ORIGINAL ARTICLE

Change of plasma amylin after bariatric surgery challenged by oral glucose is associated with remission of type 2 diabetes mellitus

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Abstract

Background: Gastric bypass (GB) and sleeve gastrectomy (SG) were found to achieve different remission rates in the treatment of type 2 diabetes (T2DM). The alteration in several gut hormones after bariatric surgery has been demonstrated to play a key role for T2DM remission. Nevertheless, amylin, one of the diabetes-associated peptides, so far has an undetermined position on T2DM remission after bariatric surgery.

Methods: Sixty eligible patients with T2DM (GB, 30; SG, 30) were initially enrolled in the hospital-based randomized trial. Twenty patients (GB, 10; SG, 10) who met the inclusion criteria and agreed to undergo 75-g oral glucose tolerance test (OGTT) were recruited. The recruited subjects underwent anthropometric measurements, routine laboratory tests, and 75-g OGTT before and 1 year after bariatric surgery. Enzyme immunoassays for plasma amylin were analyzed.

Results: All subjects that underwent GB and half of those who underwent SG achieved T2DM remission. Plasma amylin levels significantly decreased 60–90 min after OGTT in the GB group ($p < 0.05$) and 30–60 minutes after OGTT in the SG group ($p < 0.05$). Significantly decreased plasma amylin levels were observed at 30–90 minutes after OGTT in the noncomplete remitters of the GB group ($p < 0.05$). Plasma amylin levels initially increased ($p < 0.05$) within 30 minutes after OGTT and then decreased ($p < 0.05$) in the next 30-minute interval in the nonremitters of the SG group.

Conclusion: Postoral glucose challenge amylin levels could be as one of the parameters to evaluate T2DM remission after bariatric surgery, especially in those after SG.

Keywords: Amylin; Bariatric surgery; Diabetes mellitus; Gastric bypass; Sleeve gastrectomy

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**Author Contributions: Dr Jiunn-Wei Wang and Dr Chun Yeh contributed equally to this work.*

Conflicts of interest: Dr Chih-Yen Chen, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 1001-1006.

Received May 23, 2021; accepted July 28, 2021.

doi: 10.1097/JCMA.0000000000000602.

1. INTRODUCTION

The total number of individuals with type 2 diabetes mellitus (T2DM) is estimated to be approximately 366 million by the year 2030.[1] In fact, patients with T2DM attain the treatment goal through drugs, and many of them develop microvascular and macrovascular complications over time. Bariatric surgery is so far the only therapy to resolve T2DM, bringing hope to this unsolved but important issue. Gastric bypass (GB) and sleeve gastrectomy (SG), the two effective surgical procedures for weight loss treatment, were found to achieve different remission rates in the treatment of Asian patients with T2DM at 1 and 2 years of follow-up studies.[2–5]

Previous studies have demonstrated the alteration in several gut hormones after bariatric surgery.[6,7] The regulation of these hormones might be the key for T2DM remission.

One of them is amylin, also known as diabetes-associated peptide, which is cosynthesized and coreleased with insulin from pancreatic β-cells.[8] Amylin not only acts on different aspects of energy homeostasis but also plays a crucial role in reducing the amount of food intake by inducing feelings of satiation.[9,10] Several studies have demonstrated the glucose-stabilizing and weight-lowering features of amylin and the associated disorders under dysregulation of amylin, such as T2DM and obesity.[11–13] Patients with T2DM have a diminished amylin response to energy intake, potentially related to the degree of β-cell impairment.[14] Hyperamylinemia is observed in earlier stages of T2DM, and amylin levels decrease as the disease progresses.[15] Likewise, obese individuals often have hyperamylinemia with downregulation of amylin receptors, followed by amylin resistance.[16]

There is insufficient evidence to prove the relationship between amylin levels and different T2DM remission rates after bariatric surgery with GB and SG. In this study, we evaluated the change in plasma amylin via oral glucose tolerance test (OGTT) 1 year after the two different kinds of surgery to elucidate the underlying mechanism associated with T2DM remission.

2. METHODS

2.1. Patients and bariatric surgery

We designed a hospital-based randomized trial and enrolled 60 eligible patients with T2DM (GB, n = 30; SG, n = 30). The study was conducted in Min-Sheng General Hospital, Cheng Hsin General Hospital and Taipei Veterans General Hospital and approved by the Ethics Committee of all hospitals. The bariatric surgery with laparoscopic GB and SG were performed as previously described.[3] We included the patients who met the following criteria: (1) onset of T2DM for >6 months with hemoglobin A1c (HbA1c) level ≥8%, under the intensive medical care; (2) body mass index (BMI) ≥25 kg/m^2, the optimal cutoff value for obesity in Asian population suggested by the International Obesity Task Force,[17] and ≤40 kg/m^2; (3) willingness to receive accessory therapy with diet control and exercise; (4) willingness to undergo follow-up; and (5) willingness to provide written informed consent. Those who had underlying malignancy and active pulmonary tuberculosis, were human immunodeficiency virus-positive, underwent previous gastrointestinal surgery, and those who presented uncooperative conditions were excluded. Participants who use amylin analogues or agonists were excluded. Twenty of 60 patients (GB, n = 10; SG, n = 10) who agreed to undergo OGTT were recruited in this trial. Another 10 age- and sex-matched healthy control participants from health check-up examinations were also enrolled. Written informed consents were obtained before the study.

2.2. Definition of diabetes remission

In the absence of active pharmacologic therapy or ongoing procedures, partial remission of T2DM was defined as fasting glucose level of 100–125 mg/dL with HbA1c level <6.5%, and complete remission was defined as fasting glucose level <100 mg/dL with normal range of HbA1c level (<6.0%).[18] We defined patients with T2DM who achieved either complete remission or partial remission 1 year after bariatric surgery as remitters. On the contrary, those who failed to achieve remission were defined as nonremitters.[3,18]

2.3. 75-g OGTT and measurement of insulin resistance and amylin levels

The recruited subjects underwent anthropometric measurements, routine laboratory tests, and 75-g OGTT before and 1 year after bariatric surgery.[19] We used homeostatic model assessment index for insulin resistance (HOMA-IR), calculated as plasma glucose level (mmol/L) × insulin level (μU/mL)/22.5, to measure insulin resistance. Enzyme immunoassays for plasma amylin (Bertin Pharma, Montigny le Bretonneux, France; normal range: 0–25 ng/mL) were performed in a blinded and single batch run, similar to our previous study.[20] The variation of area under the curve of plasma amylin levels per minute (ΔAUC of plasma amylin) during the OGTT was calculated with the trapezoidal method.[2,21]

2.4. Statistical analysis

The statistical software used in this study was Statistical Package for Social Sciences version 12.01 (SPSS, Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD). The chi-square test or Fisher's exact test was used to compare categorical variables, while the Mann–Whitney U test was used to compare continuous variables. The Wilcoxon signed-rank test was used to compare baseline and postoperative variables. Friedman's one-way analysis of variance followed by a post hoc test was used to analyze the differences among plasma amylin levels at 0, 30, 60, 90, and 120 minutes after 75-g OGTT 1 year postoperatively. Statistical significance was set at a p value <0.05.

3. RESULTS

The preoperative baseline characteristics of the recruited subjects are shown in the Table. The participants in the GB group had significantly lower BMI (28.4 ± 3.1 kg/m^2) than those in the SG group (31.7 ± 2.3 kg/m^2). The healthy controls (five males and five females with average 42.2 ± 4.8 y old) had average BMI of 25.2 ± 4.5 kg/m^2. Higher preoperative HOMA-IR score was noted in the SG group (11.1 ± 7.0) than in the GB group (3.3 ± 2.3). Moreover, other clinical features, including demographic data, smoking habits, anthropometric data, duration of diabetes, glycemic profiles, and lipid profiles, were not significantly different between the two groups before bariatric surgery. In the GB group, nine patients used oral antidiabetic drugs only, and the other one received oral antidiabetic drugs combined with insulin therapy. In the SG group, six patients used oral antidiabetic drugs only, one used insulin only, and the other three received oral antidiabetic drugs combined with insulin therapy (data not shown).

3.1. Treatment effect 1 year after bariatric surgery

Continuing in the Table, all participants (n = 10) in the GB group achieved remission (half (n = 5) in complete remission and the others (n = 5) in partial remission) of T2DM, and half of the participants (n = 5) in the SG group achieved remission of T2DM 1 year after bariatric surgery. On further correlation analysis between gender and T2DM remission, 50% of male and female presented complete remission in the GB group, as well as also 50% of male and female presented remission in the SG group (data not shown). Compared with those before surgery, all anthropometric data, such as systolic/diastolic blood pressure, BMI, waist circumference, and hip circumference, and glycemic profiles (including fasting glucose levels, HbA1c level, and HOMA-IR), and lipid profiles (including high-density lipoprotein cholesterol and triglyceride) decreased. Among them, patients in the GB group had significantly lower BMI and HbA1c level than those in the SG group. In addition, there was no significant difference in percent of total body weight loss (%TWL) between the two groups after bariatric surgery. Intragroup analysis presented no significant different %TWL in the GB group between complete and noncomplete remitters (22.6% ± 7.3% vs 17.9% ± 6.9%, respectively, p = 0.421). The similar result was also found in the SG group, which demonstrated no significant

Table 1

Baseline characteristics of patients with T2DM before bariatric surgery and outcomes 1 year after bariatric surgery

	Before bariatric surgery			After bariatric surgery		
Characteristic	**GB (n = 10)**	**SG (n = 10)**	***p***	**GB (n = 10)**	**SG (n = 10)**	***p***
Age (y)	44.5 ± 6.7	46.7 ± 8.8	0.570	—	—	—
Sex (male/female)	4/6	6/4	0.656	—	—	—
Smoking (yes/no)	4/6	2/8	0.628	—	—	—
SBP (mmHg)	133.1 ± 8.6	129.9 ± 9.9	0.740	120.0 ± 15.6	120.4 ± 8.1	0.147
DBP (mmHg)	80.2 ± 6.7	81.8 ± 7.6	0.861	72.0 ± 7.9	73.6 ± 7.2	0.945
BMI (kg/m^2)	28.4 ± 3.1	31.7 ± 2.3	0.017	22.7 ± 2.7	24.5 ± 2.0	0.038
Waist circumference (cm)	95.9 ± 11.0	102.0 ± 16.7	0.150	80.0 ± 8.7	85.2 ± 3.7	0.112
Hip circumference (cm)	103.4 ± 6.0	104.5 ± 14.9	0.161	93.1 ± 5.7	96.0 ± 5.1	0.384
Waist-to-hip ratio	0.98 ± 0.04	0.93 ± 0.07	0.121	0.86 ± 0.06	0.89 ± 0.04	0.162
Duration of T2DM (y)	5.7 ± 5.0	7.0 ± 4.7	0.471	—	—	—
Fasting glucose levels (mg/dL)	179.1 ± 84.4	244.2 ± 91.1	0.104	103.0 ± 20.4	130.2 ± 53.3	0.226
HbA1c (%)	9.9 ± 2.1	10.2 ± 2.6	0.970	5.8 ± 0.6	7.4 ± 1.9	0.019
HOMA-IR	3.3 ± 2.3	11.1 ± 7.0	0.009	1.4 ± 1.5	1.8 ± 1.5	0.345
HDL-C (mg/dL)	44.9 ± 7.7	42.5 ± 7.5	0.771	47.8 ± 6.9	44.4 ± 7.4	0.646
TG (mg/dL)	236.4 ± 223.2	252.7 ± 145.3	0.499	96.6 ± 37.8	139.3 ± 61.3	0.170
Weight loss (kg)	—	—	—	15.8 ± 5.9	20.0 ± 8.2	0.257
%TWL	—	—	—	20.2 ± 7.1	22.2 ± 7.3	0.571

Data are presented as mean ± SD.
%TWL = percent of total body weight loss; BMI = body mass index; DBP = diastolic blood pressure; GB = gastric bypass; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment index for insulin resistance; SBP = systolic blood pressure; SG = sleeve gastrectomy; TG = triglyceride; T2DM = type 2 diabetes mellitus.

difference of %TWL between remitters and non-remitters (25.3% ± 7.6% vs 19.1% ± 6.3%, respectively, $p = 0.421$). All patients in the GB group did not use any medical therapy for T2DM, and four patients in the SG group still needed oral antidiabetic drugs for blood sugar control after bariatric surgery (data not shown).

3.2. Plasma amylin levels during OGTT in all patients with T2DM

Postoperative fasting amylin concentrations were within normal range in all subjects of GB group and SG group, and there was no significant difference of mean fasting amylin concentrations between health controls, GB group and SG group (0.59 ± 0.35 vs 0.72 ± 0.13 vs 0.60 ± 0.13 ng/mL, respectively, $p = 0.377$). The dynamic changes in plasma amylin after OGTT in all patients with T2DM after GB and SG are demonstrated in Fig. 1. Average plasma amylin levels ranged from 0.698 to 0.849 ng/mL during OGTT in the GB group and from 0.583 to 0.779 ng/mL in the SG group. In the GB group, plasma amylin levels significantly decreased 60–90 minutes after receiving 75 g glucose in OGTT ($p < 0.05$). Similarly in the SG group, there was a significant decrease in plasma amylin levels 30–60 minutes after receiving 75 g glucose in OGTT ($p < 0.05$). No significant differences in plasma amylin levels presented at each time point between the two groups.

3.3. Plasma amylin levels during OGTT in patients with T2DM in the two groups

Figs. 2 and 3 showed plasma amylin levels after OGTT in the two groups. In the GB group, lower plasma amylin levels after OGTT were noted in patients with T2DM with complete remission (0.679–0.778 ng/mL) than in those with noncomplete remission (0.707–0.967 ng/mL). A significant decrease in plasma amylin levels was observed at the interval 30–90 minutes after receiving 75 g glucose in the non-complete remitters ($p < 0.05$). Besides, plasma amylin levels presented no significant differences at each time point between complete and noncomplete remitters in the GB group (Fig. 2A). Likewise, there were lower plasma amylin levels in remitters (0.503–0.743 ng/mL) than in nonremitters (0.628–0.935 ng/mL) in the SG group. Plasma amylin levels ($p < 0.05$) initially increased within 30 minutes after receiving 75 g glucose and then decreased ($p < 0.05$) at the next 30 minutes in the nonremitters of the SG group. Moreover, there were also no significant differences in plasma amylin levels at each time point between remitters and nonremitters in the SG group (Fig. 2B).

3.4. Variation in plasma amylin levels during OGTT in patients with T2DM in the two groups

The AUC of plasma amylin levels had no significant difference either between complete and noncomplete remitters in the GB

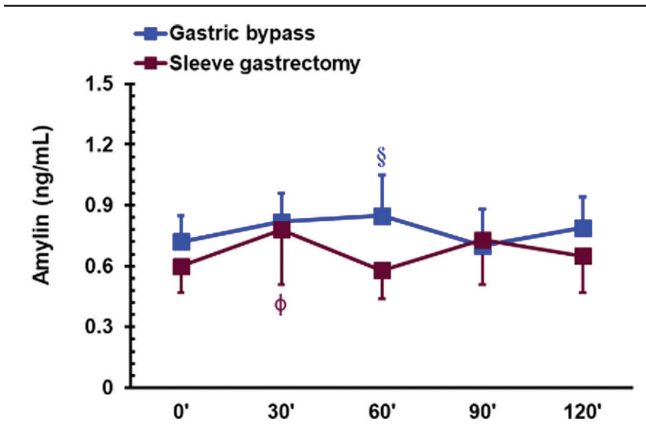

Fig. 1 The plasma amylin levels after OGTT in all T2DM patients after gastric bypass and sleeve gastrectomy. The blue line shows the dynamic changes in average plasma amylin levels after OGTT in patients undergoing gastric bypass. The purple line illustrates the dynamic changes in average plasma amylin levels after OGTT in those undergoing sleeve gastrectomy. §, $p < 0.05$ between 60 and 90 min; ϕ, $p < 0.05$ between 30 and 60 min. Statistical analysis with Friedman's one-way analysis of variance followed by a post hoc test. OGTT = oral glucose tolerance test; T2DM = type 2 diabetes mellitus.

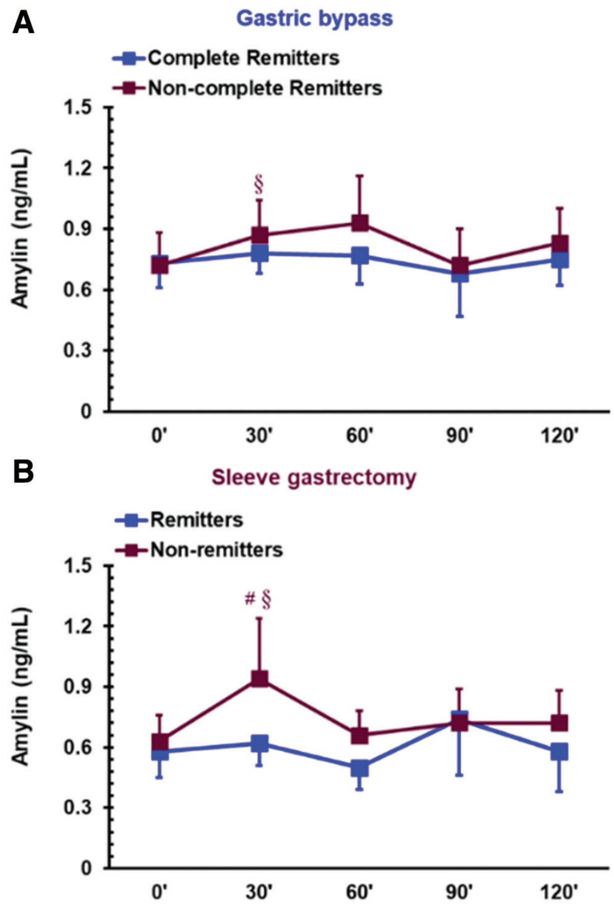

Fig. 2 Intragroup analyses of plasma amylin levels after OGTT in the two groups. A, The dynamic changes in average plasma amylin levels after OGTT in complete remitters and non-remitters after gastric bypass. §, $p < 0.05$ between 30 and 90 min. B, The dynamic changes in average plasma amylin levels after OGTT in remitters and non-remitters after sleeve gastrectomy. #, $p < 0.05$ between 0 and 30 min; §, $p < 0.05$ between 30 and 60 min. Statistical analysis with Friedman's one-way analysis of variance followed by a post hoc test. OGTT = oral glucose tolerance test.

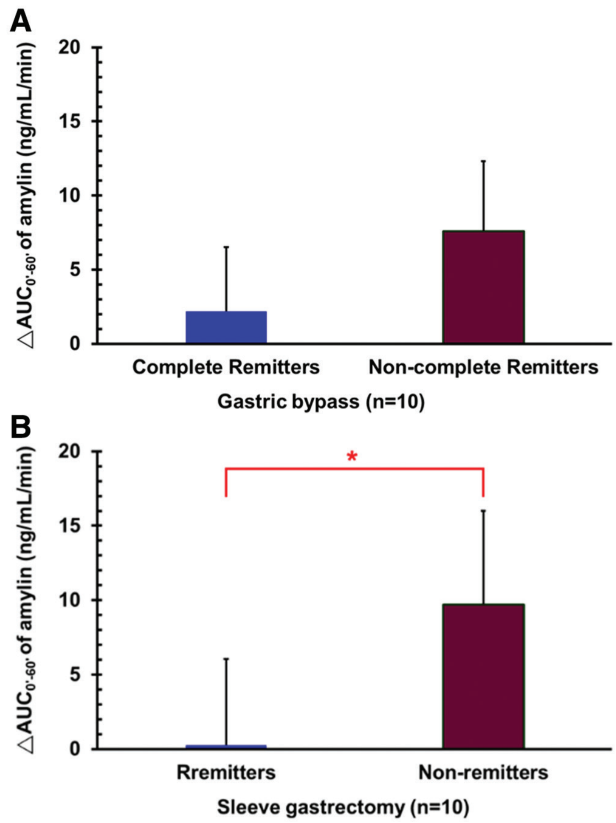

Fig. 3 Intragroup analyses of ΔAUC of plasma amylin after OGTT in the two groups. A, ΔAUC of plasma amylin (change in the plasma amylin level per minute) in the GB group at the initial 60 min after OGTT. B, ΔAUC of plasma amylin in the SG group at the initial 60 min after OGTT. ΔAUC, = the variation in area under the curve per minute; GB = gastric bypass; OGTT = oral glucose tolerance test; SG = sleeve gastrectomy. *$p < 0.05$. Statistical analysis with Mann–Whitney U test.

group or between remitters and nonremitters in the SG group. Furthermore, ΔAUC of plasma amylin (change in the plasma amylin level per minute) at the initial 60 minutes after OGTT presented no significant difference between complete remitters and noncomplete remitters in the GB group (Fig. 3A) while significantly higher in nonremitters than in remitters in the SG group ($p < 0.05$) (Fig. 3B).

4. DISCUSSION

The metabolic effect of bariatric surgery was already proven by several literature even though there are some other controversial viewpoints against it. Our previous studies have demonstrated the association with changes in some gut hormones, such as insulin, interleukin-1β, ghrelin, cholecystokinin, and resistin.[2,3,19,20] Apart from these hormones, plasma amylin has been well known for glycemic regulation and energy balance.[11] This is the first study to discuss the dynamic variation in amylin levels after bariatric surgery in patients with T2DM.

Obviously decreased BMI, waist circumference, hip circumference, HbA1c level, and HOMA-IR 1 year after either GB or SG were noted in our study, indicating the clinical effects of bariatric surgery in weight loss and glycemic control. More subjects presented remission of T2DM in the GB group than the SG group postoperatively, and the GB group had significantly lower HbA1c level than the SG group. A similar result was observed in previous studies.[2,3,19,20,22] Comparing the target hormone amylin in our study, the decreasing timepoint of amylin levels was 60–90 minutes after OGTT in the GB group and 30–60 minutes after OGTT in the SG group. Amylin usually acts as a satiation signal to slow gastric emptying and reduce food intake.[9] It could be inferred that the maintaining time of high amylin levels might be one of the key factors in glycemic control.

Amylin as an adipose signal is secreted by the pancreas in proportion to body adiposity. Hou et al[23] discovered the higher basal amylin levels in obese than in thin subjects, and the stimulated amylin response to OGTT was also more prominent in obese subjects.[24] Furthermore, it has been known for decades that obesity has a strong relationship with diabetes. It can be explained that plasma amylin levels after OGTT was higher in noncomplete remitters after GB and nonremitters after SG in our study. Hyperamylinemia in these patients may cause downregulation of amylin receptors and lead to amylin resistance, which would decrease the effect of postprandial amylin secretion on satiety and gastric emptying.[25] Higher plasma amylin levels may suggest the compensatory increase in the amylin level to overcome amylin resistance in nonremitters in the SG group. Additionally, the association between body weight change and alternation of plasma amylin in complete and noncomplete remitters of the GB group or in remitters and nonremitters of the SG group could not be identified because no significant difference of intragroup %TWL was detected.

Plasma amylin is physiologically coreleased with insulin in a consistent ratio in healthy nondiabetic subjects,[26] but our study only expressed partially comparable trend of postoperative amylin change with postoperative insulin secretion in our previous studies.[27,28] The phenomenon might be explained by altering feedback mechanisms of amylin and insulin by bariatric surgery. Moreover, amylin levels are thought to directly reflect changes in β-cell secretion,[29] so patients with T2DM may present with fluctuating amylin levels based on the pathology of β-cell dysfunction. Our study showed the comparable result that a greater fluctuation of plasma amylin levels was also observed in noncomplete remitters after GB and nonremitters after SG. Furthermore, Inoue et al[30] proved amylin release from perfused rat pancreas was stimulated by glucagon-like peptide 1 (GLP-1) ex vivo, while Asmar et al[31] proposed the concept of controlling metabolism by a multifactorial hormonal control system, and the plasma amylin level can be augmented by GLP-1. Lee et al[2] have demonstrated the changes of GLP-1 levels, increasing within 30 minutes provoked after mixed meal and decreasing since then, in subjects with T2DM after bariatric surgery. Our current study presented the corresponding trend of plasma amylin levels, especially observed in nonremitters in the SG group.

Our study presented normal and low postoperative fasting amylin concentrations in all healthy controls and type 2 diabetes patients. The result differs from the previous experiment,[32] in which increment in amylin concentrations in healthy adults and no significant change of amylin in type 1 diabetes patients after OGTT were observed. The incompatible results between the two studies might be derived from possible statistical errors in both small study sizes, diverse pathophysiologies in different types of diabetes (type 1 vs type 2), and ethnic causes which could affect glycemic control of diabetes patients.[33–35]

There are two major limitations in the present study. First, not all subjects had the intention of undergoing OGTT, so the small sample size might decrease the statistical power of the study and possibly result in a type II error. The difference in amylin levels either between the GB and SG groups or between remitters and nonremitters might become significant in a larger number of subjects. Second, there were significant differences in BMI and HOMA-IR between the two groups at baseline. The two parameters, especially HOMA-IR, might affect plasma amylin levels according to the above discussion. Nevertheless, the difference in HOMA-IR disappeared and no significant difference in %TWL between the two groups presented after bariatric surgery, and we could boldly infer that the differences might have little impact on the results in either intergroups or intragroup.

In conclusion, postoral glucose challenge amylin levels could be one of the parameters to evaluate T2DM remission after bariatric surgery, especially in those after SG. Future large cohort investigations including preoperative and postoperative plasma amylin values and associated basic studies are needed to identify the position of plasma amylin in T2DM remission after bariatric surgery.

ACKNOWLEDGMENTS

The authors would like to thank the Clinical Research Core Laboratory of Taipei Veterans General Hospital for providing experimental space and facilities, as well as grants from Min-Sheng General Hospital, Taoyuan, and Taipei Veterans General Hospital (V100C-077, V101C-118, V102C-019 and V103C-056), Taipei, Taiwan, the Cheng Hsin General Hospital and the National Yang-Ming University Joint Research Program (CY10824), Intramural grants of Cheng Hsin General Hospital [CHGH108-FA01, CHGH109-(N)07 and CHGH109-(N)17].

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