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Gastrointestinal Metabolic Surgery for the Treatment of Diabetic Patients: A Multi-Institutional International Study

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Abstract
Background Gastrointestinal metabolic surgery has been proposed for the treatment of not well-controlled type 2 diabetes mellitus (T2DM) patients with a body mass index (BMI) <35 kg/m^2. This study aims to describe recent experience with surgical treatment of T2DM in Asian centers.
Methods Patients aged 20 to 70 years with not well-controlled T2DM [glycated hemoglobin (HbA1C) >7.0%] and BMI< 35 kg/m^2 were included at five institutes between 2007 and 2010. The end point is T2DM remission, defined by fasting plasma glucose <110 mg/dl and HbA1C <6.0%.
Results Of the 200 patients, 172 (86%) underwent gastric bypass, 24 (12%) underwent sleeve gastrectomy, and the other 4 underwent adjustable banding. Laparoscopic access was used in all the patients. Gender (66.5% female), age (mean 45.0±10.8), and HbA1C (mean 9.3±1.9%) did not differ between the procedure among the groups. Until now, 87 patients had 1-year data. One year after surgery, the mean BMI decreased from 28.5±3.0 to 23.4±2.3 kg/m^2 and HbA1C decreased to 6.3±0.5%. Remission of T2DM was achieved in 72.4% of the patients. Patients with a diabetes duration of <5 years had a better diabetes remission rate than patients with duration of diabetes >5 years (90.3% vs. 57.1%; p=0.006). Patients with BMI>30 kg/m^2 had a better diabetes remission rate than those with BMI<30 kg/m^2 (78.7% vs. 62.5%; p=0.027). Individuals who underwent gastric bypass loss more weight and had a higher diabetes remission rate than individuals who underwent restrictive-type procedures. Multivariate analysis confirmed that the duration of diabetes and the type of surgery predict the diabetes remission. No mortalities were reported and two (1.0%) patients had major morbidities.
Conclusion Gastrointestinal metabolic surgery is an effective treatment for not well-controlled T2DM treatment. Diabetes remission is significantly higher in those with duration of diabetes less than 5 years and BMI>30 kg/m^2.

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Obesity and type II diabetes mellitus (T2DM) are currently two pandemic health problems in both developed and developing countries and are associated with considerable increase in morbidity and mortality.[1,2] Both diseases are closely related and are very difficult to be controlled by current medical treatment, including diet, drug therapy, and behavioral modification.[3–5] Bariatric surgery has been proven successful in treating not just obesity but also T2DM in morbid obese patients [body mass index (BMI) >35 kg/m^2].[6–12] Recently, gastrointestinal (GI) metabolic surgery has been proposed as a new treatment modality for obesity-related T2DM for patients with BMI<35 kg/m^2.[13] However, most of the reported studies concerning GI metabolic surgery are small in number or retrospective studies with insufficient data.[14–18] Optimal outcomes for diabetes remission after GI metabolic surgery will occur if the patients best suited to the surgery are selected and those who will predictably have a poor result are excluded. It could also be that certain categories of patients are better suited to one type of bariatric procedure. In any case, this calls for a prospective study with large number of patients and detail clinical information on the association between possible predictors and outcome after GI metabolic surgery.

The aim of this study was to examine the efficacy of GI metabolic surgery on diabetes remission. Furthermore, we look for the preoperative predictors of diabetes resolution after GI metabolic surgery.

Methods

Study Design

In the present trial, five centers participated and prospectively evaluated 200 patients who underwent GI metabolic surgery for not well-controlled T2DM with BMI<35 kg/m^2. The patients were recruited to participate at the bariatric and metabolic center of each respective institution. The institutional review board of each center approved the present study. The study was also registered on the ClinicalTrials.gov website (NCT00540462). The patients were eligible for the study if they had not well-controlled T2DM after 6 months of medical treatment (HbA1c >7%), a body mass index <35 but >22 kg/m^2, had an accepted operative risk, and were aged 18–67 years. The exclusion criteria were the presence of end organ damage, pregnancy, and previous GI surgery. Participants were excluded if their C-peptide is below 0.9 ng/ml. Recruitment commenced in September 2007 and all data were available for analysis in June 2010.

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 of endocrinologist, psychiatrist, cardiologist, and dietician. A thorough assessment was performed of each patient's general condition and mental status, complications of obesity and diabetes, risk factors, and motivations for surgery. The endocrinologist and surgeon co-determined when a patient was ready for randomization. Baseline weight, blood pressure, anthropometric measures, and blood chemical data [levels of fasting plasma glucose, glycated hemoglobin (HbA1c), C-peptide, serum insulin, and lipid profile] were measured immediately prior to operation. Standard oral glucose tolerance test was advised for every patient before operation.

Study Interventions

The surgical team performed standard bariatric procedures and had broad experience in these techniques.[19–22] The restrictive procedures included laparoscopic adjustable gastric banding (LAGB, using Lap Ban from Bioenterics Corp., Carpinteria, CA, USA) and laparoscopic sleeve gastrectomy (LSG). In case of laparoscopic gastric bypass (LGB) surgery, both Roux-en-Y gastric bypass and a simplified procedure "laparoscopic mini-gastric bypass" were adopted and were previously described.[20] To describe briefly, a long sleeved gastric tube was created by the EndoGIA stapler (Coviden, United States Surgical Corporation, Norwalk, CT, USA) approximately 2.0 cm wide along the lesser curvature from the antrum to the angle of His. A loop gastroenterostomy (Billroth II anastomosis) was created with the small bowel about 120 cm distal to the ligament of Trietz with the Endo-GIA stapler. For Roux-en-Y gastric bypass, a small vertical gastric pouch with antecolic and antegastric techniques was performed with 80–100 cm biliopancreatic limb and 120–150 cm alimentary limb. Sleeve gastrectomy (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 (Coviden, United States Surgical Corporation, Norwalk, CT, USA) with 60-mm cartridges (3.5-mm stapler height, blue load). The remnant stomach tube was about 2 cm wide along the lesser curvature side. The resected portion of the stomach was extracted from the extended periumbilical trocar site.

All the patients received care under a standard clinical pathway. The 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 water-soluble contrast study. Patients were discharged on the third or fourth postoperative day if they felt that they were able to return home and the patients were regularly followed at the out-patient clinic by the

aforementioned multidisciplinary team, and clinical controls were scheduled once a month for the first three postoperative months and every 3 months thereafter. Patients were advised to take a daily multivitamin tablet as a supplement. Iron supplement, vitamin B_{12} injection, and blood transfusion were given only in symptomatic patients. Radiological controls or endoscopic examination were scheduled if clinically indicated.

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

Remission of Diabetes

Patients were followed up and assessed for the diabetic state at 1 year postoperatively. Remission of T2DM was defined as fasting glucose levels less than 110 mg/dL in addition to HbA1c value less than 6.0% without the use of oral hypoglycemic or insulin as complete remission at 1 year after surgery.[23] Routine laboratory tests and anthropometric measurements were also performed. Ideal body weight was calculated using BMI 22 as a standard.

Statistical Analysis

All statistical analyses were performed using SPSS version 12.01 (SPSS Inc, Chicago, IL. USA), with baseline comparison made using chi-square tests and two-sample *t* tests. Continuous variables were expressed as mean (standard deviation), with differences expressed as mean (95% CI). A two-sided *p* value of 0.05 was considered statistically significant.

We performed a predictor of diabetes resolution analysis using binary logistic regression, and a data mining technology of artificial neural networks (ANN) was used to examine the associates of diabetes remission. Neural networks are mimicking human neurobiological information-processing activities. Analyses applied in this study were back propagation neural networks (BPN) conformed to a three-layered perception architecture. All preoperative factors were set as the input nodes in the input layer with only one dependent factor (successful diabetes remission) as the output node in the output layer. Detail of this analysis had been described elsewhere.[24,25] We further compared the performance of ANN and logistic regression model by using the cross-validation method. ANN was constructed by using Qnet97 (Vesta Services Inc., 1998).

Results

Patient Characteristics

A total of 200 not well-controlled diabetic patients (HbA1c >7%) with BMI<35 but >22 kg/m^2 were recruited from five hospitals participating the ADSS. Their preoperative characteristics were 67 males and 133 females; mean age 45.0±10.8 years, BMI 28.5±3.3 kg/m^2, waist circumference 81.1±8.3 cm, C-peptide 2.8±0.8 ng/ml, and duration of T2DM 7.9±5.1 years. Of the patients, 30% had insulin usage. Baseline demographic data are presented in Table 1.

Among the 200 patients in the study group, the surgical procedures performed included 28 (14%) restrictive procedures and gastric bypass in 172 (86%) patients. LAGB was performed in 4, LSG in 24, LRYGB in 53, and LMGBP in 119 patients

Table 1 Comparison of clinical data before and after metabolic surgery

	Before (*n*=200) RYG	After (*n*=87)	*p* value
BMI (kg/m^2)	28.5±3.3	23.4±3.1	0.027*
Waist (cm)	103.4±7.1	81.9±7.3	0.002*
Weight loss (%)		19.4%	–
SBP (mmHg)	130.1±14.8	126.8±18.2	0.003*
DBP (mmHg)	82.0±10.2	79.0±11.6	0.005*
Glucose (mg/dl)	188.0±10.3	116.3±41.4	0.041*
Total cholesterol (mg/dl)	202.8±44.7	119.9±58.8	0.000*
Triglyceride (mg/dl)	233.6±265.8	119.9±58.8	0.016*
LDL (mg/dl)	119.3±37.8	105.4±33.2	0.000*
HbA1C%	9.3±0.8	6.3±1.5	0.002*
C-peptide (ng/ml)	2.8±0.8	1.9±1.0	0.046*
HOMA	9.5±13.7	2.3±2.7	0.021*

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *HOMA* homeostatic model assessment, *HbA1C* glycated hemoglobin

*$p<0.05$

Surgical Treatment and Complications

All the procedures were completed by laparoscopic approach. No mortality was reported but two (1.0%) major complications were reported in the series. The two major complications all occurred in gastric bypass patients, one was gastrojejunostomy leakage and the other was enteroenterostomy leakage. Both patients received laparoscopic reoperation and recovered uneventfully. Minor complications were reported in 16 (8%) patients, including bleeding, wound complication, and gout attack. The mean surgical time was 112±39 min. The mean postoperative hospital stay was 2.2±0.9 days.

Treatment Effects

Among all the patients, 87 patients had completed 1-year follow-up. One year after surgery, the mean BMI decreased to 23.4±2.3 kg/m^2 and the mean HbA1C decreased from 9.7±1.9% to 6.3±0.5%. Overall, 63 participants (72.4%) had their diabetes complete remission at 12 months after surgery. The surgical outcomes are provided in Table 1. Individuals who underwent gastric bypass lost more weight (20.3±11.6 kg vs. 15.4±9.4 kg, p=0.068), weight loss (9.2%±11.7% vs. 13.0%±11.4%, p=0.195), and achieved a lower BMI (23.2±2.7 vs. 24.8±3.1, p=0.027) than individuals who underwent restrictive-type surgery.

Predictor Analyses for Diabetes Remission

We employed logistic regression analysis between those with T2DM remission and without remission and which disclosed five positive preoperative clinical predictors of T2DM remission (Table 2). The duration of T2DM, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, HOMA, and type of surgery were significantly different between those with T2DM remission and without. There was no difference in age, BMI, and HbA1c level. Multivariate analysis confirmed that duration of DM history and type of surgery had significant effects on diabetes remission (p<0.01). The average correct classification rate of logistic regression was 90.3%.

In consistency with the logistic regression model, ANN also confirmed that the duration of DM history and the type of surgery are the significant predictors of diabetes remission. Figure 1 showed the relative importance of preoperative predictor variables. The average correct classification rate of the BPN model was 95%.

Duration of T2DM and Diabetes Remission

T2DM remission rate was analyzed in subgroups of different clinical parameters (Table 3). The T2DM remission rates for those with duration of T2DM <5, 5–10, and >10 years were 28/31 (90.3%), 18/33 (54.5%), and 10/16 (62.5%), respectively (p=0.006). Patients with BMI> 30 kg/m^2 also had a better diabetes remission rate than those with BMI<30 kg/m^2 (78.7% vs. 65.5%; p=0.027). Bypass group had a higher ratio of successful treatment of T2DM than the other two restrictive types but with only borderline significance (79.3% vs. 55.3%; p=0.062). There was no difference between subgroups of age, gender, preoperative C-peptide levels, and waist/hip ratio.

Discussion

GI metabolic surgery is the state of art for the treatment of T2DM. However, little data are available now. A recent review

Table 2 Univariate analysis of preoperative factors in patients with and without diabetes remission

Factor	Remission (n=63)	No remission (n=24)	p value
Age, years	44.7±10.0	47.5±9.5	0.252
Weight (kg)	81.4±10.8	78.4±13.9	0.422
BMI (kg/m^2)	30.7±3.2	29.2±3.9	0.109
Waist (cm)	101.0±8.1	99.2±12.6	0.912
FPG (mg/dl)	212.9±72.1	234.4±59.7	0.119
AST (IU/L)	37.8±25.9	21.1±9.0	0.015*
ALT (IU/L)	48.5±30.7	29.1±14.5	0.013*
Insulin (IU/l)	24.4±26.9	16.8±20.6	0.078
HbA1C (%)	9.5±1.9	9.9±1.3	0.084
C-peptide (ng/ml)	2.9±1.2	2.5±1.1	0.111
Duration of DM history (years)	6.3±5.1	10.2±5.6	0.002*
Insulin case (no)	17 (34.0%)	5 (33.3%)	0.962
HOMA	2.3±2.7	9.5±13.7	0.021*
Bypass vs. restrictive surgery	12/51	12/12	0.004*

DM diabetes mellitus, *HbA1C* glycated hemoglobin, *BMI* body mass index, *FPG* fasting plasma glucose, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HOMA* homeostasis model assessment[18]

*p<0.05

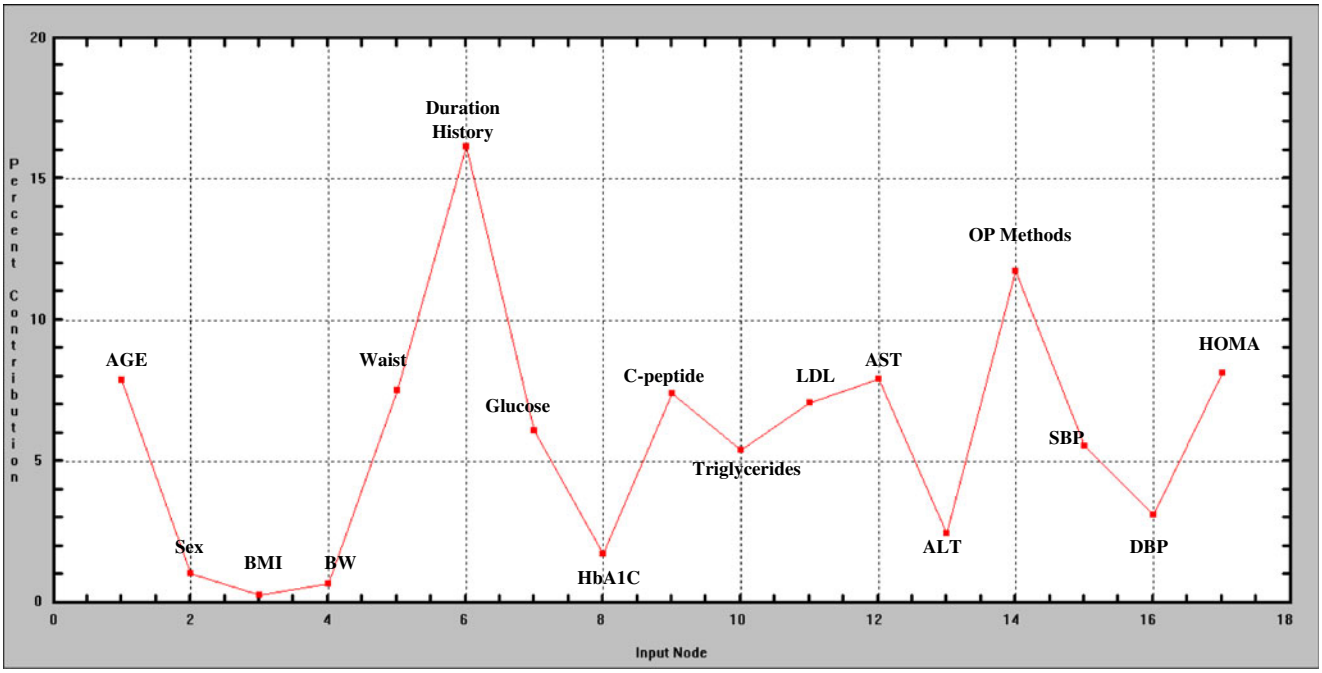

Fig. 1 The relative importance of preoperative predictor variables

only collected 14 trials of 289 patients with BMI<35 kg/m^2.[26] Most of the studies were small in number or retrospective.

Table 3 T2DM remission rate according to different clinical factors

Factors		No.	Remission rate (%)	*p* value
BMI (kg/m^2)	<25	9	55.5	0.027*
	25–30	31	67.7	
	30–35	47	78.7	
Age (years)	<35	14	85.7	0.469
	35–50	41	70.7	
	>50	32	68.7	
Gender	Female	60	73.3	0.775
	Male	27	70.3	
Duration (years)	<5	31	90.3	0.006*
	5–10	33	54.5	
	>10	16	62.5	
C-peptide	<2	17	52.9	0.115
	2–3	35	77.1	
	>3	33	78.7	
Surgery	LGB	63	79.3	0.062
	LSG	20	55.0	
	LAGB	4	50.0	
Waist/hip ratio	<0.9	10	76.9	0.976
	0.9–1.0	33	75.0	
	>1.0	11	73.3	

BMI body mass index, *LGB* laparoscopic gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *LAGB* laparoscopic adjustable gastric banding

*p<0.05

Another two recent reports of lower BMI T2DM patients were also retrospective and without important diabetes-related data, such as HbA1c or C-peptide.[18,27] This is the first large series report of a prospective open trial aimed at surgical treatment of not well-controlled T2DM in non-morbid obese patients (<35 kg/m^2). In this study, all the data are prospectively collected with complete preoperative diabetes-related information.

The most important finding of this study is that the duration of T2DM is the most important predictor of diabetes remission after surgery. Old age, longer T2DM history, and the use of insulin had been found to be negative predictors of T2DM remission in the previous studies of bariatric surgery on morbid obese patients.[6–8] However, the duration of T2DM is the most important predictor in this study of non-morbid obese patients. Although the duration might be inconsistent and might be influenced by the attitude of both patients and doctors, duration of diabetes does reflect the residual beta-cell mass in T2DM patients, both in morbid obese and in non-morbid obese patients.

Some previous studies had supported the thesis that duration of diabetes is probably more important than type of surgery to predict a successful result of surgical treatment of diabetes.[28–30] For restrictive-type surgery, Dixon et al. reported a T2DM remission rate of 73% for gastric banding which is much higher than the 45% in this study.[28] However, in Dixon's study, only newly diagnosed patients with duration of T2DM less than 2 years were recruited. Another recent study reported that remission of T2DM after SG dropped to 13% in those with duration of T2DM of longer than

5 years.[29] For gastric bypass, a recent study demonstrated a decrease of diabetes remission in those with a duration of T2DM longer than 10 years.[30] Therefore, the duration of diabetes may not only be a criterion for patient selection but also for a choice of different surgical procedures as well.

In this study, elevated liver enzymes AST and ALT were associated with higher remission rate of T2DM. Elevated liver enzyme is closely related to non-alcohol steato-hepatitis and insulin resistance.[31] Because the major mechanism of T2DM remission after bariatric surgery is the reduction of insulin resistance,[32] thus elevated liver enzyme may predict the success of metabolic surgery for T2DM. That is also why T2DM patients with higher BMI have a better T2DM remission rate. In this study, patients with BMI>30 also had a better diabetes remission rate those with their BMI<30. This finding highlights the importance of patient selection in performing GI metabolic surgery.

In this study, the type of surgery was another independent predictor of diabetes remission. Gastric bypass has been reported to have a better weight reduction and higher diabetes remission rate compared with purely restrictive procedure,[18,27] and it should be considered as a first choice in GI metabolic surgery.[32] Because of this, LAGB was very rarely to be used as diabetes treatment in this study and LSG occasionally. Most of our patients choose LGB for the treatment of their T2DM. However, restrictive-type surgery is ten times safer than a complex gastric bypass procedure and avoids the long-term sequels of micronutrient deficiency following duodenum exclusion. Therefore, although less effective in diabetes remission than gastric bypass surgery, LAGB or LSG still may be considered as the GI metabolic surgery in selected patients.[33] For example, LAGB may be considered for diabetes treatment in patients with duration of T2DM of less than 2 years and LSG may be considered in patients with duration of T2DM of less than 5 years. Gastric bypass surgery is recommended for the rest of T2DM patients but the patients should have their C-peptide >1 ng/ml with central obesity.[34] Further studies are required before the conclusion is made as well as other surgical procedures.

T2DM is now a global health priority. More than 60% of the world's population with diabetes comes from Asia and the incidence of T2DM is increasing more rapidly than the rest of the world.[35] In Taiwan, the T2DM incidence of adult increased more than double from 4.6% to 9.3% in the past decade.[36] Unlike in the West, where older population is most affected, the burden of diabetes in Asian countries is disproportionately high among young to middle-aged adults.[37] For those early onset T2DM patients, the incidence rate of diabetic nephropathy is alarmingly high, especially in those not well-controlled patients.[38] In Asia, 55% of newly diagnosed end-stage renal disease patients are due to T2DM.[37] How to control this chronic and deliberating disease will be a very important health issue in Asia. This study has shown that GI metabolic surgery is an effective treatment for those not well-controlled T2DM patients. Although the remission rate may decrease in lower BMI patients, it is still a novel treatment option for those not well-controlled T2DM patients under current intensive medical treatment. However, how to incorporate this treatment into current treatments of T2DM and how to select appropriate patients requires further cooperative works between endocrinologists and GI surgeons.

The limitation of this study is the lack of the long-term follow-up. Although studies have illustrated the remission of T2DM after metabolic surgery, some of the patients whose T2DM remission after surgery experienced a recurrence of their disease over times, especially in lower BMI, older with longer duration of the disease.[39,40] We need data of the long-term follow-up to 5 or 10 years in order to support surgery as a treatment option in non-morbid obese diabetes patients. Further elaborate clinical studies with long-term follow-up are indicated to elucidate this issue.

In conclusion, bariatric or GI metabolic surgery is a promising treatment for inadequate controlled obese-related T2DM patients with a 72.4% remission rate of associated diabetes. Although gastric bypass surgery is more effective on diabetes remission than restrictive-type surgery, duration of diabetes is the most important predictor of T2DM remission after metabolic surgery.

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Discussant

Dr. Patrick M. Forgione (Burlington, VT): Thank you for submitting this excellent and provocative study. You and your group should be congratulated for this collaborative, multi-institutional effort involving 200 patients.

This study shows that metabolic surgery is an effective treatment for poorly controlled type 2 diabetes in those who had diabetes for <5 years with BMI greater than 30. I think most would agree, and as you pointed out in your manuscript, that although successful in this population the follow-up was short, 1 year; that these conclusions were based on 87 of your 200 (46%) patients and need longer term data to make any formal recommendations. I have several questions.

In your manuscript, you state the endocrinologist and the surgeon co-determined when the patients were ready for randomization, yet based on the unequal distribution of your procedural groups, it is hard to believe this occurred; therefore, how were the patients assigned to the procedural groups?

Your study showed that patients who underwent a restrictive procedure and had a BMI<30 did not do as well as those who had BMI>30 and who underwent a gastric bypass. Since we know that in the bariatric population the

duration of diabetes is a negative preoperative indicator as to how well a patient will do postoperatively with regards to remission of type 2 DM, and since duration of diabetes was not equally distributed between the procedural groups, is it possible that those with BMI<30 who had restrictive procedures simply had a higher percentage of individuals with a longer duration of diabetes in their groups and subsequently poorer response rates? Thank you and the society for the opportunity to review your manuscript, I look forward to your response.

Closing Discussant

Dr. Wei-Jei Lee: Thank you for this excellent discussion. And yes, there is one particular weakness to this paper insofar as that the follow-up is short. We intend to include more patients and continue to follow-up these patients up to 5 years. Maybe we can have a final conclusion at that time.

With regard to your first question, this is not a randomized trial. The endocrinologist, surgeon, and patient co-determined the operation after detail discussion and analyst. That is why we can only have a limited number in restrictive-type procedures. The majority choose gastric bypass because of the higher resolution rate of diabetes treatment.

With regard to the second question, it is true that lower BMI patients had a longer mean duration of diabetes. That is why BMI itself is not an independent predictor for diabetes remission after metabolic surgery by multivariate analysis of decision tree analysis. However, we need more cases and longer follow-up to make a final conclusion.