Title: Roux-en-Y Gastric Bypass Versus Medical Treatment for Type 2 Diabetes Mellitus in Obese Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

**Table S1.** Patient Recruitment of the Studies included in the Meta-analysis

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| --- | --- | --- | --- | --- |
| **Study** | **Trial ID** | **Recruitment Period** | **Inclusion Criteria** | **Exclusion Criteria** |
| Ikramuddin 2015 | NCT00641251 | April 21, 2008 to Nov 21, 2011 | HbA1c≥8.0% despite at least 6 months care from a doctor for T2DM, BMI of 30.0 to 39.9, age 30 to 67 years, and a willingness and ability to accept random assignment and follow the full treatment protocol | Cardiovascular event (such as myocardial infarction or stroke) in the previous 6 months, or current evidence of congestive heart failure or angina pectoris |
| Courcoulas 2015 | NCT01047735 | October 1, 2009 to May 31, 2012 | Age 25 to 55 years, BMI of 30 to 40, diagnosis of T2DM was confirmed by a documented FPG≥7.0mmol/L and/or treatment with antidiabetics to include a broad spectrum of T2DM severity. For participants with grade I obesity, treatment with antidiabetics and permission from their treating physician were required to participate | Prior weight loss surgery, impaired mental status, alcohol or other drug addiction, current smoking, pregnancy or planned pregnancy, inability to tolerate general anesthesia owing to poor health, T1DM, failed nutritional or psychological assessment, unwillingness to be randomized, inability to provide informed consent, or being deemed unlikely to comply with study visits or procedures |
| Halperin 2014 | NCT01073020 | March 12, 2010 to September 7, 2011 | Age 21 to 65 years with at least 1 year of T2DM, BMI 30 to 42, a strong desire for substantial weight loss, and a commitment to life-long medical and nutritional follow-up. Free from active cardiovascular or other diseases prohibiting them from exercising safely or undergoing a bariatric surgical procedure. Additionally, potential participants had HbA1c＞7%, regardless of ongoing treatment, or ≥6.5% while receiving either 2 oral antihyperglycemic agents at greater than or equal to half-maximal dose or insulin, and with stable-dose treatment for more than 8 weeks | Detectable levels of anti-GAD antibody, a history of diabetic ketoacidosis, uncontrolled T2DM (HbA1c>12%), gastrointestinal disease, malignant disease within 5 years, significant cardiopulmonary or renal disease, active eating disorder, drug and/or alcohol abuse, impaired mental status, weight loss greater than 3% within the previous 3 months, participation in another weight reduction program, or were using weight-reduction medications and/or supplements |
| Schauer 2014 | NCT00432809 | March 2007  to January 2011 | Age 20 to 60 years, a diagnosis of T2DM (HbA1c＞7.0%), and BMI of 27 to 43 | Undergone previous bariatric surgery or other complex abdominal surgery or had poorly controlled medical or psychiatric disorders |
| Liang 2013 | NCT01435980 | June 30, 2008 to July 1, 2011 | (1) obesity (BMI>28) in accordance with the WHO Asia-Pacific classification for obesity; (2) T2DM with hypertension of 5–10 years with hypertension defined as SBP≥140mmHg and/or DBP≥90mmHg as per 1999 WHO/ISH criteria; (3) insulin therapy in combination with oral administration of drugs for 12 months; (4) HbA1c>7%; (5) age: 30–60 years; (6) seronegative for antibodies against insulin, islet cells and GAD; (7) C-peptide level≥0.3 mg/L | (1) people without diabetes; (2) T1DM, presence of autoimmune diabetes indicated by antibodies to insulin, islet cells, and GAD, and gestational diabetes; (3) patients with heart, liver, or renal function impairment; (4) presence of severe infections or cerebrovascular disease; (5) fasting serum insulin was less than one-third of the normal value; (6) diabetes of more than 10 years duration; (7) age > 60 years or <30 years |
| Mingrone 2015 | NCT00888836 | April 30, 2009 to October 31, 2011 | Age of 30 to 60 years, BMI≥35, a history of T2DM of at least 5 years, HbA1c≥7.0% (as confirmed by at least three analyses), and an ability to understand and comply with the study protocol | T1DM, diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, pregnancy, other medical conditions requiring short-term hospitalization, severe diabetes complications, other severe medical conditions, and geographic inaccessibility |

FPG=fasting plasma glucose; T2DM=type 2 diabetes mellitus; HbA1c=hemoglobin A1c; T1DM=type 1 diabetes mellitus; SBP=systolic blood pressure; DBP=diastolic blood pressure; GAD=glutamic acid decarboxylase.

**Table S2.** Risk of bias assessment for the studies included in the Meta-analysis

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Sequence Generation Adequate** | **Allocation Concealed** | **Blinding of Patients** | **Blinding of Healthcare Providers** | **All Randomized Patients Analyzed** | **Patients Analyzed as Randomized** | **Incomplete Outcome Data Addressed** | **Selective Reporting** |
| Ikramuddin 2015 | Yes | Yes | No | No | No | Yes | Yes | No |
| Courcoulas 2015 | Yes | Yes | No | No | No | Yes | Yes | No |
| Halperin 2014 | Yes | Yes | No | No | Yes\* | Yes | Yes | No |
| Schauer 2014 | Yes | Yes | No | No | No | Yes | Yes | No |
| Liang 2013 | Yes | Unclear | No | No | No | Yes | No | Unclear |
| Mingrone 2015 | Yes | Yes | No | No | No | Yes | Yes | No |

\*Primary outcome analysis included all randomized participants can available as supplemental content.

**Table S3.** Medication Use

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Intervention** | **Antidiabetic Drug** | **Antihypertensive Drug** | **Lipid lowering Drug** |
| Ikramuddin 2015 | RYGB | A significant reduction | A significant reduction | A significant reduction |
| Medical | Without significant change | Without significant change | Without significant change |
| Courcoulas 2015 | RYGB | Significant reduction | Reduced or discontinued in 7 participants (58%) at 1 year | More patients experienced remission of dyslipidemia at 1 year |
| Medical | Without significant improvement | Without significant improvement | Without significant improvement |
| Halperin 2014 | RYGB | All patients in the surgical group who achieved target glycemia were no longer receiving diabetes  medications at 1 year | A greater reduction | A greater reduction |
| Medical | Without significant change | Without significant change | Without significant change |
| Schauer 2014 | RYGB | No. of medications, no. of patients using insulin, and no. of patients not taking this class of medication all improved significantly | No. of medications, no. of patients using ACEI or ARB, and no. of patients not taking cardiovascular medications all improved significantly | A significant reduction in the number of medications needed to treat hyperlipidemia |
| Medical | Without significant improvement | Without significant improvement | Without significant improvement |
| Liang 2013 | RYGB | All patients in the surgical group discontinued pharmacologic treatment (oral hypoglycemic agents and insulin) within 14 days after the operation on the basis of daily seven-point glucose profiles | The requirement for antihypertensive drugs decreased from a mean of 2.8 to 0.5 (P < 0.05) | - |
| Medical | - | Unchanged | - |
| Mingrone 2015 | RYGB | Fewer diabetes medications than did medically treated patients at year 5 and throughout the study | Significant reduction | Significant reduction |
| Medical | Insulin use increased | Without significant improvement | Without significant improvement |

ACEI= angiotensin-converting enzyme inhibitor; ARB=angiotensin-receptor blocker; No.= number.

**Table S4.** Quality of Life

|  |  |  |
| --- | --- | --- |
| **Study** | **Intervention** | **Quality of Life** |
| Ikramuddin 2015 | RYGB | - |
| Medical | - |
| Courcoulas 2015 | RYGB | - |
| Medical | - |
| Halperin 2014 | RYGB | Short Form-36 physical and mental health scores and Problem Areas in Diabetes scores improved. The Impact of Weight on Quality of Life-Lite score improved more with RYGB compared with medical intervention. |
| Medical | Short Form-36 physical and mental health scores and Problem Areas in Diabetes scores improved. The Impact of Weight on Quality of Life-Lite score improved. |
| Schauer 2014 | RYGB | There were significant improvements in five of eight mental and physical domains among patients (The RAND 36-Item Health Survey) |
| Medical | Without significant improvement |
| Liang 2013 | RYGB | - |
| Medical | - |
| Mingrone 2015 | RYGB | Surgical patients scored significantly better than medically treated patients for all subdomains of quality of life and for the total score domains of the 36-Item Short Form Health Survey |
| Medical | Without significant improvement |

**Table S5.** Adverse Events

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Intervention** | **Adverse Events (n)** | **Total** |
| Ikramuddin 2015 | RYGB(60) | Distal anastomotic leak leading to sepsis, brain injury, and amputation below the knee (1), proximal anastomotic leak (1), anastomotic ulcer (3), anastomotic stricture (2), wound infection (1), wound haematoma (1), pouch gastritis (1), small-bowel obstruction (2), cholelithiasis (1), abdominal pain (6), reflux oesophagitis (3), deep venous thrombosis (1), nephrolithiasis (1), loss of body strength (1), amputation below the knee (1), toe amputation (1), herniated spinal disc with foot drop (1), multiple sclerosis (1) , fall with fracture (5), fall with other injury (2), hypertension with admission to hospital (1), unwanted pregnancy (1), infections (8) , nutritional deficiencies (49) | 46§ |
| Medical(59) | Anastomotic ulcer\* (1), acute pancreatitis (3), pancreatic carcinoma (2), abdominal pain (2), reflux oesophagitis (2), duodenitis (1), congestive heart failure (1), nephrolithiasis (1), diabetic ketoacidosis (1), partial third cranial nerve palsy (1), depression (1), suicide attempt (1), fall with fracture (1), fall with other injury (2), abnormal uterine bleeding (1), infections (4), nutritional deficiencies (14) | 25§ |
| Courcoulas 2015 | RYGB(20) | Anastomotic ulcer (1), additional night hospital stay (2), nausea and emesis requiring intravenous hydration (1), renal lithiasis (1) | 5 |
| Medical(20) | No | 0 |
| Halperin 2014 | RYGB(19) | Ischemic heart disease with coronary artery bypass surgery, new breast cancer diagnosis, nephrolithiasis, exacerbated depression with suicide attempt, and hip arthroplasty | 5 |
| Medical(19) | Presyncope (3) | 3 |
| Schauer 2014 | RYGB(50) | Bowel obstruction (1), stricture (1), ulcer (4), intraabdominal bleeding (2), dumping syndrome (4), gallstone diseases (1), retinopathy (1), nephropathy (7), foot ulcer (2), anemia (8), intravenous treatment for dehydration (7), hypoglycemic episode (32), severe hypoglycemia requiring intervention (1), wound infection (1), hernia (3), pneumonia (2),renal calculus (5), cancer (2) | 84 |
| Medical(43) | Bowel obstruction (1), ulcer (1) , nephropathy (4) , anemia (6), intravenous treatment for dehydration (3), hypoglycemic episode (39), excessive weight gain† (7) , hernia (1), renal calculus (6), cancer (2) | 70 |
| Liang 2013 | RYGB(31) | Nausea (5), local inflammation around the drainage port (6) | 11 |
| Medical(34) | Vomiting (13) | 13 |
| Mingrone 2015 | RYGB(19) | Intestinal occlusion (1), iron-deficiency anemia (3), osteopenia (1), renal calculus (1), nephropathy (1), symptomatic hypoglycaemia¶ (2) | 9 |
| Medical(15) | Persistent diarrhea (2), osteopenia (1), myocardial infarction‡ (1), retinopathy (1), nephropathy (1), neuropathy (2) | 8 |

RYGB=Roux-en-Y Gastric Bypass Surgery. \*Participant was randomly assigned to lifestyle and medical management but obtained a Roux-en-Y gastric bypass outside the study. †Excessive weight gain was defined as a 5% increase in body weight over baseline. §Excluded nutritional deficiencies. ‡Fatal myocardial infarction that led to the death of the patient. ¶Symptomatic or severe hypoglycaemia is defined, according to American Diabetes Association definitions, as a hypoglycaemia requiring the assistance of another individual.

**Table S6.** Description of Study Groups

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Groups (n)** | **Roux-en-Y Gastric Bypass Surgery** | **Medical Treatment** | | | | **Goal of Treatment** | **Follow Up Visits** |
| **In General** | **Diet** | **Exercise** | **Medications** |
| Ikramuddin 2015 | 2 | Laparoscopic RYGB was standardized across all sites and was performed with construction of a 20ml lesser curvature gastric pouch, a 100cm biliopancreatic limb, and an antecolic 150cm Roux limb with closure of all mesenteric defects. Daily multivitamin and mineral supplements to prevent nutritional deficiencies. Same therapy as medical treatment group. | Modelled on the Diabetes Prevention Program and the Look AHEAD trial  Protocol. Participants met regularly with a dietitian or registered nurse to discuss strategies for weight management and increasing physical activity, including self-monitoring, stimulus control, problem-solving, social support, cognitive behavior modification, recipe modification, eating away from home, and relapse prevention. Smoking cessation was strongly recommended for all. | Calorie intake targets of 1200, 1500, or 1800 kilocalories per day, depending on body weight, with the goal of producing a weight loss of 1 to 2 pounds per week. | Advised to progressively increase their amount of moderate-intensity physical activity (such as walking) to 325 min per week. | Medicines to control glycaemia, dyslipidaemia, and BP were used according to standard algorithms. Aspirin (81–100 mg daily) was added, when not contraindicated. Medicines approved by the US Food and Drug Administration (FDA) for long-term obesity treatment were used. | Achievement of the composite triple endpoint of HbA1c＜7.0%, LDL＜2.59 mmol/L and SBP＜130 mmHg. | Counselling sessions consisted of 24 weekly meetings during the first 6 months, biweekly between months 7 and 9, monthly between months 10 and 15, and one meeting every 3 months either up to 24 months or until a total of 40 modules were completed. Visits with an endocrinologist took place each month for 6 months, then every 3 months (or monthly if not at goal) for the next 6 months, then every 3 months through the second year. |
| Courcoulas 2015 | 3 | The RYGB was performed with a standard retrocolic-retrogastric technique using a linear stapled and hand-sewn gastrojejunal anastomosis. Those participants undergoing surgical intervention were counseled on a diet program consistent with postbariatric surgery recommendations and were encouraged to exercise a minimum of 3 to 4 times per week and to focus on weight-bearing aerobic activity. On completing 1-year follow-up, participating for 2 more years with annual visits and the addition of structured later low-level (LLLI) lifestyle interventions | A standard behavioral weight control program delivered using an in-person, individual format based on the intervention developed for the Diabetes Prevention Program and the Look AHEAD trial and adapted into a 12-month program for subjects with grades I to II obesity. On completing 1-year follow-up, participating for 2 more years with annual visits and the addition of structured LLLI lifestyle interventions modeled after the Diabetes Prevention  Program and Look AHEAD | An energy-restricted diet (1200-1800 kcal/d) and were provided meal plans, meal replacements, and calorie-counter books. | Moderate-intensity exercise was prescribed 5 days each week beginning at 20 minutes per day and gradually progressing to at least 60 minutes per day, with bouts of activity encouraged to be longer than 10 minutes. | - | - | At 2 weeks and 3, 6, 9, and 12 months postoperatively in the RYGB group. Weekly in-person intervention sessions during the initial 6 months, then twice a month thereafter for medical intervention. During LLLI, all groups consisted of twice-monthly contact (1 in-person session and 1 brief telephone contact) and regular refresher group series. |
| Halperin 2014 | 2 | The RYGB procedure involved a 75cm antecolic, antegastric Roux limb created with a 50cm biliopancreatic limb. A 15 to 20ml gastric pouch was created along the lesser curve of the stomach, and the lesser omentum was divided at that level. A gastrojejunostomy was constructed using a linear cutter stapler, and the gastroenterotomy was closed using a running polyglactin 910 suture. Provocative leak tests were performed, including “blue dye” and “bubble” tests. | Multidisciplinary approach includes an endocrinologist, registered dietician, exercise physiologist, mental health provider, and certified diabetes nurse educator. Patients receive individual medication adjustments and participate in supervised group exercise and support/didactic sessions. | Hypocaloric (1500-1800 kcal) diet with carbohydrates (40%-45%), protein (20%-30%), and saturated fat intake reduced to less than 7%. | Up to 300 minutes per week of graded, balanced, and individualized exercise, with emphasis on strength training. | Diabetes medications are adjusted in order to reduce or eliminate anti-hyperglycemic medications that may contribute to weight gain. | - | Weekly group sessions during a 12-week initiation phase. Monthly counseling follows for the remainder year. |
| Schauer 2014 | 3 | Laparoscopic RYGB consisted of the creation of a 15 to 20ml gastric pouch, a 150cm Roux limb, and a 50cm biliopancreatic limb. Daily multivitamin and mineral supplements to prevent nutritional deficiencies. Same therapy as medical treatment group. | American Diabetes Association (ADA) guidelines: including lifestyle counseling, weight management, frequent home glucose monitoring, and the use of newer drug therapies (e.g., incretin analogues) approved by the FDA. | Patients will receive dietary and lifestyle recommendations, as recommended by the ADA, to optimize glucose control. | Encouraged to engage in regular aerobic exercise and participate in the Weight Watchers program. | All patients were treated with lipid lowering and antihypertensive medications, according to ADA guidelines, with targets: SBP≤130mmHg; DBP≤80mmHg; and LDL≤2.6mmol/L. | The goal of medical management was modification of diabetes medications until the patient reached the therapeutic goal of a HbA1c≤6.0% without unacceptable side effects associated with medical treatment. | Every 3 months for 2 years and every 6 months thereafter. |
| Liang 2013 | 3 | A standard 5-port laparoscopic technique, the greater and lesser curvatures of the stomach were separated, the gastric cavity closed with a disposable closure device, and a gastric pouch created that was completely separated from the gastric remnant and anastomosed to the jejunum. An entero–entero anastomosis was created between the pancreatobiliary limb and alimentary limb 100 cm distally from the gastrojejunostomy. | Patients were assessed and treated by a multidisciplinary team that included an endocrinologist, a dietitian, a cardiologist, and a nurse. Medical therapy was adjusted according to the seven-point glycemic profile during the first 3 months and according to HbA1c levels thereafter. | The nutrition goal was based on individual energy intake and reducing fat intake to <30%, saturated fat to <10% and increasing high fiber intake. | Physical exercise ≥30 min of brisk walking every day associated with moderate-intensity aerobic activity twice a week. | Oral hypoglycemic medications, antihypertensive drugs, insulin, and exenatide subcutaneously twice daily | Reaching HbA1c < 7% and BP≤140/90 mmHg in medical therapy. Discontinuation of medical therapy was considered in cases of normalization of the glycemic profile, HbA1c, or BP in RYGB group. | At baseline, 3, 6, 9 and 12 months |
| Mingrone 2015 | 3 | Laparoscopic RYGB, daily multivitamin and mineral supplementation, discontinuation of medical therapy was considered in cases of normalization of the glycemic profile, HbA1c, or both. | Assessed and treated by a multidisciplinary team that included a diabetologist, a dietitian, and a nurse. | Reduced overall energy and fat intake (<30% total fat, <10% saturated fat, and high fiber content). | Increased physical exercise (≥30 minutes of brisk walking every day, possibly associated with moderate-intensity aerobic activity twice a week). | Glucose-lowering drugs, insulin, and glucagon-like peptide-1 (GLP-1) analogues were optimised on an individual basis with the aim of reaching HbA1c＜7%. | Diet, lifestyle modification and medications were optimised on an individual basis with the aim of reaching HbA1c＜7%. | At baseline and at 1, 3, 6, 9, and 12, and then every 6 months until month 60. |

RYGB=Roux-en-Y Gastric Bypass Surgery; LDL=low density lipoprotein; HbA1c=hemoglobin A1c; SBP=systolic blood pressure; DBP=diastolic blood pressure; BP=blood pressure; LLLI=later low-level; GLP-1= glucagon-like peptide-1.