Insulin Secretion and Interleukin-1β Dependent Mechanisms in Human Diabetes Remission after Metabolic Surgery

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Abstract

To compare endocrine, metabolic, and inflammatory changes induced by gastric bypass (GB) and sleeve gastrectomy (SG) in patients with type 2 diabetes mellitus (T2DM), and to investigate the mechanisms of success after metabolic surgery. Sixteen GB and 16 SG patients were followed up before and at 1 year after surgery. The 75-g oral glucose tolerance test (OGTT) was performed before and after surgery. Glucose homeostasis, serum interleukin-1β, plasma gut hormones and adipokines, and the United Kingdom Prospective Diabetes Study (UKPDS) ten-year cardiovascular risks were evaluated. The diabetes remission rate was significantly higher in GB than SG. Changes in the area under the curve (AUC) for glucose were greater in those with complete and partial remission after GB and remitters after SG than non-remitters after SG, whereas changes in AUC for C-peptide were higher in complete and partial remitters after GB than non-remitters after SG. Insulinogenic index was enhanced and serum interleukin-1β was reduced in complete remitters after GB and remitters after SG. Logistic regression analysis confirmed that insulinogenic index and interleukin-1β, not insulin resistance, were the factors determining the success of diabetes remission after metabolic surgeries. GB and SG significantly reduced the ten-year risk of coronary heart disease and fatal coronary heart disease in T2DM patients after surgery, while GB had the additional benefit of reduced stroke risk. Human diabetes remission after metabolic surgery is through insulin secretion and interleukin-1β dependent mechanisms. GB is superior to SG in cardiocerebral risk reduction in Asian non-morbidly obese T2DM patients.

Keywords: cardiovascular risk, gastric bypass, glucose homeostasis, insulin secretion, interleukin-1β, sleeve gastrectomy.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major chronic and debilitating disease that has a disproportionate impact in developing countries with epidemic growth at an alarming state [1]. In Asia, including Taiwan, T2DM is characterized by rapid rates of increase over short periods, onset at a relatively young age, in low body mass index (BMI), and driven by economic development, nutrition transition, and a sedentary lifestyle [1]. Because current intensive medical treatment only achieves well-controlled status (HbA1c <7%) in less than half of patients, most T2DM patients do not meet their treatment goals and develop cardiovascular morbidity and mortality. Thus, more effective treatment is imperative to prevent the long-term complications of T2DM and increase survival in poorly-controlled patients [2].

Prospective and meta-analysis researches provide strong evidence corroborating metabolic surgery as an option for the treatment of morbid obese T2DM patients (BMI >35 kg/m^2) and to reduce diabetes-related all-cause mortality [2, 3]. A previous randomized trial has proven that metabolic surgery, including gastric bypass (GB) and sleeve gastrectomy (SG), is effective as surgical treatment of Asian non-morbidly obese (BMI <35 kg/m^2), poorly-controlled T2DM at 1 year after surgery [4]. However, although interesting, the underlying mechanisms of success after metabolic surgery remain unclear. Besides, the big differences in the extent of visceral obesity between Asian and USA/European populations strongly indicate the need to examine Asian patients with T2DM [5].

Chronic inflammation may participate in the pathogenesis of T2DM [6], while cytokines are

major determinants of inflammatory responses. Moreover, after metabolic surgery, whether or not the anatomic rearrangement of the gastrointestinal tract affects glucose homeostasis by changing the secretion of gut hormones is a provocative yet reasonable hypothesis [7, 8]. How the inflammatory cytokines and gut hormones influence glucose metabolism and insulin secretion and resistance, which are closely linked with diabetes remission, is an intriguing and important issue worth considering.

The aims of this study were to prospectively evaluate serum interleukin-1β and plasma gut hormones and adipokines before and at 1 year after metabolic surgery, and to correlate these factors with the improved glycemia, insulin secretion and resistance, as well as the ten-year predicted cardiovascular risks in T2DM patients in Asia. We hypothesized that adipocytokines and gut hormones might contribute to diabetes remission, and hope to gain further mechanistic insight into the success of metabolic surgery.

MATERIALS AND METHODS

Patients

A hospital-based design was adapted in the present study. T2DM Patients aged between 30 and 60 years with a BMI between 25 and 35, as having clearly documented poorly-controlled T2DM (HbA1c >7.5%), and treated by an endocrinologist for 6 months or more, having no evidence of renal impairment or diabetic retinopathy, and able to understand and comply with the study process were assigned to receive bariatric surgery. The exclusion criteria were: having a specific disease, previous bariatric surgery, a history of major medical problems such as mental impairment, drug or alcohol addiction, recent major vascular event, internal malignancy, or portal hypertension, or a contradiction for either surgery. Treatment decision of GB or SG was based on clinical background of individual subject. The procedures of laparoscopic GB and SG were performed as previously [4]. Before and at 1 year after metabolic surgery, 32 subjects (GB, n = 16; SG, n = 16) agreed to receive the 75-g oral glucose tolerance test (OGTT) and were recruited for this study.

The study was conducted in the Department of Surgery of the Min-Sheng General Hospital, and Taipei Veterans General Hospital, and approved by the ethics committee of each hospital.

Definition of Diabetes Remission, Insulin Resistance, and Insulinogenic Index

Partial remission of T2DM was defined as fasting glucose 100-125 mg/dL with HbA1c value <6.5% in the absence of pharmacotherapy. Complete remission was defined as fasting glucose <100 mg/dL aside from HbA1c value <6.0% without the use of oral hypoglycemics or insulin [9, 10]. Those

T2DM patients who achieved either complete remission or partial remission at 1 year after GB or SG were defined as the remitters [4, 9, 10]. Otherwise, those who failed to achieve diabetes remission after metabolic surgery were defined as the non-remitters. Routine laboratory tests and anthropometric measurements were also performed.

The 75-g glucose in 300 ml of water was given and drunk in 5 min after an overnight fast before and at 1 year after GB or SG. Insulin resistance was measured by the homeostatic model assessment index (HOMA-IR), calculated as plasma glucose (mmol/L) × insulin (μU/mL)/22.5. Total blood glucose, insulin or C-peptide secretion during OGTT was measured by the area under the curve (AUC) of blood glucose, insulin or C-peptide using the trapezoidal method [11, 12]. The insulinogenic index was obtained by dividing plasma insulin enhancement above the fasting value by the corresponding net increase of blood glucose (△insulin: △glucose) at 30 min during the OGTT test [11, 12].

Measurement of Plasma Gut Hormones and Adipokines

After overnight fasting, blood samples were obtained to determine gut hormones and adipokines before and at 1 year after GB or SG. Enzyme immuno-assays for plasma acyl ghrelin (Bertin Pharma, Montigny le Bretonneux, France), des-acyl ghrelin (Bertin Pharma), cholecystokinin (CCK; Peninsula Laboratories, San Carlos, CA, USA), glucose-dependent insulinotropic peptide (GIP; Peninsula), glucagon-like peptide-1 (GLP-1; ALPCO Diagnostics, Salem, NH, USA), peptide YY (PYY; ALPCO Diagnostics), leptin (R&D Systems, Minneapolis, MN, USA), and adiponectin (Bertin Pharma) were carried out in a single batch run and in a blinded fashion, similar to our previous study [13].

Measurement of Serum Cytokines and Chemokines

Fasting serum samples of T2DM before and at one year after metabolic surgery were collected and measured for interleukin-1β (R&D) levels using EIA.

Fasting serum samples of T2DM at 1 year after surgery were collected and tested simultaneously for cytokines and chemokines using a Bio-Plex human cytokine 17-Plex assay (Bio-Rad Laboratories, Hercules, CA, USA). The data were analyzed using Bio-Plex Manager software version 3.0 with 5PL curve fitting [14]. Combined pro-inflammatory cytokines were calculated as: (interleukin-1β + interleukin-7 + interleukin-8 + interleukin-12 + granulocyte colony-stimulating factor + granulocyte-macrophage colony-stimulating factor + interferon-γ + tumor necrosis factor-α), whereas combined anti-inflammatory cytokines were calculated as: (interleukin-4 + interleukin-10 + interleukin-13), modified from a previous study [14].

UKPDS Ten-year Cardiovascular Risk Predictions

Prediction of ten-year cardiovascular risks, including pre- and post-operative risks of coronary heart disease, fatal coronary heart disease, stroke, and fatal stroke, were calculated from the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine [15].

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences, version 12.01 (SPSS, Inc, Chicago, Illinois). Continuous variables were expressed as mean ± SD. Chi-square test or Fisher's exact test was used to compare categorical variables, while Student's *t*-test or

Mann-Whitney test was used to compare continuous data. Paired *t*-test or Wilcoxon signed ranks test was used to compare between baseline and post-operative variables when applicable. One-way analysis of variance (ANOVA) followed by a Student-Newman-Keuls *post hoc* test was used to analyze the differences among groups. Logistic regression was applied to analyze potential factors influencing the success of diabetes remission after metabolic surgery. Correlations between two groups were analyzed using Spearman's correlation method. A P value < 0.05 was considered to be statistically significant.

RESULTS

Comparison of T2DM Patients after GB and SG

Baseline characteristics, including demographic data, smoking habits, duration of diabetes, biochemical features, glycemic profiles, β-cell functions, interleukin-1β, as well as gut hormones and adipokines in T2DM patients were comparable before GB and SG (Table **1**).

At 1 year after surgery, 9 patients achieved complete remission and 7 achieved partial remission after GB, whereas 1 patient achieved complete remission and 7 achieved partial remission after SG. Diabetes remission rate was significant higher in GB than SG (100% vs 50%, $P = 0.002$). Both GB and SG potentially reduced weight, HOMA-IR, serum insulin, C-peptide, high-sensitivity C-reactive protein (hsCRP) and adiponectin levels, and the post-operative values between the two groups were comparable. GB induced lower BMI and waist circumference than SG after surgery, but the alterations of them were not significantly different. On the other hand, only GB reduced systolic blood pressure and total cholesterol post-operatively.

GB reduced fasting blood glucose and HbA1c more than SG after surgery, but the alterations of them were not significantly different. GB, instead of SG, increased insulinogenic index after surgery (Table **1**). GB reduced AUC for glucose and increased AUC for C-peptide after 75-g oral glucose challenge, whereas SG did not alter either AUC for glucose or AUC for C-peptide (data not shown). Post-operative value of AUC for glucose was lower in GB than SG (data not shown). Notably, the changes in AUC for glucose and AUC for C-peptide were significantly greater in the complete and

partial remitters in GB than the non-remitters in SG Fig. (**1A**) and (**1B**).

GB also induced significant reduction of serum interleukin-1β at one year after surgery, while the alteration was significantly greater in GB than SG (Table **1**). Post-operative serum tumor necrosis factor-α and interleukin-1β levels were significantly higher in the non-remitters after SG than those with complete and partial remission after GB Fig. (**1C**) and (**1D**). However, post-operative serum interleukin-6 levels were not different among the 4 groups (data not shown). Post-operative serum combined anti-inflammatory cytokines were significantly higher in SG than GB (4.3 ± 2.6 vs 2.0 ± 1.2 ng/mL, $P < 0.01$), while post-operative serum combined pro-inflammatory cytokines were tended to be higher in SG than GB ($P = 0.051$, data not shown).

Plasma levels of acyl ghrelin and des-acyl ghrelin were reduced after SG not GB, while the alteration in acyl ghrelin was greater in SG than GB. Contrary, GB but not SG reduced plasma CCK after surgery. Both plasma PYY and adiponectin concentrations were elevated after GB and SG.

Comparison between the Complete Remitters and Partial Remitters after GB

All T2DM patients achieved diabetes remission at 1 year after GB. Table **2** showed the complete remitters exhibiting older age than partial remitters. Both complete remitters and partial remitters potentially reduced weight, BMI, waist circumference, plasma total cholesterol, and hsCRP. The complete remitters reduced systolic blood pressure. HOMA-IR was lower in those with complete remission than partial remission after surgery, but the alterations were not significantly different.

Only complete remitters revealed significantly reduced fasting blood glucose after surgery, and

the post-operative value was lower in complete remitters than partial remitters. Both complete remitters and partial remitters achieved reduction of HbA1c after surgery, but the post-operative level was lower and the alteration in HbA1c was greater in complete remitters than partial remitters. The complete remitters increased insulinogenic index, while the post-operative levels were comparable between those with complete remission and partial remission. Both complete and partial remitters exhibited reduced AUC for glucose and increased AUC for C-peptide after surgery, and the post-operative values were comparable between the two groups Fig. (**1A**) and (**1B**).

The complete remitters reduced serum interleukin-1β, while the post-operative levels were comparable between those with complete remission and partial remission (Table **2**). Post-operative serum combined pro-inflammatory and anti-inflammatory cytokines were not different between the complete and partial remitters after GB (data not shown).

Plasma adiponectin was increased after GB in complete remitters. Plasma PYY was significantly elevated in both groups, but the post-operative level was higher in partial remitters than complete remitters.

Comparison between the Remitters and Non-remitters after SG

The diabetes remission rate was 50% at 1 year in the SG group (Table **1**). In the SG group, the remitters exhibited significantly shorter history of T2DM than the non-remitters. Both remitters and non-remitters potentially reduced weight, BMI, insulin, C-peptide, and HOMA-IR at 1 year after SG. The post-operative values of these factors were comparable between the two groups. Only the remitters

significantly reduced waist circumference, but the post-operative levels were comparable between the remitters and non-remitters.

Both groups showed reduced fasting blood glucose and HbA1c, while the post-operative levels were lower in remitters than non-remitters. Only remitters, not non-remitters, exhibited increased insulinogenic index (Table **3**) and decreased AUC for glucose (data not shown) after SG. Concomitantly, the post-operative level of insulinogenic index (Table **3**) was higher, whereas that of AUC for glucose (data not shown) was lower in remitters than non-remitters. In addition, the increase in insulinogenic index (Table **3**) and the decrease in AUC for glucose Fig. (**1A**) were significantly greater in remitters than non-remitters after SG. Notably, AUC for C-peptide after OGTT was unaltered in the remitters, but was significantly reduced in the non-remitters after SG Fig. (**1B**).

Blood leukocyte and serum interleukin-1β were significantly reduced in the remitters than non-remitters after SG. The remitters exhibited lower post-operative serum interleukin-1β values and greater changes in blood leukocyte and serum interleukin-1β than non-remitters. Post-operative serum combined pro-inflammatory ($P = 0.057$) and anti-inflammatory cytokines ($P = 0.079$) tended to be higher in the non-remitters than remitters after SG (data not shown).

Plasma des-acyl ghrelin was reduced, while plasma PYY and adiponectin was elevated after SG in both remitters and non-remitters. The post-operative values of these factors were comparable between the two groups. Only the remitters significantly reduced plasma acyl ghrelin, but the post-operative values were comparable between the two groups.

UKPDS Ten-year Cardiovascular Risk Predictions

Both GB and SG were effective in reducing the ten-year risks of coronary heart disease and fatal coronary heart disease in T2DM patients (Table **4**). The relative risk reduction of coronary heart disease and fatal coronary heart disease was significantly more in GB than in SG (Table **4**). However, both surgeries did not affect the risk of fatal stroke, while risk reduction of stroke was significant only after GB (Table **4**).

Factors Determining the Success of Diabetes Remission undergoing Metabolic Surgery

Table **5** reveals the odds ratio and 95% confidence interval (95% CI) for those factors affecting the success of diabetes remission undergoing GB or SG, using the logistic regression analysis. T2DM patients who had longer T2DM duration before surgery, higher pre-operative AUC for C-peptide, higher post-operative interleukin-1β, higher post-operative AUC for glucose, as well as less reduction of interleukin-1β and less reduction of AUC for blood glucose after surgery, exhibited significantly lower successful chance to achieve diabetes remission. However, on the contrary, those demonstrating the increased changes of insulinogenic index and AUC for C-peptide achieved significantly higher rate for diabetes remission after metabolic surgery. However, neither pre-operative, post-operative nor altering levels of HOMA-IR (odds ratio (95% CI): 1.012 (0.949 – 1.079), 0.614 (0.334 – 1.131), 0.982 (0.906 – 1.064), respectively) was the determining factor for the success of diabetes remission undergoing metabolic surgery.

Correlations between Glycemic profiles, Insulinogenic Index and Interleukin-1β

At 1 year after metabolic surgery, the reduction of HbA1c did not correlate with weight loss or reduction of BMI. Besides, the reduction of HbA1c did not correlate with the decreases in either waist or HOMA-IR, as well as alterations in plasma fasting levels of acyl ghrelin, des-acyl ghrelin, PYY and adiponectin. The post-operative insulinogenic index significantly correlated with post-operative levels blood glucose and AUC for glucose negatively, and with post-operative AUC for C-peptide positively Fig. (**2A**). The post-operative interleukin-1β significantly correlated with post-operative levels of blood glucose, HbA1c, and AUC for glucose positively, and with post-operative insulinogenic index negatively Fig. (**2B**). The improvement in insulinogenic index significantly correlated with the alterations in blood glucose, HbA1c, AUC for glucose and interleukin-1β negatively after metabolic surgery Fig. (**2C**).

DISCUSSION

T2DM has become a major health public problem and is the 5th leading cause of death in Taiwan. However, there is relatively little data regarding this issue from Asia. Because the big variations in visceral fat content exist between Asians and Caucasians, namely the Y-Y paradox [5], the investigation should be conducted in different races in a prospective, longitudinal manner. In the current study, both metabolic surgeries not only achieved potent reduction of fasting blood glucose, HbA1c, and insulin resistance, but also significantly improved blood pressure and lipid profiles at 1 year post-operatively. Weight loss at 1 year after surgery was comparable between GB and SG. However, GB and SG achieved significantly different rates of diabetes remission (100% vs 50%), which were consistent with our previous study (93% vs 47%) [4]. The complete remission rate of our patients after GB is also comparable with western people (56.3% vs 42%) at 1 year after surgery, but, however, our complete remission rate after SG is much lower than that in Caucasians (6.3% vs 37%) [2]. The mechanisms underlying poor restoration of normal glucose homeostasis after SG in Asian non-morbidly obese T2DM patients deserve investigation. The current study demonstrates that improvement in glycemia after metabolic surgery is independent of weight loss, since there was no any correlation between changes in HbA1c level and reduction of either body weight or BMI.

Previous studies showed that the resolution rate in morbidly obese T2DM patients was higher than in non-morbidly obese ones at 1 year after SG [16, 17], while the latter might have a higher incidence of β-cell failure due to lower BMI. Our results demonstrate that GB is superior to SG in

achieving higher rate of diabetes remission [4], which may result from its capability of reversing β-cell failure in lower BMI patients after GB. In the current study, GB and SG corrected fasting hyperinsulinemia and lowered fasting C-peptide levels. The reduction of fasting insulin and C-peptide may result from the improvement in insulin resistance after both surgeries, which is consistent with our previous findings [11, 12]. However, the changes in AUC for glucose after oral glucose challenge were significantly greater in those with complete and partial remission after GB and remitters after SG than non-remitters after SG. In addition, the alterations in AUC for C-peptide were higher in complete and partial remitters after GB than non-remitters after SG, suggesting that enhanced insulin secretion responding to OGTT plays an important role in determining the success of diabetes remission after metabolic surgery. Postprandial hyperinsulinemic hypoglycemia has been reported in patients undergoing GB, and immunohistochemical staining studies confirmed hypertrophic pancreatic β-cells of Langerhans islets, known as nesidioblastosis, in such patients [18]. Increased levels of pancreatic β-cell trophic factors, such as glucagon-like peptide 1 or others [18, 19], have been proposed to contribute to the hyperplasia of β-cells in these patients after GB, leading to hyperfunction of β-cells. Evidence suggests the potential effect of "rejuvenation" on islet β-cells after metabolic surgery, such as GB. In accordance with the above-mentioned findings, our results suggest the differential remission of T2DM between two metabolic surgeries, as well as between remitters and non-remitters, through distinct pathways governing glucose homeostasis and insulin secretion in response to oral glucose challenge.

The dynamics of insulin secretion, especially the first phase of insulin secretion, play a crucial role in the pathogenesis of diabetes [20]. However, very few data are available in the relevant literature concerning the changes in insulin secretion and insulin sensitivity related to diabetes remission following metabolic surgery. The complete remitters after GB and the remitters after SG both showed significant improvement of early insulin secretion (insulinogenic index), i.e. insulin secretion 30-min after OGTT. Contrary, early insulin secretion was unaltered in the non-remitters in the SG group despite markedly improved HOMA-IR, and post-operative insulinogenic index was significantly lower in the non-remitters than the remitters after SG. In addition, the increase in insulinogenic index after SG was significantly higher in the remitters than non-remitters. In addition, post-operative insulinogenic index correlated negatively with post-operative blood glucose and AUC for glucose, but correlated positively with AUC for C-peptide. Moreover, the enhancement in the insulinogenic index negatively correlated with the alterations of blood glucose, HbA1c, and AUC for glucose after metabolic surgery. Collectively, our results showed that early insulin secretory ability of islet β-cells is restored in the complete remitters after GB and the remitters after SG, while insulinogenic index highly determined the improved glycemic profiles after metabolic surgery. On the other hand, HOMA-IR was comparable between the remitters and non-remitters in the SG group. In addition, HOMA-IR was corrected after GB or SG, irrespective of the surgical methods and the remission status of diabetes. Further logistic regression analysis confirmed that the increment in insulinogenic index, but not either the pre-operative, post-operative or alteration of HOMA-IR, was the crucial factor to determine the diabetes remission

after metabolic surgery. Taken together, the current study demonstrated that human diabetes remission after metabolic surgery is through an insulin secretion dependent mechanism.

T2DM is associated with a subclinical systemic auto-inflammation, driven by glucose, free fatty acid, leptin and interleukin-1β. Emerging evidence supports a causative role for interleukin-1β as the primary agonist in the loss of pancreatic β-cell function and mass in T2DM, since interleukin-1β has been shown to induce the death of insulin-producing β-cells while sparing α-cells [21]. Second, hyperglycemia was revealed to induce β-cell production of interleukin-1β, contributing to glucotoxicity in human pancreatic islets [22]. Third, increased circulating interleukin-1β causes inhibition of insulin release and β-cell failure in normal rats [23, 24]. Fourth, systemic blockade of interleukin-1β with interleukin-1 receptor antagonist or interleukin-1β neutralizing monoclonal antibody improved glycemia and β-cell secretory function with sustained effects in T2DM patients [25-27]. However, information regarding the changes in serum interleukin-1β following metabolic surgery is essential, but is lacking at this time.

In the present study, the complete remitters in the GB group and the remitters in the SG group exhibited significant reduction of serum interleukin-1β concentrations at 1 year after surgery. Furthermore, post-operative serum interleukin-1β levels were significantly higher in the non-remitters than the remitters after SG, as well as those with complete and partial remission after GB. The findings were parallel with the significantly higher levels of tumor necrosis factor-α (the upstream of interleukin-1β) but not interleukin-6 (the downstream of interleukin-1β) in the non-remitters after SG.

Moreover, the alteration was significantly higher in the remitters than non-remitters in SG. In addition, post-operative serum combined anti-inflammatory cytokines were significantly higher after SG than GB, while the blood leukocyte was significantly reduced in the remitters than non-remitters in the SG group, indicating a more favorable inflammatory milieu in GB than SG, as well as in the remitters than non-remitters after SG. As interleukin-1β induces it own gene expression and secretion of the active cytokines [28], successful metabolic surgery results in the effective reduction of serum interleukin-1β after intervention, and is potentially capable of breaking this vicious auto-inflammatory circuitry which damages β-cell islets in T2DM. The impacts of the reduced interleukin-1β after metabolic surgery may be systemic, and reflect less interleukin-1β-induced toxicity on the β-cell in the islet as well as interleukin-1β-mediated attenuation of inflammation in the adipose tissue [29], contributing to normalization of glycemic control. Moreover, post-operative interleukin-1β positively correlated with post-operative blood glucose, HbA1c, and AUC for glucose, but negatively correlated with post-operative insulinogenic index. In addition, the alteration in interleukin-1β negatively correlated with the increase in insulinogenic index after metabolic surgery. Collectively, these data are in accordance with the emerging concept that low concentration of interleukin-1β induces β-cell proliferation in human pancreatic islets [30], as well as the increased interleukin-1β activation is the culprit not only for defective insulin secretion but also for insulin resistance [31]. Logistic regression analysis revealed that lower post-operative interleukin-1β level and more reduction of serum interleukin-1β by metabolic surgery achieved higher rate of diabetes remission. Therefore, metabolic

surgery may play an important role in correcting pro-inflammatory imbalance in T2DM patients, and rejuvenating insulin secretory ability of residual β-cells via reducing serum interleukin-1β activity. Post-operative suppressed serum interleukin-1β levels paralleled by enhanced glucose-stimulated insulin secretion of β-cells are strongly associated with the resolution of T2DM after surgery. Hence, human diabetes remission after metabolic surgery is noted through an interleukin-1β dependent mechanism.

In our previous study, we have demonstrated differential preprandial and postprandial patterns of gut hormones in response to a mixed meal in T2DM patients after GB and SG [13]. In the present study, we comprehensively investigated the fasting concentrations of gut hormones and adipokines before and at 1 year after surgery. We proposed that the activity of the entero-endocrine system following GB and SG might be enhanced. Plasma acyl ghrelin and des-acyl ghrelin did not show any significant changes after GB, but were significantly reduced after SG. Moreover, only GB significantly suppressed plasma CCK after surgery. Further analysis revealed that acyl ghrelin and des-acyl ghrelin levels were not different between the remitters and non-remitters after SG, while comparable CCK levels were detected between those with complete and partial remission after GB. Notably, both GB and SG significantly increased plasma PYY and adiponectin. The post-operative levels of plasma adiponectin were comparable between the complete remitters and partial remitters in GB, as well as between the remitters and non-remitters in SG. However, post-operative PYY level was significantly higher in the partial remitters than complete remitters in GB, which may be explained by the fact that PYY injection

in humans increased glucose excursions [32]. Based on the findings that comparable post-operative CCK between those with complete and partial remission in GB as well as comparable acyl ghrelin and des-acyl ghrelin levels between remitters and non-remitters in SG were shown, fasting acyl ghrelin, des-acyl ghrelin and CCK may not necessarily be associated with the mechanisms of diabetes remission after metabolic surgery. The differences in post-operative ghrelin and CCK levels may be entirely due to differences in anatomical modification of gastrointestinal tract produced by two surgical procedures, for instance, the more preservation of the stomach in GB than SG, and the duodenal exclusion effect after GB.

In the present study, there are significant risk reductions in coronary heart diseases in T2DM patients after GB and SG, supporting the crucial role of metabolic surgery in the prevention of T2DM-related cardiovascular complications. Furthermore, GB is more effective than SG in reducing risks of coronary heart disease and fatal coronary heart disease. Interestingly, only GB, not SG, reduces the risk of stroke in the Asian T2DM patients here. Whether diabetes remission with reduced predicted cardiovascular risks can be translated into reductions of target organ damage and all-cause mortality deserves long-term follow-up.

CONCLUSIONS

GB and SG are both effective in achieving T2DM remission and reducing ten-year predicted risks of coronary heart disease and fatal coronary heart disease in Asian, non-morbidly obese, T2DM patients. GB had the additional benefit of reduced ten-year predicted risk of stroke. The discrepancy in

diabetes remission is not associated with weight loss, insulin resistance, or fasting gut hormone effect. Human diabetes remission after metabolic surgery is through enhanced insulin secretion and reduced interleukin-1β dependent mechanisms. Poor restoration of β-cell secretory function and less reduction of serum interleukin-1β account for the worse glycemic control after SG in Asian non-morbidly obese T2DM patients.

CONFLICT OF INTEREST

These authors declare no conflict of interest.

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Figures Legends

Fig. 1. The alterations in β-cell secretory function, and post-operative levels of serum tumor necrosis factor-α and interleukin-1β in patients with type 2 diabetes mellitus at 1 year after metabolic surgery. Changes in (**A**) AUC for glucose in response to 75-g oral glucose tolerance test were significantly greater in those with complete and partial remission after gastric bypass and the remitters after sleeve gastrectomy than the non-remitters after sleeve gastrectomy. Changes in (**B**) AUC for C-peptide in response to 75-g oral glucose tolerance test were significantly higher in those with complete and partial remission after gastric bypass than the non-remitters after sleeve gastrectomy. Post-operative serum (**C**) tumor necrosis factor-α and (**D**) interleukin-1β levels were significantly higher in those with complete and partial remission after gastric bypass and the remitters after sleeve gastrectomy than the non-remitters after sleeve gastrectomy.

Fig. 2. Bivariate correlations between post-operative insulinogenic index, interleukin-1β and glycemic profiles at 1 year after metabolic surgery.

(**A**) Post-operative insulinogenic index significantly correlated with post-operative blood glucose and AUC for glucose in response to 75-g oral glucose tolerance test negatively, and with AUC for C-peptide in response to 75-g oral glucose tolerance test positively. (**B**) Post-operative interleukin-1β significantly correlated with post-operative blood glucose, HbA1c, AUC for glucose in response to 75-g oral glucose tolerance test positively, and with insulinogenic index negatively. (**C**) The

improvement of insulinogenic index significantly correlated with the changes in blood glucose, HbA1c, AUC for glucose in response to 75-g oral glucose tolerance test and interleukin-1β after metabolic surgery.