*** VS Conventional Medical Therapy
Outcome Primary Secondary (included outcomes for comparison)	Remission (FPG < 12 6mg/dl or 7mmol/L and Hba1c < 6.2% while taking no glycemic therapy) Hba1c, Body weight	Remission (FPG < 100 mg/dl or 5.6 mmol/L and Hba1c < 6.5% in the absence of pharmacologic therapy) Hba1c, Body weight	Remission (Hba1c ≤ 6.0% in 12 months without medications) Hba1c, Body weight
Duration of Study/Follow up Selection Bias	2 yrs (Every 4-6 wks) B Subtle Bias: The study is non-blinded. Treatment allocation is not concealed. Frank Bias: The groups being compared were balanced in terms of known determinants of outcome.	2 yrs (1,3,6,9,12,24 mos post exposure) B Subtle Bias: The study is non-blinded. Treatment allocation is not concealed. Frank Bias: The groups being compared were balanced in terms of known determinants of outcome.	1 yr (3,6,9,12 mos post exposure) B Subtle Bias: The study is non-blinded. Treatment allocation is not concealed. Frank Bias: The groups being compared were balanced in terms of known determinants of outcome.
Performance Bias	B Subtle Bias: The physician caring for the patient is not blinded. Frank Bias: The treatment groups equally received other medications and general quality of care. All were followed up equally.	B Subtle Bias: The physician caring for the patient is not blinded. Frank Bias: The treatment groups equally received other medications and general quality of care. All were followed up equally.	B Subtle Bias: The physician caring for the patient is not blinded. Frank Bias: The treatment groups equally received other medications and general quality of care. All were followed up equally.

Exclusion Bias	A Subtle Bias: Intention to Treat Analysis was conducted. Frank Bias: Drop-out rates in between groups are comparable.	A Subtle Bias: Intention to Treat Analysis was conducted. Frank Bias: Drop-out rates in between groups are comparable.	B Subtle Bias: Intention to Treat Analysis was not conducted. Frank Bias: Drop-out rates in between groups are comparable.
Detection Bias	B Subtle Bias: Blinding of the person making an outcome assessment was not stated Frank Bias: Outcome detection methods used are similar in all treatment groups.	B Subtle Bias: The person making an outcome assessment is also not-blinded. Frank Bias: Outcome detection methods used are similar in all treatment groups.	B Subtle Bias: Blinding of the person making an outcome assessment was not stated. Frank Bias: Outcome detection methods used are similar in all treatment groups.
Overall Quality Score	B	B	B

Table 3. *Summary of Included Studies.*

Legend:

**in addition to all aspects of the conventional-therapy program*

***with adjusted medical therapy and/or discontinuation of medical therapy*

****plus intensive medical therapy*

Comparison of Outcomes

All 3 studies reported remission rates, however each having a different definition for remission. Proportions of patients who achieved remission under each treatment arms were compared. Results showed favorable response with Bariatric Surgery as compared to those who received conventional medical therapy. Percent changes in Hba1c levels and body weight were also calculated. Results showed larger percent changes in both Hba1c and weight with Bariatric Surgery.

Effect of Bariatric Surgery on Glucose Control

All three studies included HbA1c as outcome measure for glycemic control. Both percent change and absolute HbA1c were reported.

Participants who underwent Bariatric surgery achieved 23% to as high as 44% decrease (from baseline) in the levels of HbA1c, compared to 5 to 15.7% decrease in HbA1c achieved by medical therapy alone. Bariatric surgery appears to be 3-4x better than medical therapy alone in decreasing the HbA1c level during the first 1 to 2 years after surgery.

At the end of the study, as figure 2 (below) demonstrates, there is a trend of lower HbA1c levels among participants who underwent bariatric surgery compared to those participants who were given medical therapy alone. This difference appears to be statistically significant (p value = 0.03). However, the Tau2 of 0.16 and I2 of 72% indicate substantial heterogeneity.

Article	Surgery (n)	Control (n)	Primary-Outcome	Definition of Primary Outcome	Proportion reaching Primary Endpoint (Surgery) ITT	Proportion reaching Primary Endpoint (Control) ITT	Percent changeŦ in Hba1c (Surgery)	Percent changeŦ in Hba1c (Control)	Percent Weight changeŦ (Surgery)	Percent Weight changeŦ (Control)
Dixon 2008 (LAGB)	30	30	Remission	FPG < 126 mg/dl or 7 mmol/L and Hba1c < 6.2% while taking no glycemic therapy	22/30 (73%)	4/30 (13%)	-23.08%	-5.13%	-19.87%	-1.04%
Mingrone 2012 (BPD)	20	20	Remission	FPG < 126 mg/dl or 7 mmol/L and Hba1c < 6.2% while taking no glycemic therapy	19/20 (95%)	0/20	-44.26%	-9.64%	-35.05%	-6.11%
Mingrone 2012 (RYGB)			Remission	FPG < 126 mg/dl or 7 mmol/L and Hba1c < 6.2% while taking no glycemic therapy	15/20 (75%)	0/20 (0%)	-25.82%	-9.64%	-34.61%	-6.11%
Schauer 2012 (RYGB)	50	50	Remission	Hba1c ≤ 6.0% in 12 months without medications	21/50 (42%)	0/50 (0%)	-31.18%	-15.73%	-27.55%	-5.17%
Schauer 2012 (SG)	50	50	Remission	Hba1c ≤ 6.0% in 12 months without medications	13/50 (26%)	0/50 (0%)	-30.53%	-15.73%	-24.95%	-5.17%

Table 4: *Comparison of Outcomes for All Included Studies.*

LAGB: Laparoscopic Adjustable Gastric Banding; BPD: Biliopancreatic Division; RYGB: Roux-en-Y- Gastric Bypass; SG: Sleeve Gastrectomy

**in addition to all aspects of the conventional-therapy program*

***with adjusted medical therapy and/or discontinuation of medical therapy*

****plus intensive medical therapy*

Ŧ Calculated

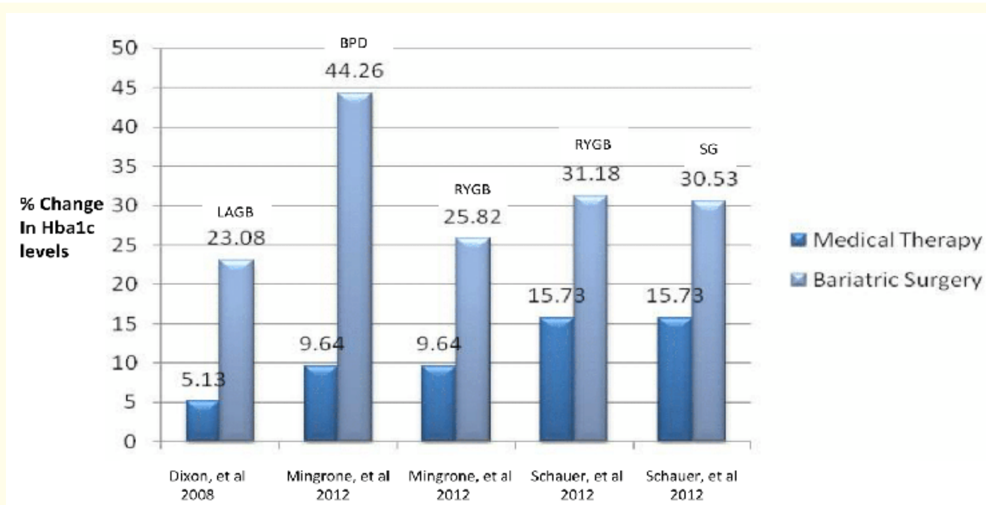


Figure 1: *Percent Changes on Hba1c levels among Included Studies.*

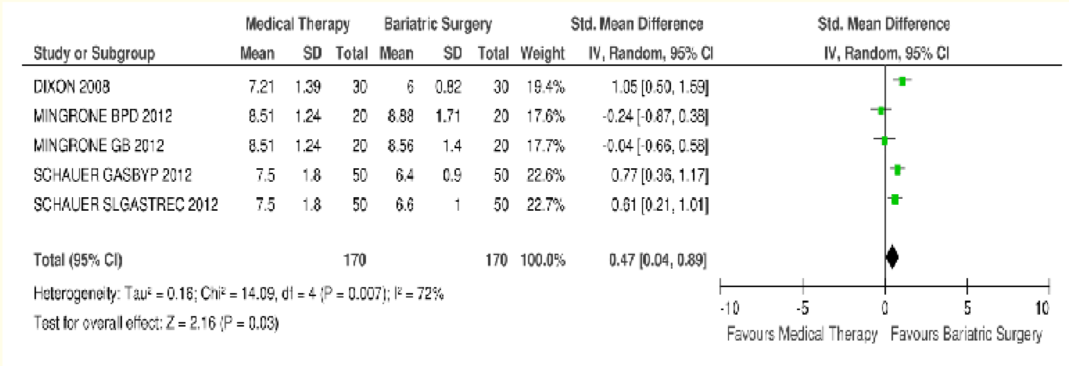


Figure 2: *Overall Result on HbA1c.*

In the study by Mingrone., *et al*. medications were adjusted or discontinued depending on a seven-point glycemic profile during the first 3 months post-operatively and according to HbA1c levels thereafter. The same criteria for modification of medication were not employed by the other studies. The other studies based their adjustments, either on HbA1c level alone or as determined by the physicians' discretion. This presents significant methodological difference which may contribute to the significant heterogeneity, hence the study by Mingrone., *et al*. was excluded in the sensitivity analysis.

After doing sensitivity analysis, there is still a statistically significant lower Hba1c among participant who underwent Bariatric Surgery and the heterogeneity is now statistically insignificant ($Tau^2 = 0$; $I^2 = 0\%$) (Figure 3).

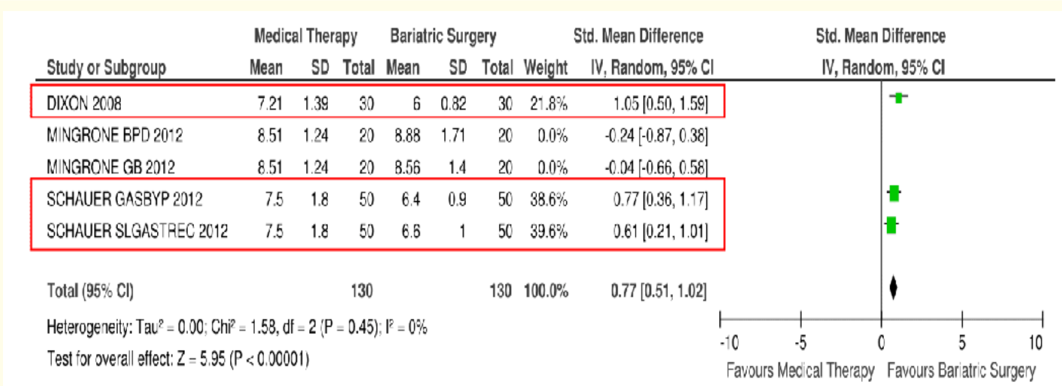
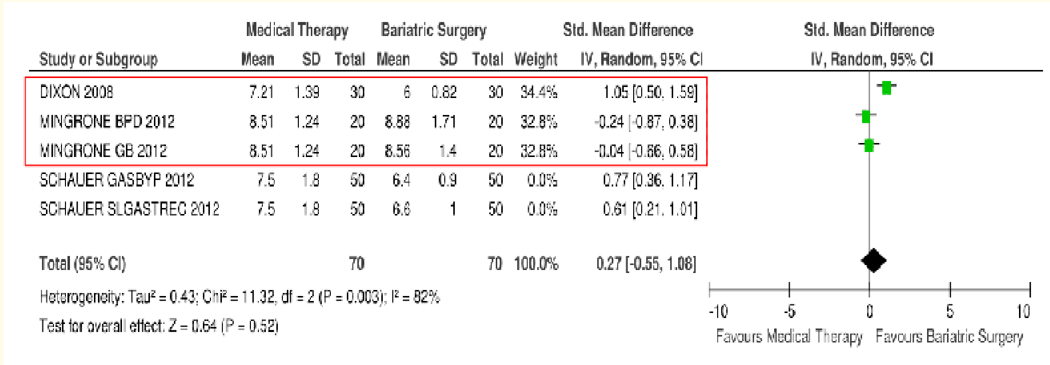


Figure 3: *Sensitivity Analysis on Hba1c.*

In addition, we have performed a sensitivity analysis now excluding the study with follow-up of less than 2 years, (in particular the study by Schauer., *et al*).

Including only studies with follow up of 2 years, the difference between Hba1c levels of patients who underwent bariatric surgery and conventional medical therapy is no longer statistically significant. Furthermore, the Tau^2 of 0.43 and I^2 of 82% indicate substantial heterogeneity (Figure 4).



Study or Subgroup	Medical Therapy Mean	SD	Total	Bariatric Surgery Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
DIXON 2008	7.21	1.39	30	6	0.62	30	34.4%	1.05 [0.50, 1.59]
MINGRONE BPD 2012	8.51	1.24	20	8.88	1.71	20	32.8%	-0.24 [-0.87, 0.38]
MINGRONE GB 2012	8.51	1.24	20	8.56	1.4	20	32.8%	-0.04 [-0.66, 0.58]
SCHAUER GASBYP 2012	7.5	1.8	50	6.4	0.9	50	0.0%	0.77 [0.36, 1.17]
SCHAUER SLGASTREC 2012	7.5	1.8	50	6.6	1	50	0.0%	0.61 [0.21, 1.01]
Total (95% CI)			70			70	100.0%	0.27 [-0.55, 1.08]

Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 11.32$, df = 2 (P = 0.003); $I^2 = 82\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Figure 4: *Hba1c Levels after 2-year Follow up.*

Congruent with many observational studies, the most significant effect of Bariatric Surgery is seen during the first few months or years after the procedure. If fact there is a concern whether the beneficial effect of surgery is sustained or lost after several years. The initially seen significant difference in HbA1c may start to diminish as early as 1 to 2 years after the surgery.

Effects of Bariatric Surgery on Weight Loss

Unsurprisingly, all 3 studies studies reported significant weight loss after Bariatric surgery. The greatest weight lost was achieved after BPD followed by RYGB.

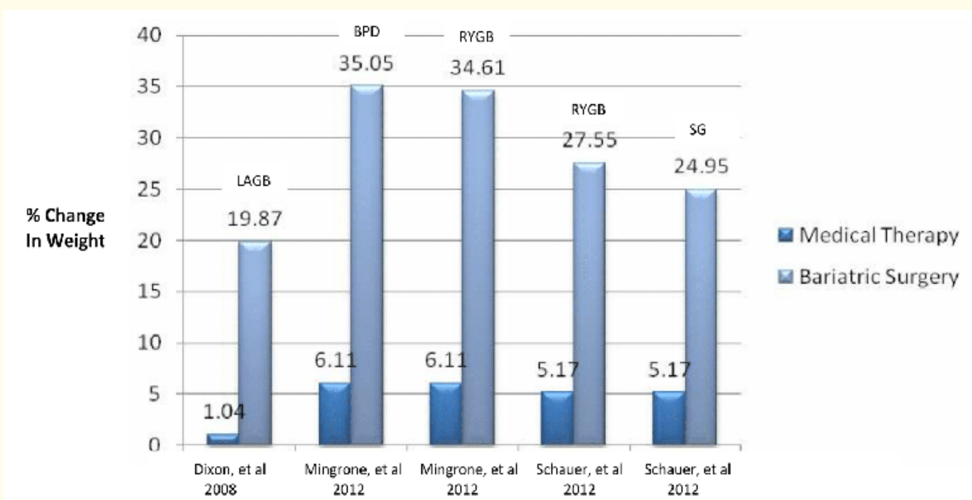


Figure 5: *Percent Changes in Weight.*

Statistically significant lower post-treatment weight is demonstrated among patients who underwent Bariatric Surgery compared to those who receive conventional medical therapy alone. However, Tau^2 of 21.71 and I^2 of 70% indicate substantial heterogeneity (Figure 6).

After doing sensitivity analysis excluding Mingrone., *et al*. the statistically significant lower post-treatment weight among patients who underwent Bariatric Surgery is still demonstrated, and the heterogeneity is no longer statistically significant (Tau^2 of 0 and I^2 of 0%) (Figure 7).

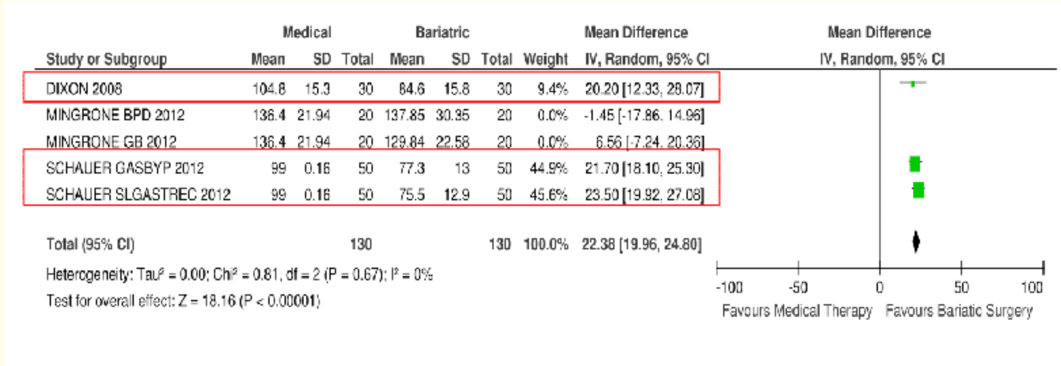


Figure 6: *Overall Change in Post-Treatment Weight.*

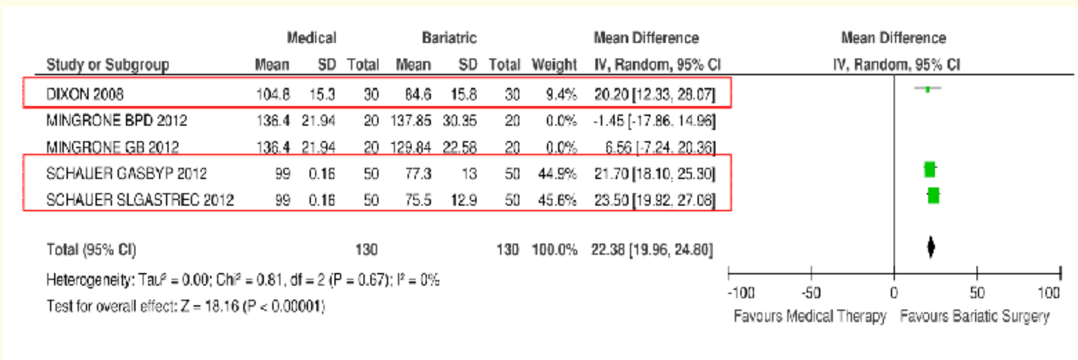


Figure 7: *Sensitivity Analysis on Weight Change.*

Effect of Bariatric Surgery on Remission of Diabetes

All 3 studies reported remission rate as their primary outcome of interest, however as previously mentioned, each study has a different definition for remission.

Higher remission rate has been achieved with Bariatric Surgery as compared with Conventional Medical therapy. This observation is statistically significant ($p < 0.00001$) however there is significant homogeneity ($Chi^2 = 3.02$; $I^2 = 0\%$) (Figure 8).

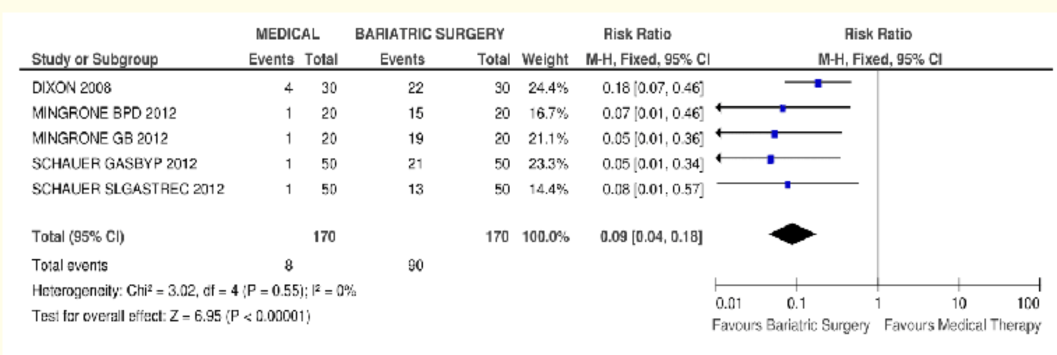


Figure 8: *Overall Result on Remission of Diabetes.*

After performing sensitivity analysis on remission by excluding Mingrone., *et al.* (Figure 9), substantial homogeneity is still present (Chi^2 = 1.98; I^2 =0%).

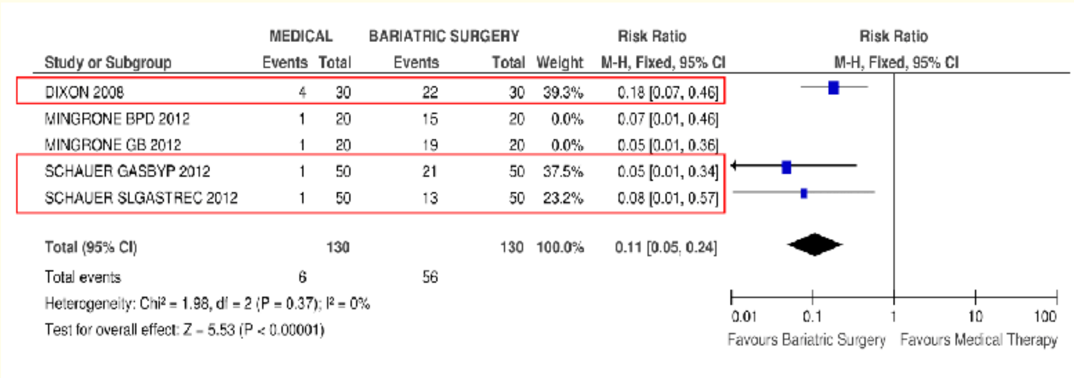


Figure 9: *Sensitivity Analysis on Remission.*

Subgroup Analysis

A subgroup analysis for population who underwent RYGB, which was the most common Bariatric surgical procedure performed as identified in this review was done.

Analysis revealed significantly lower post-treatment HbA1c levels among patients who underwent RYGB (p value = 0.03). However, there is significant heterogeneity (Tau^2 = 0.25 and I^2 = 78%) (Figure 10). This heterogeneity is most probably due to difference in follow up duration.

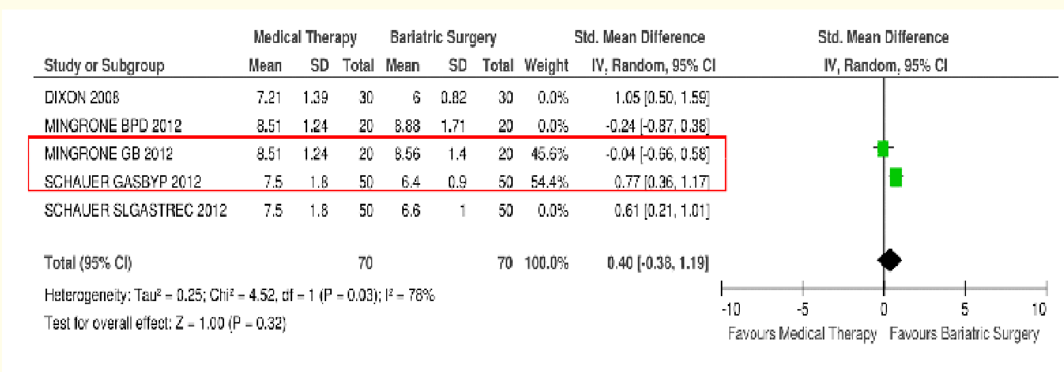


Figure 10: *Hba1c levels Post-RYGB.*

Comparing the body weight post-RYGB versus medical treatment alone, lower weight was achieved by patients who underwent surgery (P value = 0.04) however, again substantial heterogeneity is seen (Tau^2 = 0.88 and I^2 = 77%) (Figure 11). As mentioned above, the difference in follow up duration probably accounts for the heterogeneity seen.

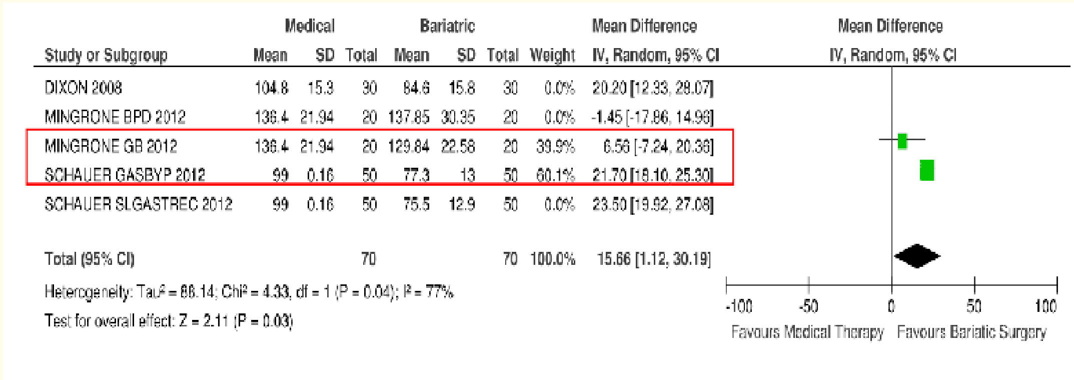


Figure 11: *Body Weight Post-RYGB.*

Adverse Effects of Bariatric Surgery

As seen in previous observation studies, Bariatric surgery can be associated with high post-operative complications. Below is the table of the reported adverse events following bariatric surgery.

	Dixon., *et al.* 2008 LAGB (N = 30)	**Mingrone., *et al.* 2012 BPD (N=20)**	**Mingrone., *et al.* 2012 RYGB (N = 20)**	**Schauer., *et al.* 2012 RYGB (N = 50)**	**Schauer., *et al.* 2012 SG (N = 50)**
Requiring Hospitalization (8.8%)				11	4
Surgical/Gastrointestinal Complications (9.0%)					
Reoperation (2.4%)				3	1
Hernia (1.2%)		1		1	
Gastrointestinal Leak (0.6%)					
Gastric Pouch Enlargement (1.2%)	2				1
Cholelithiasis (0.6%)				1	
Anastomotic Ulcer (2.4%)				4	
Intestinal occlusion (0.6%)			1		
Systemic Complications (3.0%)					
Transient Renal Insufficiency (0.6%)				1	
Arrhythmia or palpitations (1.2%)				1	1
Pleural Effusion (0.6%)					1
Ketoacidosis (0.6%)				1	
Wound Infection (0.6%)				1	
Pneumonia (1.2%)				2	
Nutritional Related (87.5%)					
Hypoglycemic Episode (68%)	1			28	39
Intravenous Treatment for Dehydration (3.5%)				4	2
Transfusion (1.2%)				1	1
Anemia (10%)		2	2	7	6
Hypokalemia (2.4%)				2	2
Hypoalbuminemia (1.2%)		2			

Osteopenia (0.6%)		1			
Osteoporosis (0.6%)		1			
Others (1.2%)					
Eating difficulties (0.6%)	1				
Persistent regurgitation (0.6%)	1				

Table 5: *Adverse Events Reported after Bariatric Surgery.*

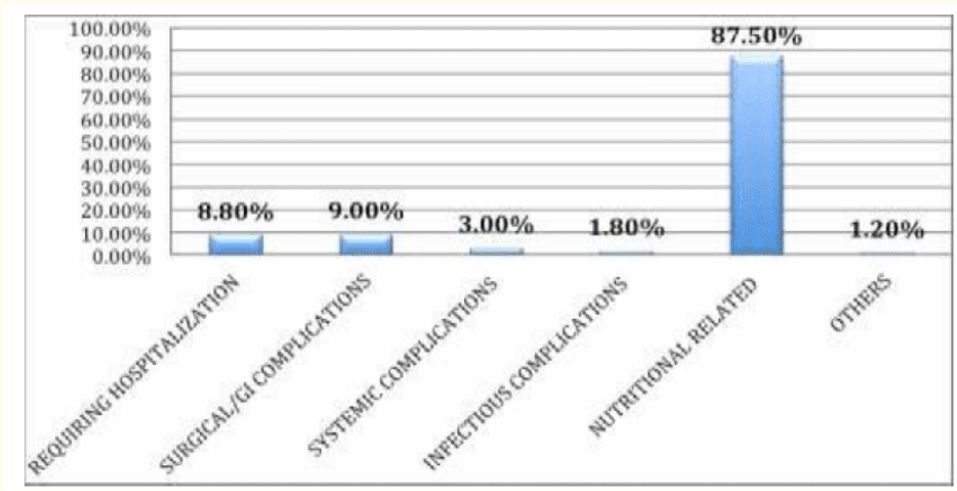


Figure 12: *Adverse Events Reported after Bariatric Surgery.*

A substantial number of patients had surgical complications and other adverse events that required hospitalization after Bariatric Surgery. However, the surgical complication after procedure is purported by many authors to be similar to other procedures such as cholecystectomy.

Of greater concern, is the high incidence of nutrition related complications such as anemia. There is also high incidence of hypoglycemia (68%). These complications were also documented in many studies, and has caused many to raise concerns regarding the risk benefit ratio of Bariatric surgery in the long term management of diabetics whose is already prone to hypoglycemia and other nutritional problems to begin with [34].

Conclusion

Among patients with type 2 diabetes mellitus, better glycemic control (in terms of lower HbA1c level) and significantly lower body weight was achieved after Bariatric surgery compared to medical therapy alone. This beneficial effect is seen and sustained 1 to 2 years following the procedure. A substantial number of patients also achieved clinical remission of diabetes.

However, the high incidence of adverse effects is a cause for concern. Of particular major issue is the exceedingly high incidence of nutrition related complications and hypoglycemia.

There is little doubt that Bariatric surgery has beneficial effects for patients with type 2 diabetes mellitus. The improvement in glycemic control, weight loss and even the rate of remission is substantial and seen early following the surgery. The magnitude of these effects are rarely achieved with conventional therapy alone, even with strict lifestyle modification and multiple pharmacologic therapies.

However, there is little evidence that these effects are sustained over the long term. In this review, when the study whose follow up duration is only 1 year was excluded, the difference between the HbA1c level between the two treatment arms became statistically insignificant. It is not inconceivable to hypothesize that the therapeutic advantage of Bariatric surgery over conventional therapy is lost over time.

Bariatric surgery remains an option for morbidly obese patients with type 2 diabetes mellitus especially among those whose have failed intensive medical therapy. However, the procedure is associated with significant number complications. Newer (and future) pharmacologic therapies such as incretin mimetics, which has similar mechanism of action to the weight-independent effects of Bariatric surgery are becoming more and more available and may be associated with less side effect. Furthermore evidence is still lacking (especially on its long term effects) for it to be recommended as primary treatment for patients with type 2 diabetes mellitus outside the indications as recommended by the most current clinical guidelines.

Future researches should focus on answering whether the beneficial effects of Bariatric surgery is maintained over a long period of time. Likewise, issues on risk benefit ratio must be addressed. Other clinically relevant parameters such as mortality and cardio-vascular events should be included as outcome of interest. Until evidence regarding the long term clinically important benefits and safety becomes available, Bariatric surgery will remain as a therapeutic option reserved for selected diabetic patients who fit the limited indications as recommended by current clinical guidelines.

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