

Gastric Bypass vs Sleeve Gastrectomy for Type 2 Diabetes Mellitus

A Randomized Controlled Trial

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Objectives: To determine the efficacies of 2 weight-reducing operations on diabetic control and the role of duodenum exclusion.

Design: Double-blind randomized controlled trial.

Setting: Department of Surgery of the Min-Sheng General Hospital, National Taiwan University.

Patients: We studied 60 moderately obese patients (body mass index >25 and <35) aged >30 to <60 years who had poorly controlled type 2 diabetes mellitus (T2DM) (hemoglobin A_{1c} [HbA_{1c}] $>7.5\%$) after conventional treatment (>6 months) from September 1, 2007, through June 30, 2008. Patients and observers were masked during the follow-up, which ended in 2009, 1 year after final enrollment.

Interventions: Gastric bypass with duodenum exclusion (n=30) vs sleeve gastrectomy without duodenum exclusion (n=30).

Main Outcome Measures: The primary outcome was remission of T2DM (fasting glucose <126 mg/dL and

HbA_{1c} $<6.5\%$ without glycemetic therapy). Secondary measures included weight and metabolic syndrome. Analysis was by intention to treat.

Results: Of the 60 patients enrolled, all completed the 12-month follow-up. Remission of T2DM was achieved by 28 (93%) in the gastric bypass group and 14 (47%) in the sleeve gastrectomy group ($P=.02$). Participants assigned to gastric bypass had lost more weight, achieved a lower waist circumference, and had lower glucose, HbA_{1c}, and blood lipid levels than the sleeve gastrectomy group. No serious complications occurred in either group.

Conclusions: Participants randomized to gastric bypass were more likely to achieve remission of T2DM. Duodenum exclusion plays a role in T2DM treatment and should be assessed.

Trial Registration: clinicaltrials.gov Identifier: NCT00540462 (<http://www.clinicaltrials.gov>).

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OBESITY AND TYPE 2 DIABETES mellitus (T2DM) are currently 2 of the most common chronic, debilitating diseases in Western countries.^{1,2} Both diseases are closely related and difficult to control by current medical treatment, including diet, drug therapy, and behavioral modification.³⁻⁵ There is strong evidence that bariatric operations, mostly gastric bypass (GB) surgical procedures, can cure most of the associated T2DM in morbidly obese patients.⁶⁻¹¹ Current consensus for bariatric surgery is set at a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) greater than 35 with comorbidities, but gastrointestinal metabolic surgery recently has been proposed as a new treatment modality for obesity-related T2DM in patients with a BMI less than

35.¹¹⁻¹³ It has been hypothesized that changes in gastrointestinal hormone secretion would favor an early improvement of T2DM in GB surgery that bypasses the duodenum and upper jejunum (foregut theory).¹⁴⁻¹⁶ However, it has also been proposed that weight loss accounts for the resolution of T2DM by more simple, purely restrictive procedures, such as gastric banding and sleeve gastrectomy (SG).^{7,17-20} This study aims to evaluate the efficacy of 2 different gastrointestinal metabolic operations for the treatment of T2DM and to test the foregut hypothesis.

METHODS

STUDY DESIGN

We designed a randomized, double-blind trial of the effects of 2 different bariatric opera-

tions with or without duodenum exclusion on T2DM resolution in nonmorbidly obese patients who had diabetes mellitus that was inadequately controlled. The study was conducted in the Department of Surgery of the Min-Sheng General Hospital, National Taiwan University. The trial was conducted from September 1, 2007, through June 30, 2009. A run-in period of at least 2 weeks was undertaken in which further alterations to eating, glucose self-monitoring, and vitamin supplementation were suggested. During this time, study adherence was assessed using attendance at appointments and completion of questionnaires. The study was reviewed and approved by the human ethics committees of the Min-Sheng General Hospital and the Department of Health of Taiwan.

PATIENT POPULATION AND RANDOMIZATION

Patients were recruited via a newspaper advertisement and were neither paid to participate nor paid any medical costs. Recruitment commenced in September 2007, the last participant was randomized in June 2008, and all data were available for analysis in June 2009. Patients were eligible if they were between >30 and <60 years old, had a BMI of >25 to <35, had been diagnosed as having clearly documented but poorly controlled ($HbA_{1c} > 7.5\%$ [to convert to proportion of total hemoglobin, multiply by 0.01]) T2DM and were treated by an endocrinologist for 6 months or longer, had no evidence of renal impairment or diabetic retinopathy, and were able to understand and comply with the study process. Candidates were excluded if they had a specific disease; had previously undergone bariatric surgery; had a history of major medical problems, such as mental impairment, drug or alcohol addiction, a recent major vascular event, internal malignant neoplasm, or portal hypertension; or had a contradiction for either surgery. Participants were excluded if their C-peptide level was below 1.0 ng/mL (to convert to nanomoles per liter, multiply by 0.331) or they did not attend 2 initial information visits.

In addition to any assessments required for inclusion, each potential participant was assessed by a multidisciplinary and integrated medical unit, with the aid of a team including a general physician, endocrinologist, psychiatrist, and dietician. A thorough assessment was performed of each patient's general condition and mental status, complications of obesity and diabetes mellitus, risk factors, and motivations for surgery. The endocrinologist and surgeon codetermined when a patient was ready for randomization. Baseline weight, blood pressure, anthropometric measures, and blood chemical data (levels of fasting plasma glucose, glycated hemoglobin [HbA_{1c}], C-peptide, and serum insulin and lipid profile) were measured immediately before randomization.

A computer-generated variable block schedule was used for randomization. The block size was 10 cases for orderly recruitment into both study groups and to reduce the risk of uneven recruitment late in the series. Randomization was performed in the operation theater after pneumoperitoneum was completed. The study was double-blinded.

STUDY INTERVENTIONS

The surgical team performed both types of surgical procedures and had broad experience in both techniques. Surgery was performed with the patients under general anesthesia in the reversed Trendelenburg position with the operator standing between the legs of the patient. A standard laparoscopic surgical technique with 5 to 6 trocars was used for both procedures. An SG was performed by resecting the greater curvature from the distal antrum (4 cm proximal to the pylorus) to the angle of His, including the complete fundus, by using a laparoscopic stapler (EndoGIA; Covidien, Norwalk, Connecticut) with 60-mm car-

tridges (3.5-mm stapler height, blue load). The remnant stomach tube was approximately 2 cm wide along the less curved side. The resected portion of the stomach was extracted from the extended periumbilical trocar site. A running absorbable suture was applied to the stapler line to prevent hemorrhage and leakage. No drainage tube was left. For the case of GB surgical procedure, a simplified laparoscopic mini-GB was adopted and has been previously described.²¹ To describe briefly, a long-sleeved gastric tube was created (EndoGIA; Covidien), approximately 2.0 cm wide along the less curved side from the antrum to the angle of His. A loop gastroenterostomy (Billroth II anastomosis) was created with the small bowel approximately 120 cm distal to the ligament of Treitz. No drainage tube was left.

All patients received care via a standard clinical pathway. The nasogastric tube was removed on the first postoperative day in both groups, and patients were encouraged to ambulate as soon as they felt comfortable. Oral feeding was allowed starting on the second postoperative day, provided the patient had flatus passage and a normal Gastrografin contrast study result. Patients were discharged on the third or fourth postoperative day if they felt able to return home, patients were regularly followed up at the outpatient clinic by the aforementioned multidisciplinary team, and clinical controls were scheduled once a month for the first 3 postoperative months and every 3 months thereafter. Patients were advised to take a daily multivitamin tablet as a supplement. Iron supplement, vitamin B₁₂ injection, and blood transfusion were given only in symptomatic patients. Radiologic study or endoscopy examination was scheduled if clinically indicated.

A complication was defined as the occurrence of an unexpected medical event that made departure from the clinical pathway necessary. An early complication was defined as a complication that occurred within 30 days postoperatively. A major complication was defined as a complication that required interventional management and hospitalization for more than 14 days. Complications related to the operation occurred more than 30 days postoperatively, and complications that required readmission were defined as late complications.

OUTCOMES MEASURES

The primary end point of the study was glycemic control at 12 months after randomization. This was assessed as the proportion of participants achieving remission (exceptional glycemic control) of T2DM, defined as fasting plasma glucose levels less than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) in addition to HbA_{1c} values less than 6.5% without the use of oral hypoglycemics or insulin.

Secondary outcome measures included percentage change in HbA_{1c} levels, weight, blood pressure, waist circumference, and levels of fasting lipids, including total cholesterol, triglyceride, and high-density and low-density lipoprotein cholesterol. Changes in medication use, changes in the proportion of participants with metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria,²² and changes in indirect measures of insulin resistance using the homeostasis model assessments were measured.²³ Adverse events and effects were recorded.

Insulin secretion was measured at 12 months postoperatively. An oral glucose tolerance test with 75 g of glucose (in a total volume of 300 mL) was administered in the morning after a 12-hour overnight fast. A sample of blood was collected before and 30, 60, and 120 minutes after oral glucose load. The blood sample was checked for blood glucose and insulin levels. The insulin secretion during the oral glucose tolerance test was measured by insulin total area under the curve (AUC) using the trapezoidal method.

STATISTICAL ANALYSIS

Sample size was selected to provide a statistical power for diabetes mellitus remission rates on the basis of an approximate expected 80% remission in the GB group and 40% in the SG group. This study was designed to have a power of 80% and an α risk of .05; at least 28 patients per group were required to demonstrate a significant difference. Recruitment size was therefore set at 60.

All statistical analyses were performed using SPSS statistical software, version 12.01 (SPSS Inc, Chicago, Illinois), with baseline comparison made using χ^2 tests and 2-sample *t* tests. Continuous variables were expressed as mean (standard deviation), with differences expressed as mean (95% confidence interval). A 2-sided $P < .05$ was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

From September 1, 2007, through June 30, 2008, sixty of 209 eligible patients were enrolled in the randomized trial (30 in the GB group and 30 in the SG group). All patients were successfully randomized and completed the 12-month program. The mean BMI was 30.3 (range, 25.0-34.0), mean age was 45 years (range, 34-58 years), and mean HbA_{1c} level was 10.0% (range, 7.5%-15.0%). There were no statistically significant differences in demographics or values contributing to study outcomes between the groups.

SURGICAL TREATMENT AND COMPLICATIONS

All procedures were successfully performed by a laparoscopic technique, with no deaths or major complications in either group. Minor complications occurred in 6 patients (10%), 3 in each group. The surgical time was similar between the GB and SG groups (117 vs 127 minutes; $P = .09$). The mean postoperative hospital stay was 2.2 days for the GB group and 2.1 days for the SG group ($P > .05$).

TREATMENT EFFECTS

Overall, 42 participants (70%) experienced T2DM resolution at 12 months after surgery. Resolution of T2DM was significantly better in the GB group than in the SG group (93% vs 47%; $P = .02$). The **Figure** shows the weight and HbA_{1c} reduction curves of the groups. Both groups had significant weight loss after surgery without difference at 1 and 3 months postoperatively, but the GB group had better weight loss at 6 and 12 months postoperatively. Although the weight reduction was similar between the groups at 1 and 3 months postoperatively, the GB group had significantly lower fasting glucose and HbA_{1c} levels than the SG group since 1 month after surgery (Figure). The mean reduction in the HbA_{1c} level was 3.0% in the SG group and 4.2% in the GB group 1 year after surgery, an approximately 30% discrepancy between the groups. During the 12 months of follow-up, no differences were found in diabetes mellitus resolu-

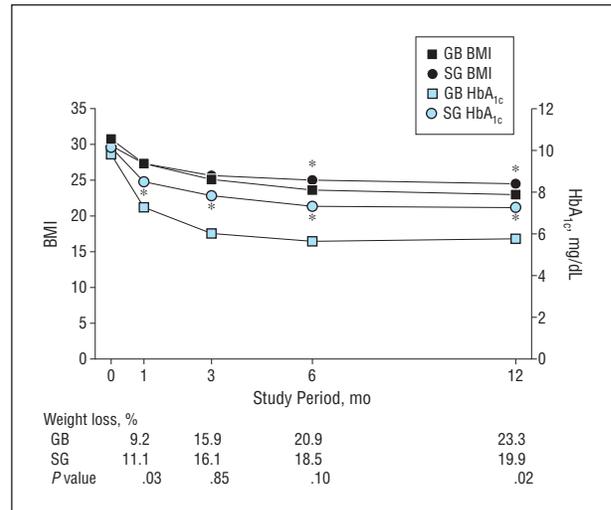


Figure. Weight reduction and hemoglobin A_{1c} (HbA_{1c}) curves of the sleeve gastrectomy (SG) and gastric bypass (GB) groups. Asterisks indicate $P < .05$; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared). To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

tion between the groups at 1 and 3 months postoperatively, but this became significant at 6 and 12 months postoperatively.

At 12 months after surgery, both groups had a marked reduction in body weight and improvement of other associated metabolic disorders, including reduction of waist circumference, blood pressure, and insulin, C-peptide, and blood lipid levels (**Table**). However, the GB group had a significantly lower BMI, waist circumference, and glucose, HbA_{1c}, and blood lipid levels than the SG group at 12 months after surgery. Therefore, 18 patients (60%) in the SG group still had metabolic syndrome compared with only 2 patients (7%) in the GB group ($P < .001$). The GB group also had a higher ratio of successful treatment of T2DM (HbA_{1c} < 7%, low-density lipoprotein cholesterol < 100 mg/dL [to convert to millimoles per liter, multiply by 0.0259], and triglycerides < 150 mg/dL [to convert to millimoles per liter, multiply by 0.0113]) than the SG group (57% vs 0%; $P < .001$). Late complications occurred in 2 patients (3%), 1 in each group, and required hospitalization for conservative treatment, but no major adverse effects were observed.

COMPARISON OF INSULIN SECRETION AFTER ORAL GLUCOSE INTAKE

After the oral glucose load, the SG group had a continuously higher level of plasma glucose at all points and AUC than the GB group. However, there was no difference in the insulin secretion at any point and total insulin secretion (ie, AUC) after oral glucose challenge between the groups.

COMMENT

To our knowledge, this is the first randomized trial to study surgical treatment of nonmorbidly obese patients (BMI < 35) with poorly controlled T2DM. In this study,

Table. Primary and Secondary Outcomes at 12 Months^a

Outcome	Gastric Bypass (n=30)	Sleeve Gastrectomy (n=30)	P Value ^b
Remission of diabetes mellitus (HbA _{1c} <6.5%), No. (%)	28 (93)	14 (47)	.02
Successful treatment of diabetes mellitus (HbA _{1c} <7%, LDL-C <100 mg/dL, and triglycerides <150 mg/dL), No. (%)	17 (57)	0 (0)	<.001
BMI	22.8 (2.2)	24.4 (2.4)	.009
Weight, kg	60.7 (10.1)	65.7 (7.9)	.03
Excess weight loss, %	94.4 (33.1)	76.3 (38.9)	.06
Waist circumference, cm	79.7 (7.4)	85.3 (5.7)	.002
HbA _{1c} , %	5.7 (0.5)	7.2 (1.5)	<.001
C-peptide, ng/mL	1.6 (1.1)	1.6 (0.5)	.92
Glucose, mg/dL	99.3 (19.4)	140.1 (53.0)	<.001
Blood pressure, mm Hg			
Systolic	119.6 (17.3)	123.5 (9.8)	.29
Diastolic	74.2 (12.3)	75.4 (8.5)	.68
Lipids, mg/dL			
Total cholesterol	162.2 (26.6)	207.8 (67.0)	.001
Triglycerides	104.9 (62.0)	144.2 (58.9)	.02
HDL-C	49.3 (7.7)	45.4 (7.9)	.06
LDL-C	96.9 (21.5)	136.6 (40.8)	<.001
Insulin, μ U/mL	4.9 (3.8)	4.7 (2.7)	.86
HOMA	1.2 (1.2)	2.5 (3.4)	.08
Glucose AUC	22 459 (4465)	29 077 (11 300)	.005
Insulin AUC	3382 (1419)	2871 (1887)	.24
Metabolic syndrome, No. (%)	2 (6.6)	18 (60.0)	<.001

Abbreviations: AUC, area under the curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; to convert C-peptide to nanomoles per liter, multiply by 0.331; to convert glucose to millimoles per liter, multiply by 0.0555; to convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; to convert insulin to picomoles per liter, multiply by 6.945; to convert triglycerides to millimoles per liter, multiply by 0.0113.

^aData are presented as mean (SD) unless otherwise indicated.

^b*P* < .05 is considered statistically significant.

both GB and SG were effective in the treatment of patients with T2DM in whom current medical treatment had failed. However, the 93% resolution rate and 57% success rate for T2DM treatment in the GB group were superior to the 47% and 0% rates in the SG group at 12 months after surgery. These results corroborate previous reports that GB may achieve an 80% diabetes mellitus remission and pure restrictive-type procedures may achieve a rate of approximately 50%.^{24,25} Besides weight loss, the GB group also achieved lower waist circumference, fasting plasma glucose level, HbA_{1c} level, and blood lipid level. That is why the GB group also had a higher metabolic syndrome remission rate than the SG group. Although more clinical trials are needed, this study and other previous studies have strongly recommended that laparoscopic GB as a metabolic surgery should be included in the armament of diabetes mellitus treatments in less obese populations (BMI of 25-35) and in the morbidly obese population (BMI >35).

The underlying mechanism for diabetes mellitus remission after GB surgical procedures is intriguing. Four possible mechanisms have been proposed, including the starvation followed by weight loss hypothesis, the ghrelin hypothesis, the lower intestinal (hindgut) hypothesis, and the upper intestinal (foregut) hypothesis.²⁶ None of these theories necessarily precludes the others, so any combination may be operational to some degree; therefore, it is difficult to design a study to elucidate the exact mechanism. Recently, SG has emerged as a new re-

strictive bariatric procedure with a better weight loss result than gastric banding.²⁷ It has been suggested that change in ghrelin after SG may help to explain the result.¹⁹ In addition to the ghrelin effect, SG was also reported to have a hindgut effect with increasing glucagon-like peptide 1 and peptide YY because of increasing transit time after SG.²⁰ It was also reported that weight loss was similar between the GB and SG groups. The only effect that SG did not have was on the foregut; in other words, the upper intestine was excluded from contact with ingested nutrients in the GB but not in the SG group. Therefore, this study is designed to study the role of the foregut theory in diabetes mellitus resolution by comparing SG to GB.

Although a recent randomized trial to compare glucose metabolism after laparoscopic GB and SG did not support the role of duodenum exclusion, this study has some basic flaws because it was performed on morbidly obese patients without diabetes.²⁸ It had been found that obesity and diabetes mellitus have a separate effect on the incretin effect on total insulin secretion and B-cell glucose sensitivity.²⁹ Therefore, the role of duodenum exclusion was not demonstrated in the previous study of nondiabetic, morbidly obese patients. In this study of diabetic patients, the result strongly supports the finding that the duodenum may play a role in diabetes mellitus resolution after bariatric surgery. The mechanism seems to relate to postprandial glucose metabolism rather than to an increase in insulin secretion and is independent of weight reduction. Although the weight reduction is al-

most the same as that found in the first and third postoperative months, patients who underwent GB surgery with duodenum exclusion had significantly lower HbA_{1c} levels and insulin resistance than patients who underwent SG without duodenum exclusion. The role of duodenum exclusion or foregut theory on surgical treatment of diabetes mellitus is worthy of further investigation.³⁰

The foregut theory was first suggested by Hickey et al,¹⁴ and Rubino and Marescaux¹⁵ were the first to provide strong evidence supporting this model. In Goto-Kalitzak rats (Charles River Laboratories Inc, Wilmington, Massachusetts), a nonobese model of polygenic T2DM, a duodenum exclusion operation improved diabetes mellitus rapidly and durably compared with a sham operation. A similar observation has subsequently been made.^{16,31} In these studies, diabetes mellitus was eliminated or restored based on the absence or presence, respectively, of nutrient passage through the duodenum, with an unchanging degree of minor shortcutting for nutrients to reach the lower bowel. On the basis of this theory, a flexible plastic sleeve has been designed and implanted in the upper intestine, causing food to move from the pylorus to the beginning of the jejunum without coming in contact with the duodenum mucosa. Such endoluminal duodenal sleeves cause only minor or no weight loss, but they markedly improve glucose tolerance.^{15,16,32,33} All these data support the foregut theory, but this study is the first randomized trial, to our knowledge, to scrutinize the effect of duodenum exclusion through different bariatric operations. In this study, duodenum exclusion may contribute to a 30% role in the mechanism of diabetes mellitus resolution after GB. The other 3 mechanisms may play a 70% role in T2DM resolution according to the hypothesis by Thaler and Cummings.²⁶

The rapid postoperative remission of diabetes mellitus is primarily related to an improvement in insulin resistance rather than increasing insulin secretion.^{34,35} The difference in insulin resistance in the early postoperative period between the 2 procedures found in this study also supports the theory that duodenum exclusion is helpful for the reduction of insulin resistance. In recent studies, Korner et al³⁶ found that reduction of insulin resistance correlated significantly with weight loss only in gastric banding but not in GB, and Bikman et al³⁷ found that improved insulin sensitivity after GB is due to something other than weight loss. Because the duodenum was recently found to have a novel intestine-brain-liver neurocircuit to increase hepatic insulin sensitivity, it is possible that gastrointestinal surgery may help mediate antidiabetes effects, although this is unclear now.³⁸ Another possible mechanism induced by duodenum exclusion is the gut hormone. The gastric inhibitory peptide, an incretin secreted by the K cells in the proximal intestine, may play an important role in the foregut theory. Laferrière et al³⁹ found that after GB, greater gastric inhibitory peptide release could be a potential mediator of improved glucose tolerance. However, controversial data exist. The gastric inhibitory peptide was reported to decrease after GB in those with severe diabetes.^{40,41} Another gut hormone that possibly plays a role in duodenum exclusion is glucagon.³⁰ Patients with diabetes mellitus were found to have hyperglucagonemia and to lack glucagon

suppression. More elaborate studies are needed to elucidate the underlying complex mechanism of T2DM resolution after GB surgery.

When we consider the choice of surgical treatment, although GB is more effective in diabetes mellitus resolution, pure restrictive surgery, such as gastric banding and SG, still can be considered for the surgical treatment of diabetes, especially in patients with newly diagnosed diabetes and good pancreatic reserve.¹⁸ A purely restrictive procedure is 10-fold safer than a complex GB procedure and avoids the long-term sequela of micronutrient deficiency after duodenum exclusion and should be considered the first choice.²⁴ However, GB may be a better choice for patients with metabolic syndrome or hyperlipidemia. Gastric bypass can result in a lower waist circumference and blood lipid levels than purely restrictive procedures and achieve a much higher successful rate in the resolution of metabolic syndrome and successful diabetes mellitus treatment. Today, the risk of complications and mortality associated with GB has decreased significantly.⁴² The improvement certainly will help to make bariatric surgery not only a weight-reducing surgery but also a metabolic surgery.^{43,44}

The main limitation of this study is the lack of gut hormone data. Without data regarding the change in gut hormone, such as glucagon, gastric inhibitory peptide, and glucagon-like peptide 1, we cannot elucidate the underlying mechanisms for the resolution of diabetes mellitus after duodenum exclusion. Another limitation of this study is the lack of long-term follow-up. Without long-term follow-up, we cannot confirm the durability of diabetes mellitus remission after surgery and the influence of possible weight change in the future. More elaborate clinical studies are indicated to elucidate this issue.

In summary, our study has demonstrated that GB surgery is more effective than SG for surgical treatment of poorly controlled T2DM and control of metabolic syndrome. Duodenum exclusion plays a role in the mechanism of diabetes mellitus remission.

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