Neuropeptides 81 (2020) 102032

Contents lists available at ScienceDirect

Neuropeptides

journal homepage: www.elsevier.com/locate/npep

# Changes in post-oral glucose challenge pancreatic polypeptide hormone levels following metabolic surgery: A comparison of gastric bypass and sleeve gastrectomy

Ji Min Park[a,b], Ching-Feng Chiu[b,c], Shu-Chun Chen[d], Wei-Jei Lee[e,f], Chih-Yen Chen[g,h,i,j,k,*]

[a] School of Nutrition and Health Sciences, College of Nutrition, Taipei Medical University, Taipei, Taiwan
[b] Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, Taipei, Taiwan
[c] Nutrition Research Center, Taipei Medical University Hospital, Taipei, Taiwan
[d] Department of Nursing, Chang-Gung Institute of Technology, Taoyuan, Taiwan
[e] Department of Surgery, Min-Sheng General Hospital, Taoyuan, Taiwan
[f] Taiwan Society for Metabolic and Bariatric Surgery, Taipei, Taiwan
[g] Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[h] Bariatric and Metabolic Surgery Center, Taipei Veterans General Hospital, Taipei, Taiwan
[i] Faculty of Medicine and Institute of Emergency and Critical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan
[j] Taiwan Association for the Study of Small Intestinal Diseases, Guishan, Taiwan
[k] Chinese Taipei Society for the Study of Obesity, Taipei, Taiwan

## ARTICLE INFO

*Keywords:*
Gastric bypass
Oral glucose tolerance test
Pancreatic polypeptide
Sleeve gastrectomy
Type 2 diabetes mellitus

## ABSTRACT

*Background:* Pancreatic polypeptide (PP) hormone is a 36-amino-acid peptide released from the pancreas, the serum levels of which have been shown to rise upon food intake. The underlying mechanism for metabolic surgery in the treatment of patients with type 2 diabetes mellitus (T2DM) remains intriguing. We compared post-oral glucose challenge PP levels between patients undergoing laparoscopic gastric bypass (GB) and sleeve gastrectomy (SG) at 1 year after surgery.

*Methods:* This hospital-based, prospective study followed up a total of 12 laparoscopic GB and 12 laparoscopic SG patients and evaluated their glucose homeostasis. One year after metabolic surgery, 75-g oral glucose tolerance tests (OGTTs) were performed in the patients in the GB and SG groups and the blood levels of PP were evaluated.

*Results:* The laparoscopic GB group had stable serum PP levels within 120 min after OGTT; however, the levels were significantly higher in the laparoscopic SG group at 30 min after OGTT. The patients with complete T2DM remission did not exhibit significantly different PP levels at fasting and post-OGTT than those in patients without remission after GB. Similarly, after SG, patients with T2DM remission did not show significantly different PP levels at fasting and post-OGTT than those in patients without T2DM remission.

*Conclusions:* No significant difference was found in plasma PP levels after OGTT in T2DM patients that received either GB or SG, or in T2DM remitters or non-remitters 1 year after metabolic surgery.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a major global disease, with a prevalence expected to rise to 360 million by 2025 (Wild et al., 2004). Whereas simple obesity is associated with an increased risk of developing T2DM (Wang et al., 2019), its development also varies markedly according to body fat distribution. Central obesity or abdominal fat accumulation is one of the most important causes for lean individuals developing T2DM, especially among Asian populations, with higher intra-abdominal according to fat accumulation and lower muscle mass compared to those in Western populations (McKeigue et al., 1991; Ramachandran et al., 2012). With this rapid increase in prevalence, less than half of T2DM patients have achieved well-controlled status (glycated hemoglobin [HbA1c] $<$ 7%), indicating the urgent need to minimize long-term complications in patients with poorly-controlled T2DM and to develop new approaches to improve the outcomes of

---

[*] Corresponding author at: Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan R.O.C.

*E-mail address:* chency@vghtpe.gov.tw (C.-Y. Chen).

https://doi.org/10.1016/j.npep.2020.102032
Received 30 September 2019; Received in revised form 19 February 2020; Accepted 23 February 2020

diabetes care (Chen et al., 2013; Huang et al., 2019; Wu et al., 2019).

Our previous randomized study demonstrated that metabolic surgeries; namely, gastric bypass (GB) and sleeve gastrectomy (SG), are favorable options for treating non-morbidity obese patients (body mass index [BMI] < 35 kg/m$^2$) with poorly controlled T2DM (Lee et al., 2011a). The results of the study revealed more successful amelioration in T2DM patients with GB surgery than that in those with SG, as evidenced by significantly higher T2DM remission rates and lower waist circumference and glucose, HbA1c, and blood lipid levels than those in the SG group (Lee et al., 2011b, Lee et al., 2011c). However, the underlying mechanism of T2DM remission after metabolic surgery remains intriguing.

Pancreatic polypeptide (PP) is a 36-amino-acid peptide secreted by the F-cells of the endocrine pancreas. In humans, increased PP circulation has been observed after ingestion of a meal, whereas reduced postprandial PP secretion was found among individuals with morbid obesity, indicating the potential role for PP in the development of obesity (Adrian et al., 1976; Lieverse et al., 1994). Furthermore, previous studies have reported unusually high plasma concentrations of PP among the Pima Indians of Arizona, who exhibit high obesity and T2DM prevalence rates compared to those worldwide (Knowler et al., 1981; Vozarova de Courten et al., 2004; Koska et al., 2004). De Courten et al. demonstrated a dose-dependent reduction in adjusted insulin and PP secretion with increasing doses of atropine, an agent that improves insulin sensitivity, indicating that PP may play an important role in insulin responses (Vozarova de Courten et al., 2004; Walter et al., 2012). Based on these findings, we hypothesized that PP secretion might contribute to diabetes remission, which may play an important role in achieving higher remission rates among T2DM patients with GB than those with SG surgery.

The present study was designed to explore whether PP secretion is associated with insulin sensitivity and diabetes remission achievement. We performed 75-g oral glucose tolerance test (OGTT) in patients in GB and SG groups followed up at 1 year after surgery. We examined the fasting and postprandial secretion of PP in both patient groups and explored the potential underlying mechanisms associated with diabetes remission to gain additional insight into the different remission rates of diabetes.

## 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 at the Department of Surgery of Min-Sheng General Hospital and Taipei Veterans General Hospital and was approved by the Ethics Committees of both hospitals. Bariatric surgery with laparoscopic GB and SG were performed as previously described (Lee et al., 2011a). We included patients who met the following criteria: (1) onset of T2DM of > 6 months with hemoglobin A1c (HbA1c) level ≥ 8% under intensive medical care; (2) BMI ≥25 kg/m$^2$, the optimal cut-off value for obesity in Asian populations as suggested by the International Obesity Task Force, 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. Patients with underlying malignancy and active pulmonary tuberculosis, who were human immunodeficiency virus-positive, who underwent previous gastrointestinal surgery, and who presented uncooperative conditions were excluded. Twenty four of 60 patients (GB, $n = 12$; SG, $n = 12$) who agreed to undergo the OGTT were recruited in this trial. 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 a fasting glucose level of 100–125 mg/dL and HbA1c level < 6.5%, while complete remission was defined as a fasting glucose level < 100 mg/dL and normal HbA1c range (< 6.0%) (Lee et al., 2011b). We defined patients with T2DM who achieved either complete remission or partial remission at 1 year after bariatric surgery as remitters. In contrast, those patients who failed to achieve remission were defined as non-remitters (Chen et al., 2013, Lee et al., 2011c).

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

The recruited subjects were required to fast before blood samples were taken and underwent anthropometric measurements and routine laboratory tests, including plasma glucose level, insulin, and HbA1c. 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, as described by us previously (Chen et al., 2013). We used the 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 PP (Bertin Pharma, Montigny le Bretonneux, France) were performed in a blinded and single batch run, similar to our previous study (Chen et al., 2013, Lee et al., 2011a).

### 2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 12.01 (SPSS, Inc., Chicago, Illinois). Continuous variables were expressed as means ± standard deviation (SD) or median and interquartile ranges. Chi-square or Fisher's exact tests were used to compare remission rates and categorical variables, while Mann–Whitney *U* tests were used to compare continuous variables. Wilcoxon signed-rank tests were used to compare baseline and postoperative variables. Friedman's one-way analysis of variance followed by post hoc tests were used to analyze the differences among plasma PP levels at 0, 30, 60, 90, and 120 min after 75-g OGTT 1 year postoperatively. Statistical significance was set at a $P < .05$.

## 3. Results

### 3.1. Comparison of T2DM patients after GB and SG

The patients' preoperative characteristics, including demographic data, smoking habits, duration of diabetes, HbA1c, insulin, and HOMA-IR levels, were comparable before GB and SG (Table 1). There were no

**Table 1**
Baseline characteristics of T2DM patients before GB and SG.

| Characteristics | GB | SG | P value |
|---|---|---|---|
| | ($n = 12$) | ($n = 12$) | |
| Age (years) | 44.1 ± 8.3 | 46.5 ± 8.6 | 0.563 |
| Sex (male/female) | 6/6 | 5/7 | 0.680 |
| Smoking (yes/no) | 5/7 | 3/9 | 0.663 |
| BMI (kg/m$^2$) | 28.8 ± 3.2 | 30.8 ± 3.1 | 0.100 |
| Waist circumference (cm) | 96.8 ± 10.7 | 100.5 ± 15.6 | 0.298 |
| Hip circumference (cm) | 104.0 ± 5.8 | 103.2 ± 16.5 | 0.488 |
| Waist-to-hip ratio | 0.93 ± 0.07 | 0.98 ± 0.04 | 0.141 |
| Duration of T2DM (years) | 6.6 ± 6.2 | 6.4 ± 4.6 | 0.794 |
| HbA1c (%) | 9.7 ± 2.0 | 10.1 ± 2.4 | 0.908 |
| Insulin (μU/mL) | 7.1 (3.7–15.5) | 13.7 (3.8–29.9) | 0.470 |
| HOMA-IR | 4.0 (1.6–5.6) | 10.3 (3.5–14.2) | 0.089 |

Data expressed as mean ± SD or median (interquartile ranges).
Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR; homeostasis model assessment-insulin resistance; GB, gastric bypass; SG, sleeve gastrectomy; T2DM, type 2 diabetes mellitus.

**Table 2**
Outcomes one year after GB and SG.

| Characteristics | GB<br>(n = 12) | SG<br>(n = 12) | P value |
|---|---|---|---|
| BMI (kg/m$^2$) | 22.8 ± 2.6 | 23.8 ± 2.4 | 0.236 |
| Waist circumference (cm) | 80.7 ± 8.1 | 84.1 ± 4.2 | 0.260 |
| Hip circumference (cm) | 93.4 ± 5.4 | 96.1 ± 6.0 | 0.840 |
| Waist-to-hip ratio | 0.86 ± 0.06 | 0.90 ± 0.03 | 0.112 |
| Wight loss (kg) | 16.1 ± 5.4 | 18.9 ± 7.8 | 0.794 |
| HbA1c (%) | 5.8 ± 0.6 | 7.3 ± 1.7 | 0.012 |
| Insulin (μU/mL) | 4.8 ± 4.4 | 4.5 ± 2.9 | 0.436 |
| HOMA-IR | 1.3 ± 1.3 | 1.6 ± 1.4 | 0.298 |

Data are means ± SD; Chi-square or Fisher's exact tests were used to compare categorical variables, while Student's *t*- or Mann–Whitney tests were used to compare continuous data.
Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR; homeostasis model assessment-insulin resistance; GB, gastric bypass; SG, sleeve gastrectomy; T2DM, type 2 diabetes mellitus.

significant differences in baseline characteristics between the two surgical groups.

At 1 year after surgery, there was no significant difference in BMI, waist-to-hip ratio, weight loss, insulin, and HOMA-IR between the two surgical groups (Table 2). However, the diabetes remission rate was significantly higher in the GB than that in the SG group, where six laparoscopic GB patients achieved complete and partial remission, respectively, while six laparoscopic SG patients achieved partial remission and others have failed to achieve remission (100% vs 50%; $P = .002$, chi-square test). HbA1c levels in GB patients were also significantly lower than those in SG patients ($P = .012$; Table 2).

### *3.2. Plasma PP concentrations in GB and SG patients*

To further investigate the underlying mechanism associated with T2DM remission, 75-g oral glucose tolerance tests (OGTTs) were performed in the patients in the GB and SG groups at 1 year after metabolic surgery; additionally, the PP levels were also measured. The results revealed that there were no significant differences in plasma PP levels at fasting between the two groups (Fig. 1). During the 75-g OGTT, no significant change in PP concentrations was observed in the GB group (Fig. 1A), whereas plasma PP concentrations in the SG group increased significantly from 0.5 ng/mL at fasting to 1 ng/mL at 30 min post-oral glucose challenge ($P < .05$; Fig. 1B; Friedman's one-way analysis of variance followed by a Tukey's post-hoc test). At 120 min, there was a reduction in PP level in the SG patients but no statistically significant difference was found.

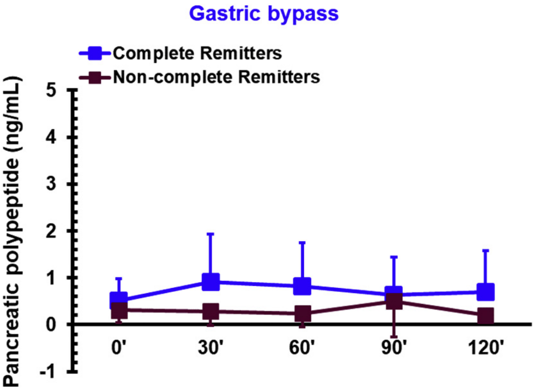

**Fig. 2.** Influences of OGTT on plasma pancreatic polypeptide levels in complete remitters (*n* = 6) and non-complete remitters (*n* = 6) after GB surgery. Continuous variables were expressed as means ± SD. OGTT, oral glucose tolerance test; GB, gastric bypass.

### *3.3. Plasma PP concentrations in GB patients with complete T2DM and non-complete remission*

Among the 12 patients, 50% of T2DM patients achieved complete T2DM remission at 1 year after GB. Throughout OGTT, both complete and non-complete remitters in the GB group showed no significant change in PP concentration during post-oral glucose challenge, with plasma PP levels stable throughout the test (Fig. 2). Although the basal PP level in complete remitters was slightly higher than that in those without complete remission during 75-g OGTT, the difference between the two groups was not statistically significant.

Next, we examined PP levels among remitters and non-remitters in the SG group at 1 year after surgery (Fig. 3). As only one subject in the SG group achieved complete remission, the PP levels in the SG were not comparable between complete remitters and non-complete remitters. Thus, we grouped those patients with complete (*n* = 1) or partial remission (*n* = 5) as “remitters” and those who did not achieve remission (*n* = 6) as “non-remitters” and compared the changes in PP secretion between these groups. The results revealed lower PP levels in remitters than those in the non-remitters at fasting and throughout the OGTT (Fig. 3). The difference showed a strong trend but did not reach statistical significance. The change was greater in non-remitters than that in remitters, where the PP level in non-remitters increased between 0 and 30 min but slowly dropped during OGTT. In contrast, the PP concentration in remitters remained stable over the entire OGTT.

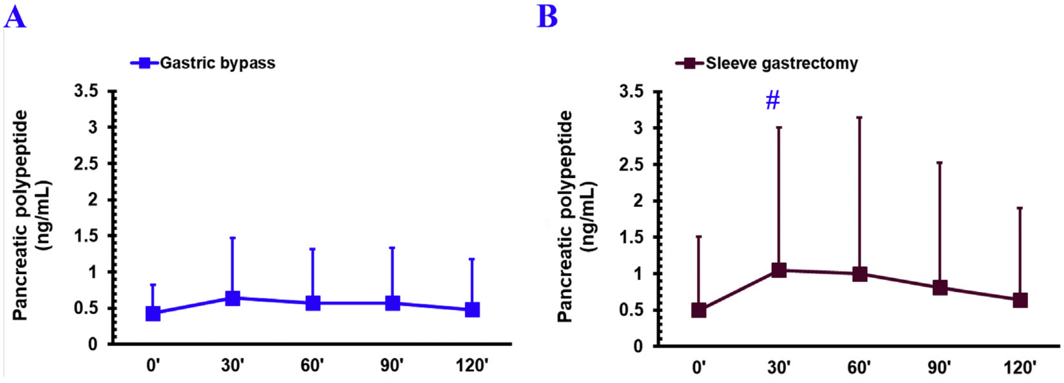

**Fig. 1.** Plasma pancreatic polypeptide concentrations in (A) GB and (B) SG patients during a 75-g OGTT at a year after the surgery. #$P < .05$; 0 min versus 30 min in SG group. Continuous variables were expressed as mean ± SD. Friedman's one-way analysis of variance followed by a Tukey's post-hoc test was used to analyze the differences among groups. OGTT, oral glucose tolerance test; GB, gastric bypass; SG, sleeve gastrectomy.

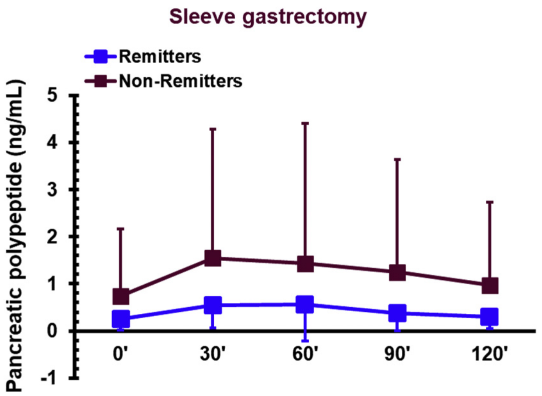

**Fig. 3.** Influences of OGTT on plasma pancreatic polypeptide levels in remitters ($n = 6$) and non-complete remitters ($n = 6$) after SG surgery. Continuous variables were expressed as means ± SD. OGTT, oral glucose tolerance test; SG, sleeve gastrectomy.

## 4. Discussion

A previous randomized trial demonstrated that gastrointestinal metabolic surgeries, namely GB and SG, are effective for the treatment of Asian non-morbidity obese patients (BMI $< 35\ \text{kg/m}^2$) with poorly controlled T2DM (Lee et al. 2011). At 1 year after surgery, both GB and SG groups showed reductions in fasting blood glucose and HbA1c levels as well as insulin resistance and strong improvement in blood pressure and lipid profiles (Chen et al., 2013). T2DM patients with GB, however, revealed more successful amelioration than that in those with SG, as evidenced by higher remission rates (100% vs. 50%) and lower HbA1c level (5.8 ± 0.6% vs. 7.3 ± 1.6%; $P = .012$) than those in the SG group. Most importantly, a year after GB surgery led to achieve well-controlled status as defined by an HbA1c < 7%, implying that GB surgery may be more effective in achieving successful diabetes remission than SG surgery.

PP is a major gut hormone responsible for regulating appetite and satiety as well as energy expenditure. Although the physiological role of PP has not been entirely elucidated, several studies have demonstrated the association between PP concentration and T2DM (Knowler et al., 1981; Vozarova de Courten et al., 2004; Walter et al., 2012; Maxwell et al., 2014). PP concentration may also be an indicator of insulin sensitivity, as both adjusted insulin and PP secretion were reduced dose-dependently with increasing atropine dose (Vozarova de Courten et al., 2004). The current study, therefore, compared PP levels during OGTT between patients with T2DM who underwent GB or SG to explore mechanisms underlying diabetes improvement after metabolic surgery. We also investigated the potential correlations between changes in PP level and achievement of diabetes remission.

In our study, the fasting PP levels in both surgical groups reached nearly 500 pg/mL. The reported fasting serum levels of PP in normal subjects and patients with diabetes were < 100 and < 200 pg/mL, respectively; thus, our findings revealed noticeably higher plasma PP concentration in those patients than that of normal and of diabetic patients described in previous studies (Floyd et al., 1976, Matsumoto et al., 1982, Walter et al., 2012, Hart et al., 2015). Although the exact cause of the abnormally elevated level of PP in both surgical groups remains unclear, several studies have proposed that PP overexpression may lead to reduced food intake, resulting in excess weight loss (Roberts et al., 2015). High circulating levels of PP may modulate gastrointestinal functions by inducing anorexigenic hypothalamic peptides and suppressing gastric ghrelin release, which may benefit patients with diabetes (McTigue et al., 1993; Asakawa et al., 2003; Chen et al., 2010; Huang et al., 2018). As both GB and SG groups showed a marked reduction in body weight and low BMI at 1 year postoperatively, the high circulating PP level was likely related to the body weight loss of T2DM patients after such surgical interventions. The similar f PP levels in the GB and SG groups may explain why there were no significant differences in body weight and BMI between those groups.

In addition, an elevated PP level may be positively associated with insulin secretion (Mandarino et al., 1981; D'Alessio et al., 1989; Kim et al., 2014; Roberts et al., 2015). For this reason, several studies hypothesized that the increased PP concentrations observed in diabetes patients may be due to compensatory mechanisms to stimulate insulin secretion and improve glycemic control (Floyd et al., 1976; Kim et al., 2014; Roberts et al., 2015). Rabiee et al., also suggested that PP plays a role in glucose homeostasis by demonstrating that subcutaneous administration of PP resulted in increased insulin sensitivity and reduced insulin requirements in diabetes patients (Rabiee et al., 2011). Our results also revealed that insulin levels were reduced at a year after the metabolic surgeries (GB, 4.8 ± 4.4 μU/mL; SG, 4.5 ± 2.9 μU/mL) which positively correlated with low HOMA-IR values for estimating insulin resistance. Elevated basal levels of PP at 1 year postoperatively, thus, may indicate that both laparoscopic GB and SG could ameliorate insulin signaling and improve insulin resistance, which also supports that both surgeries are effective in the treatment of patients with T2DM who have failed current medical treatment.

We next examined the potential role of PP in the higher remission rate for GB than that for SG. Although the basal PP levels were similar between the GB and SG groups, the change in PP concentration was greater in the SG group than that in the GB group. A significant increase in PP level was observed during OGTT between fasting and 30 min in the SG group, and then declined at 120 min. Unlike the dynamic change in the PP level observed in the SG group, the PP level remained consistent in the GB group, which may be associated with the mechanisms of diabetes remission after metabolic surgery. PP response to complete and non-complete remitters in the GB group also showed a similar trend, remaining stable during OGTT. No significant difference was observed between the complete and non-complete remitters.

The T2DM remitters in the SG group also demonstrated consistent PP secretion from fasting to post-OGTT at 120 min, with levels below 0.6 ng/mL. In contrast, the non-remitters in this group showed increased PP secretion during OGTT starting from 30 min, reaching above 1 ng/mL and remaining high over time. While the difference showed a strong trend, it did not reach statistical significance.

In summary, no significant difference was found in plasma PP levels after OGTT in either T2DM patients that received GB or SG, or in T2DM complete remitters or non-complete remitters 1 year after metabolic surgery. However, high fasting PP level and significant improvements in insulin resistance at a year after following surgeries strengthen the previous notion that PP may be positively correlated with insulin secretion. There are several limitations of our study. First, we have a small sample size used for analyses, which may lead to potential type II error (Hackshaw, 2008). Second, we have not measured serum *P* value before metabolic surgeries, which halts from making a direct comparison among participants. Third, previous study suggested that serum PP level is mainly affected by protein or mixed meal intake (Norris and Carr, 2013), explaining the potential cause of stable PP concentration during OGTT. More studies are needed to elucidate the role of PP secretion in the mechanism of T2DM remission.

## Author statement

I have no any conflict of interest.

## Funding

This work was supported by intramural grants from Taipei Veterans General Hospital, Taipei, Taiwan (V100C-077, V101C-118, V102C-019, and V103C-056).

## Declaration of Competing Interest

None.

## References

Adrian, T.E., Bloom, S.B., Bryant, M.G., Polak, J.M., Heitz, P.H., Barnes, A.J., 1976. Distribution and release of human pancreatic polypeptide. Gut 17 (12), 940–944.

Asakawa, A., Inui, A., Yuzuriha, H., Ueno, N., Katsuura, G., Fujimiya, M., Fujino, M.A., Niijima, A., Meguid, M.M., Kasuga, M., 2003. Characterization of the effects of pancreatic polypeptide in the regulation of energy balance. Gastroenterology 124 (5), 1325–1336.

Chen, C.Y., Fujimiya, M., Laviano, A., Chang, F.Y., Lin, H.C., Lee, S.D., 2010. Modulation of ingestive behavior and gastrointestinal motility by ghrelin in diabetic animals and humans. J. Chin. Med. Assoc. 73 (5), 225–229.

Chen, C.Y., Lee, W.J., Asakawa, A., Fujitsuka, N., Chong, K., Chen, S.C., Lee, S.D., Inui, A., 2013. Insulin secretion and interleukin-1β dependent mechanisms in human diabetes remission after metabolic surgery. Curr. Med. Chem. 20 (8), 2374–2388.

D'Alessio, D.A., Sieber, C., Beglinger, C., Ensinck, J.W., 1989. A physiologic role for somatostatin 28 as a regulator of insulin secretion. J. Clin. Invest. 84 (3), 857–862.

Floyd, J.C., Fajans, S.S., Pek, S., Chance, R.E., 1976. A newly recognized pancreatic polypeptide; plasma levels in health and disease. Recent Prog. Horm. Res. 33, 519–570.

Hackshaw, A., 2008. Small studies: strengths and limitations. Eur. Respir. J. 32 (5), 1141–1143.

Hart, P.A., Baichoo, E., Bi, Y., Hinton, A., Kudva, Y.C., Chari, S.T., 2015. Pancreatic polypeptide response to a mixed meal is blunted in pancreatic head cancer associated with diabetes mellitus. Pancreatology 15 (2), 162–166.

Huang, H.H., Lee, Y.C., Chen, C.Y., 2018. Effects of burns on gut motor and mucosa functions. Neuropeptides 72, 47–57.

Huang, H.H., Lee, W.J., Chen, S.C., Chen, T.F., Lee, S.D., Chen, C.Y., 2019. Bile acid and fibroblast growth factor 19 regulation in obese diabetes, and non-alcoholic fatty liver disease after sleeve gastrectomy. J. Clin. Med. 8 (6), E815.

Kim, W., Fiori, J.L., Shin, Y.K., Okun, E., Kim, J.S., Rapp, P.R., Egan, J.M., 2014. Pancreatic polypeptide inhibits somatostatin secretion. FEBS Lett. 588 (17), 3233–3239.

Knowler, W.C., Pettitt, D.J., Savage, P.J., Bennett, P.H., 1981. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. Am. J. Epidemiol. 113 (2), 144–156.

Koska, J., Delparigi, A., de Courten, B., Weyer, C., Tataranni, P.A., 2004. Pancreatic polypeptide is involved in the regulation of body weight in pima Indian male subjects. Diabetes 53 (12), 3091–3096.

Lee, W.J., Chen, C.Y., Chong, K., Lee, Y.C., Chen, S.C., Lee, S.D., 2011a. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. Surg. Obes. Relat. Dis. 7 (6), 683–690.

Lee, W.J., Chong, K., Chen, C.Y., Chen, S.C., Lee, Y.C., Ser, K.H., Chuang, L.M., 2011b. Diabetes remission and insulin secretion after gastric bypass in patients with body mass index < 35 kg/m 2. Obes. Surg. 21 (7), 889–895.

Lee, W.J., Chong, K., Ser, K.H., Lee, Y.C., Chen, S.C., Chen, J.C., Tsai, M.H., Chuang, L.M., 2011c. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Arch. Surg. 146 (2), 143–148.

Lieverse, R.J., Masclee, A.A., Jansen, J.B., Lamers, C.B., 1994. Plasma cholecystokinin and pancreatic polypeptide secretion in response to bombesin, meal ingestion and modified sham feeding in lean and obese persons. Int. J. Obes. Relat. Metab. Disord. 18 (2), 123–127.

Mandarino, L., Stenner, D., Blanchard, W., Nissen, S., Gerich, J., Ling, N., Brazeau, P., Bohlen, P., Esch, F., Guillemin, R., 1981. Selective effects of somatostatin-14,-25 and-28 on in vitro insulin and glucagon secretion. Nature 291 (5810), 76–77.

Matsumoto, M., Wakasugi, H., Ibayashi, H., 1982. Plasma human pancreatic polypeptide response in chronic pancreatitis. Gastroenterol. Jpn. 17 (1), 25–30.

Maxwell, J., O'dorisio, T.M., Bellizzi, A.M., Howe, J.R., 2014. Elevated pancreatic polypeptide levels in pancreatic neuroendocrine tumors and diabetes mellitus: causation or association? Pancreas 43 (4), 651–656.

McKeigue, P.M., Shah, B., Marmot, M.G., 1991. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in south Asians. Lancet 337 (8738), 382–386.

McTigue, D.M., Edwards, N.K., Rogers, R.C., 1993. Pancreatic polypeptide in dorsal vagal complex stimulates gastric acid secretion and motility in rats. Am. J. Phys. 265 (6 pt 1), G1169–G1176.

Norris, D.O., Carr, J.A., 2013. Vertebrate Endocrinology, Fifth ed. Elsevier-Academic Press, Amsterdam, pp. 483–500 Ch3.

Rabiee, A., Galiatsatos, P., Salas-Carrillo, R., Thompson, M.J., Andersen, D.K., Elah, I.D., 2011. Pancreatic polypeptide administration enhances insulin sensitivity and reduces the insulin requirement of patients on insulin pump therapy. J. Diabetes Sci. Technol. 5 (6), 1521–1528.

Ramachandran, A., Snehalatha, C., Shetty, A.S., Nanditha, A., 2012. Trends in prevalence of diabetes in Asian countries. World J. Diabetes 3 (2), 110–117.

Roberts, R.O., Aakre, J.A., Cha, R.H., Kremers, W.K., Mielke, M.M., Velgos, S.N., Geda, Y.E., Knopman, D.S., Petersen, R.C., 2015. Association of pancreatic polypeptide with mild cognitive impairment varies by APOE ε4 allele. Front. Aging Neurosci. 7, 172.

Vozarova de Courten, B., Weyer, C., Stefan, N., Horton, M., DelParigi, A., Havel, P., Bogardus, C., Tataranni, P.A., 2004. Parasympathetic blockade attenuates augmented pancreatic polypeptide but not insulin secretion in Pima Indians. Diabetes 53 (3), 663–671.

Walter, T., Chardon, L., Chopin-laly, X., Raverot, V., Caffin, A.-G., Chayvialle, J.-A., Scoazec, J.-Y., Lombard-Bohas, C., 2012. Is the combination of chromogranin a and pancreatic polypeptide serum determinations of interest in the diagnosis and follow-up of gastro-entero-pancreatic neuroendocrine tumours? Eur. J. Cancer 48 (2), 1766–1773.

Wang, W., Fann, C.S.J., Yang, S.H., Chen, H.H., Chen, C.Y., 2019. Weight loss and metabolic improvements in obese patients undergoing gastric banding and gastric banded plication: a comparison. Nutrition 57, 290–299.

Wild, S., Roglic, G., Green, A., Sicree, R., King, H., 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27 (5), 1047–1053.

Wu, W.C., Lee, W.J., Yeh, C., Chen, S.C., Chen, C.Y., 2019. Impacts of different modes of bariatric surgery on plasma levels of hepassocin in patients with diabetes mellitus. Reports 2 (4), 24.