Received: 9 January 2019 | Revised: 5 February 2019 | Accepted: 15 February 2019

DOI: 10.1111/dom.13676



WILEY

BRIEF REPORT

# Role of vagal activation in postprandial glucose metabolism after gastric bypass in individuals with and without hypoglycaemia

Marzieh Salehi MD[1,2,3] | Amalia Gastaldelli PhD[4] | David A. D'Alessio MD[1,5]

[1]Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

[2]Division of Diabetes, University of Texas at San Antonio, San Antonio, Texas

[3]Bartter Research Unit, Audie Murphy Hospital, South Texas Veteran Health Care System, San Antonio, Texas

[4]Cardiometabolic Risk Unit, CNR Institute of Clinical Physiology, Pisa, Italy

[5]Division of Endocrinology, Duke University Medical Center, Durham, North Carolina

**Correspondence**
Marzieh Salehi MD, University of Texas Health at San Antonio, Department of Medicine, Division of Diabetes, 7703 Floyd Curl Drive, Mail code 7886, San Antonio, TX 78229.
Email: salehi@uthscsa.edu

**Funding information**
This work was supported by grants from the National Institute of Health, DK105379 (M.S.), DK083554 (M.S.), and DK101991 (D.A.D) and in part by the National Center for Advancing Translational Sciences, National Institute of Health grant 8 UL1 TR000077.

**Peer Review**
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13676.

Patients who have undergone gastric bypass surgery (GB) have enhanced postprandial hyperinsulinaemia and a greater incretin effect is apparent. In the present study, we sought to determine the effect of vagal activation, a neural component of the enteroinsular axis, on postprandial glucose metabolism in patients with and without hypoglycaemia after GB. Seven patients with documented post-GB hypoglycaemia, seven asymptomatic patients without hypoglycaemia post-GB, and 10 weight-matched non-surgical controls with normal glucose tolerance were recruited. Blood glucose, and islet hormone and incretin secretion were compared during mixed meal tolerance tests (MMTs) with and without prior sham-feeding on two separate days. Sham feeding preceding the MMT caused a more rapid increase in prandial blood glucose levels but lowered overall glycaemia in all three groups ($P < 0.05$). Sham feeding had a similar effect to increase early ($P < 0.05$), but not overall, meal-induced insulin secretion in the three groups. Prandial glucagon concentrations were significantly greater in the GB groups, and sham feeding accentuated this response ($P < 0.05$). The effect of vagal activation on prandial glucose and islet-cell function is preserved in patients who have undergone GB, in those both with and without hypoglycaemia.

KEYWORDS

β-cell function, bariatric surgery, hypoglycaemia, incretin physiology

## 1 | INTRODUCTION

The use of bariatric surgery in clinical practice has increased over the past two decades because it is the most effective intervention for weight loss, and has profound immediate effects on glucose metabolism.[1] Procedures such as gastric bypass surgery (GB) induce diabetes remission in up to 50% of affected patients.[2,3] Surgical rearrangement of the gastrointestinal (GI) tract with GB causes rapid passage of nutrients into the small bowel, increased rates of nutrient appearance into the circulation,[4] and augmented postprandial glycaemic peaks[4]; however, people who have undergone GB have enhanced insulin secretion that contributes to rapid and efficient glucose clearance.[4–6] It is likely that improved β-cell function contributes to the rapid improvement in diabetes after surgery; however, in a subset of patients, this effect is exaggerated, causing a syndrome of hyperinsulinaemic postprandial hypoglycaemia.[5,7]

Augmentation of prandial insulin secretion after GB has been attributed to greater glycaemic stimulus and also to the effects of insulinotropic factors released from the gut.[6] There is evidence of increased stimulation by the incretin glucagon-like peptide-1 (GLP-1) after GB,[8] but it is not clear whether this explains the entirety of enhanced β-cell secretion after surgery or whether other regulatory factors account for the pathological insulin responses in patients with post-GB hypoglycaemia .

It has long been known that the central nervous system (CNS) regulates islet hormone secretion. An early demonstration of neural regulation of insulin release was in rats fed sham meals, or entrained to stimuli related to eating.[9] This response, termed cephalic insulin

  

release, has also been demonstrated in humans,[10,11] and can improve glucose tolerance.[10,12] Both cephalic[11] and prandial[10] insulin secretion is mediated in great part by parasympathetic stimuli carried in the vagus nerve.[9,12–14] It is clear that GB has substantial effects on brain centres controlling feeding behaviour[15]; thus, it is plausible that the CNS also affects islet hormone release after surgery.

## 2 | METHODS

In the present study we tested the hypothesis that cephalic insulin secretion is retained after GB, but differs post-surgery between patients with and without hypoglycaemia (see Supporting Information for study methods).

## 3 | RESULTS

### 3.1 | Patient characteristics

Patients with post-GB hypoglycaemia (HGB) and asymptomatic patients who had undergone GB (AGB) had similar values for age, preoperative body mass index (BMI), total weight loss, and time since GB. Participants in the control group (CN) had similar BMI and glycated haemoglobin values as the surgical groups, although they were younger (Table S1). Measured waist circumference, fat mass and lean mass were not significantly different among the three groups (Table S1).

### 3.2 | Glycaemic response during meal studies

Fasting glucose levels were similar in the three groups (Table 1). After meal ingestion the rise in blood glucose diverged significantly between the GB group and the non-operated control group as early as 8 minutes after the meal, leading to larger area under the curve $(AUC)_{glucose(0,30min)}$ in the surgical groups; this is a well described characteristic of GB. Despite altered glucose responses in the GB groups, $AUC_{glucose(0,180min)}$ was not different between the AGB and control groups (Figure 1A). During the MMT studies all patients in the HGB group became symptomatic coincident with low blood glucose levels within 60 to 120 minutes from meal ingestion. As a result, their overall glucose response ($AUC_{glucose[0,180min]}$) was significantly less than that of the other two groups (Figure 1A), neither of which included

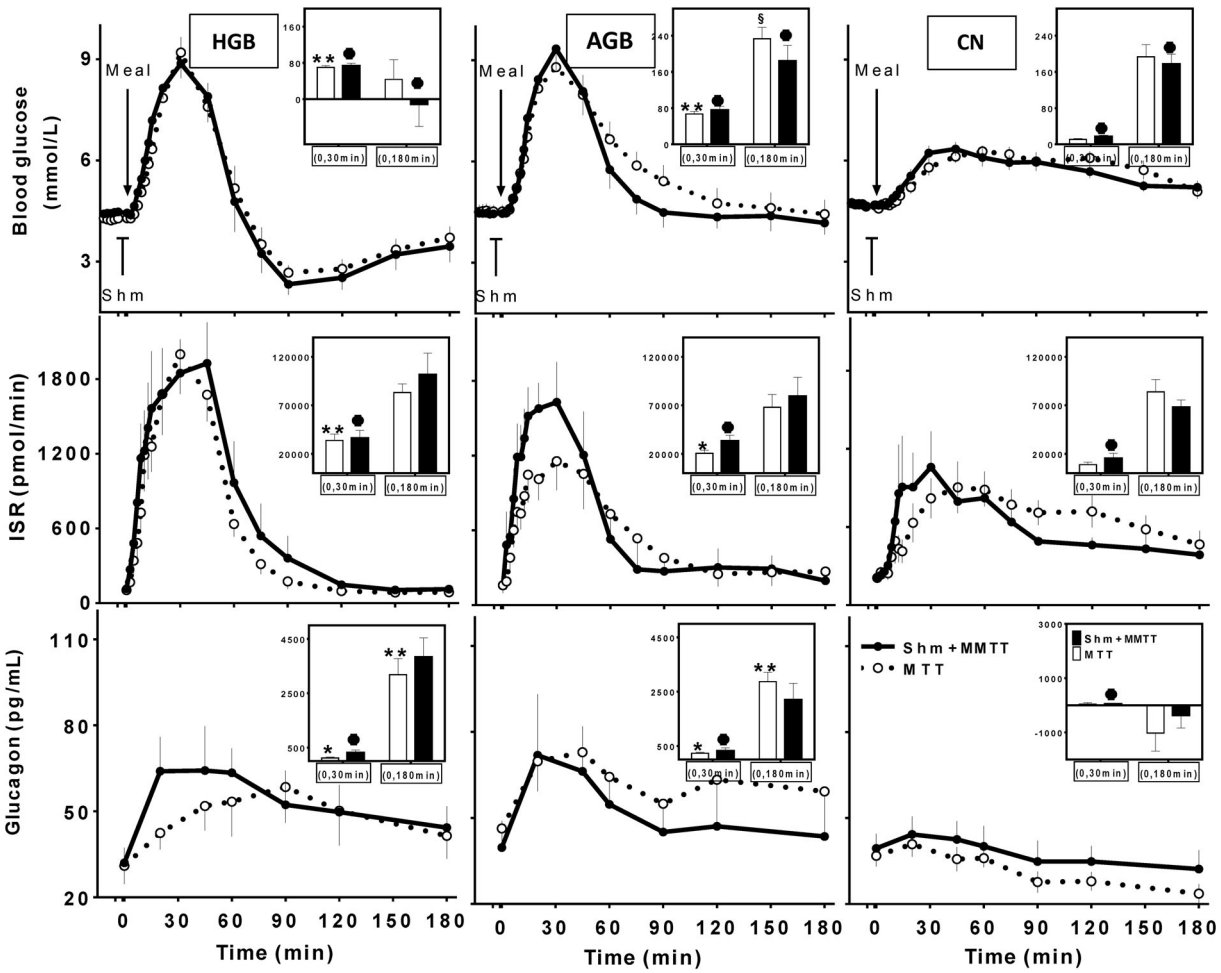


**FIGURE 1** Blood glucose, insulin and glucagon secretory response to meal ingestion preceded by a sham feeding (Shm + MMT, solid line, black bar) or not (MMT, dotted line, white bar) among patients with documented hypoglycemia after gastric bypass (HGB) and those subjects with history of gastric bypass without hypoglycaemia (AGB) as well as non-operated controls (CN). The corresponding areas under curve values for both 0 to 30 minutes as well as the entire study (0 to 180 minutes) are shown (insets). Data are presented as mean ± SEM. *$P$ < 0.05, **$P$ < 0.01 vs control group and § $P$ < 0.01 vs HGB group (group effect), $P$ < 0.05 vs MMT alone (sham feeding effect). ISR, insulin secretion rate

**TABLE 1** Blood glucose and islet-cell response during meal ingestion with and without preceding sham feeding among patients with hypoglycaemia after gastric bypass (HGB), asymptomatic patients after gastric bypass (AGB) and non-operated healthy controls (CN)

| | MMT | | | Shm + MMT | | | *P* values | | |
|---|---|---|---|---|---|---|---|---|---|
| | HGB | AGB | CN | HGB | AGB | CN | Day | Group | Day* Group |
| Fasting glucose (mmol/L) | 4.3 ± 0.2[b] | 4.5 ± 0.2 | 4.7 ± 0.1 | 4.4 ± 0.1 | 4.5 ± 0.1 | 4.7 ± 0.1 | 0.527 | 0.200 | 0.245 |
| Time to reach peak glucose (min) | 32.1 ± 2.1[a] | 39.3 ± 8.9[a] | 66.5 ± 10 | 32.9 ± 3.4 | 27.1 ± 1.8 | 40.5 ± 3.9 | 0.009 | 0.014 | 0.050 |
| Time to reach nadir glucose (min) | 98.6 ± 7.9[b] | 158.6 ± 16.9[c] | 153 ± 12.2 | 92.1 ± 7.6 | 128.6 ± 15.6 | 144 ± 14 | 0.118 | 0.004 | 0.555 |
| Nadir glucose (mmol/L) | 2.4 ± 0.3[b] | 4.4 ± 0.4[d] | 5 ± 0.2 | 2.1 ± 0.2 | 3.9 ± 0.3 | 4.9 ± 0.1 | 0.007 | 0.000 | 0.387 |
| Peak glucose (mmol/L) | 9.3 ± 0.5[b] | 9.1 ± 0.4[b] | 6.6 ± 0.2 | 9.1 ± 0.5 | 9.6 ± 0.5 | 6.6 ± 0.2 | 0.394 | 0.000 | 0.117 |
| Glucose excursion (mmol/L) | 6.9 ± 0.4[b] | 4.7 ± 0.8[c] | 1.6 ± 0.2 | 7 ± 0.5 | 5.6 ± 0.8 | 1.7 ± 0.2 | 0.007 | 0.000 | 0.047 |
| Fasting insulin (pmol/L) | 32.3 ± 4.8[a] | 50.4 ± 13.6 | 101.9 ± 22.5 | 35.3 ± 4.4 | 49.8 ± 11.9 | 101.5 ± 17.2 | 0.900 | 0.010 | 0.968 |
| Fasting ISR (pmol/min) | 104.5 ± 17.7 | 159.6 ± 63.1 | 209.7 ± 38.1 | 115.1 ± 24.5 | 156 ± 38 | 217.2 ± 51.7 | 0.723 | 0.226 | 0.911 |
| Time to reach peak ISR (min) | 47.1 ± 2.1[b] | 47.9 ± 9.7[b] | 99 ± 11.7 | 49.3 ± 2.8 | 41.4 ± 4.8 | 64.5 ± 8.4 | 0.036 | 0.001 | 0.032 |
| Peak ISR (nmol/L) | 2.1 ± 0.3[a] | 1.4 ± 0.2 | 1.1 ± 0.2 | 2.3 ± 0.4 | 1.9 ± .03 | 1.2 ± 0.4 | 0.135 | 0.033 | 0.705 |
| Fasting GLP-1 (pg/mL) | 6.0 ± 50.8 | 10.4 ± 2.8 | 6.8 ± 1.0 | 5.7 ± 1.0 | 8.6 ± 1.2 | 6.2 ± 1.1 | 0.234 | 0.711 | 0.155 |
| Fasting GIP (pg/mL) | 52.7 ± 7.9 | 71.8 ± 9.4[a] | 37.4 ± 6.3 | 65.1 ± 11.8 | 71.7 ± 6.6 | 41.8 ± 6.2 | 0.113 | 0.350 | 0.021 |
| Fasting glucagon (pg/mL) | 31.0 ± 5.4 | 46.4 ± 6.2 | 36.8 ± 3.8 | 32.0 ± 4.5 | 39.7 ± 7.9 | 39.4 ± 5.0 | 0.795 | 0.578 | 0.378 |
| Fasting PP (pg/mL) | 61 ± 18 | 100 ± 34 | 164 ± 55 | 80 ± 28 | 202 ± 120 | 157 ± 58 | 0.303 | 0.461 | 0.460 |
| Incremental $AUC_{PP\ (0,30min)}$ (ng. $mL^{-1}$.Min) | 1.4 ± 0.4 | 3.7 ± 2.3[a,c] | 1.2 ± 0.3 | 1.8 ± 0.6 | 13.3 ± 6.0 | 2.9 ± 0.8 | 0.040 | 0.130 | 0.025 |
| Fasting insulin clearance | 3.4 ± 0.5[a] | 3.2 ± 0.5 | 2.2 ± 0.2 | 3.3 ± 0.5 | 3.2 ± 0.2 | 2.1 ± 0.2 | 0.718 | 0.020 | 0.900 |
| Prandial insulin clearance | 1.4 ± 0.3 | 1.5 ± 0.2 | 1.6 ± 0.1 | 1.4 ± 0.3 | 1.5 ± 0.2 | 1.3 ± 0.1 | 0.580 | 0.798 | 0.680 |
| OGIS ($mL.Min^{-1}.m^{-2}$) | 424 ± 32 | 445 ± 35 | 392 ± 16 | 403 ± 38 | 415 ± 28 | 393 ± 13 | 0.140 | 0.058 | 0.463 |
| Disposition index | 7862 ± 1664[b] | 4951 ± 739[a] | 1563 ± 364 | 8782 ± 1712 | 6796 ± 1341 | 2775 ± 660 | 0.006 | 0.700 | 0.001 |

Abbreviations: AUC, area under the curve; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; ISR, insulin secretion rate; OGIS, meal-derived glucose insensitivity; MMT, mixed meal tolerance test; PP, pancreatic polypeptide; Shm, sham feeding.
Data are presented as mean ± SEM. Statistical effects (main effects of study day [Shm + MTT, mixed meal tolerance test preceded by sham feeding] and group status [HGB/AGB/control group], as well as their interaction [study day*group status]) are provided in the last three right-hand columns.
Post-hoc Bonferroni adjustment for within group analysis when indicated.
[a]$P < 0.05$ compared with CN.
[b]$P < 0.01$ compared with CN.
[c]$P < 0.05$ compared with HGB.
[d]$P < 0.01$ compared with HGB.

any patient who developed symptomatic or biochemical (<2.8 mM) hypoglycaemia. There was no significant correlation between nadir glucose values and baseline characteristics such as age, BMI, and either time lapsed or weight loss since surgery.

Sham feeding altered the postprandial glucose profiles in all three groups by increasing the rise in glucose shortly after meal consumption and reducing overall prandial glycaemia, as reflected in lower glucose nadir and lower $AUC_{glucose(0,180min)}$.

## 3.3 | Postprandial islet-cell secretion with and without sham-feeding

Fasting insulin was significantly higher in the control group compared with the surgical groups (Table 1); however, the patients in the surgical groups had significantly greater early β-cell responses to the MMT than those in the control group (Figure 1B). The divergence of insulin secretion was evident as early as 6 minutes from meal ingestion between the GB and control groups, but the AUC for insulin ($AUC_{insulin[0,180min]}$) and insulin secretion rate ($AUC_{ISR[0,180min]}$)was similar among the three groups. Sham feeding enhanced the early β-cell secretory responses in all groups, an effect most apparent in the AGB and control groups (Figure 1B).

Fasting levels of plasma glucagon were similar in the three groups, and, similarly to the insulin responses, prandial glucagon secretion was greater in the GB groups than in the control group; there were no differences between the AGB and HGB groups despite hypoglycaemia in the latter group during the MMT (Figure 1C, Table 1). Fasting values of pancreatic polypeptide (PP) did not differ among the three groups (Table 1) but early meal-induced PP secretion was greater in the AGB group compared to both the HGB and control groups (Figure S1). The addition of sham feeding to the MMT enhanced the early glucagon and PP responses in all three groups (Figures 1C and S1).

## 3.4 | Insulin sensitivity and clearance and disposition index

There was a trend toward higher MMT-derived insulin sensitivity (oral glucose insulin sensitivity [OGIS]) in the GB groups compared to the control group. The oral disposition index values during the MMT studies were notably higher in the GB groups than in the control group, but did not differ between the HGB and AGB groups. Fasting insulin clearance was also significantly greater in the GB group compared to the control group, whereas postprandial insulin clearance did not differ among the groups. Sham feeding had no influence on OGIS or

postprandial insulin clearance, although oral disposition indices were augmented in all three groups by sham-feeding (Table 1).

### 3.5 | Meal-induced incretin response

Circulating levels of GLP-1 were similar among the three groups at baseline but the $AUC_{GLP\text{-}1(0,180min)}$ was significantly greater in the GB groups compared with the control group, with higher levels in the HGB than in the AGB group ($P < 0.0001$) (Tabel 1, Figure S2). Fasting levels of glucose-dependent insulinotropic peptide (GIP) were different among the three groups, with the highest values found in the AGB group (Table 1). Compared with the control group, patients in the GB groups had a slightly earlier post-meal GIP response, but the $AUC_{GIP\text{-}1(0,150min)}$ was not different between the GB groups and the control group (Figure S2). Sham feeding did not affect postprandial GLP-1 responses, but meal-induced GIP secretion was increased significantly in all groups after sham feeding, without any change in pattern of GIP response (Figure S2).

## 4 | DISCUSSION

Neural factors contribute to postprandial glucose metabolism, and this has been best established for parasympathetic control of islet hormones. To our knowledge this system has not been previously investigated in the context of GB in humans. In the present study, we demonstrate that vagal activation by food-related oral stimulation is retained in patients who have undergone GB surgery, and that the effect is consistent and comparable to a matched control group without surgery. Sham feeding increased glycaemic, insulin, glucagon and GIP responses to a test meal in the GB groups; however, responses to sham feeding-induced did not distinguish patients who had undergone GB who had hypoglycaemia from those who did not. These results indicate that neural control of islet function is maintained after GB, and raise the possibility that the brain coordinates adaptations of insulin and glucagon secretion to other metabolic alterations after GB.

In the present study sham feeding was used to stimulate vagal activity, an effect demonstrated in previous studies in humans before and after truncal or gastric vagotomy.[16] This paradigm has been validated as activating the cephalic phase (ie, neural) stimulation of the islet,[11] and can be applied before meals to assess effects on glucose tolerance.[10] Our findings in the control group are consistent with previous reports using this protocol that showed greater early insulin secretion and improved glucose tolerance in patients who had not undergone surgery.[10]

The major finding in the present study was that the cephalic insulin response was intact in the GB group, and similar to that of the control group without surgery. The rise in postprandial insulin secretion rate (ISR) when sham feeding was used for vagal activation preceded corresponding changes in systemic glucose levels by 5 to 10 minutes, consistent with vagally induced β-cell secretion independent of systemic glucose levels, and comparable to the response in the control group. The effect of sham feeding to increase early insulin secretion was most evident in the AGB and control groups, both of which had a nearly 40% rise attributable to vagal activation. The HGB group tended to have larger early insulin responses to meals and smaller effect of sham feeding compared to the AGB group; however, we did not find an interaction between group and day effects on $AUC_{ISR(0,30min)}$, indicative of a difference attributable to both variables. The lack of an effect here may be attributable to the lack of statistical power from our limited sample size. Whether subtle differences in neutrally mediated islet function are present in, and perhaps contribute to, postprandial hypoglycaemia syndrome will require more detailed study.

In addition to the effects of sham feeding on β-cell secretion, early α- and PP-cell responses to meal ingestion were increased as a result of vagal activation. A large body of evidence supports the role of the parasympathetic nervous system as contributing to the control of glucagon secretion.[17] In the present study, meal-induced glucagon was significantly higher in the GB groups than in the control group, similar to results observed previously. Moreover, sham feeding increased early glucagon responses in the GB groups with only minimal effects in the CN group, raising the possibility that increased neural input to α-cells after GB surgery accounts for the relative postprandial hyperglucagonaemia; this would require more detailed study of glucagon secretion and sensitivity in the GB and control groups.

Our findings indicate an effect of vagal activation not just on islet hormone secretion but also on GI function. Blood glucose was identical in each group at the beginning of the MMT with and without sham feeding, but glycaemia rose more quickly when vagal function was activated. We did not measure gastric/gastric pouch emptying and so cannot comment on whether sham feeding increased the rate of passage of nutrients into the intestine. Whether sham feeding promotes intestinal glucose uptake is also an open question. The increased GIP response after sham feeding is consistent with more rapid passage of nutrients through the intestine,[18] although we cannot exclude direct parasympathetic stimulation of GIP-secreting K cells in this effect. It is not clear why GLP-1, which shows enhanced secretion with more rapid appearance of glucose in the gut,[19] was not affected similarly.

There are several limitations of the present study that are important to note. First, the number of participants was small and this limits the statistical power of the observations. Second, there was an absence of formal measures of nutrient and GI fluxes. This restricts our ability to comment on some of the positive effects of sham feeding, particularly those related to the early glycaemic response. Finally, we have inferred vagal, parasympathetic signalling to be responsible for the results of sham feeding. This has been demonstrated in the past with sophisticated physiological testing,[10] and we have relied on this process as being established based on these studies.

Together, our results indicate that sham feeding exaggerates the insulin, glucagon and glycaemic meal responses that are characteristic of GB. This indicates that islet innervation by parasympathetic nerves carried in the vagus is intact after GB, and affects both α and β cells. While we did not see clear differences in sham feeding effects between the AGB and HGB groups, in this small study we cannot exclude the possibility that there is a difference in islet neural function that contributes to the postprandial hypoglycaemia syndrome. Regardless, the evidence for acute neural regulation of meal-induced insulin secretion raises the possibility that chronic effects

of GB on islet function and glucose metabolism are also integrated in the CNS.

## ACKNOWLEDGMENTS

We thank Leslie Baum, Brianne Reedy and Dr Radha Krishna from the Department of Medicine of the University of Cincinnati for their technical support and nursing staff from the Clinical Research Centre of Cincinnati Children's Hospital for their expert technical assistance. We are grateful to our research participants. This work was supported by grants from the National Institute of Health, DK105379 (M.S.), DK083554 (M.S.), and DK101991 (D.D.) and in part by the National Center for Advancing Translational Sciences, National Institute of Health grant 8 UL1 TR000077.

## CONFLICTS OF INTEREST

None declared.

## Author contributions

M.S. designed and supervised the study, obtained the data, analysed and interpreted the data, and wrote the manuscript. A.G. analysed the data. D.A.D. and A.G. contributed to interpretation of data and review/editing of the manuscript. M.S. is the guarantor and takes full responsibility for the work including the study design, access to data, and the decision to submit and publish the manuscript. Parts of the present study were presented at the American Diabetes Association, 71th Scientific Session, San Diego, California.

## ORCID

*Marzieh Salehi* https://orcid.org/0000-0003-4764-739X
*Amalia Gastaldelli* https://orcid.org/0000-0003-2594-1651

## REFERENCES

1. Jorgensen NB, Jacobsen SH, Dirksen C, et al. Acute and long-term effects of roux-en-Y gastric bypass on glucose metabolism in subjects with type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab*. 2012;303(1):E122-E131.
2. Schauer PR, Bhatt DL, Kashyap SR. Bariatric surgery or intensive medical therapy for diabetes after 5 years. *N Engl J Med*. 2017;376(20):1997.
3. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med*. 2012;366(17):1577-1585.
4. Nguyen NQ, Debreceni TL, Bambrick JE, et al. Rapid gastric and intestinal transit is a major determinant of changes in blood glucose, intestinal hormones, glucose absorption, and postprandial symptoms after gastric bypass. *Obesity (Silver Spring)*. 2014;22(9):2003-2009.
5. Salehi M, Gastaldelli A, D'Alessio DA. Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia. *J Clin Endocrinol Metab*. 2014;99(6):2008-2017.
6. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. *Gastroenterology*. 2014;146(3):669-680. e662.
7. Goldfine A, Mun E, Patti ME. Hyperinsulinemic hypoglyecemic following gastric bypass surgery. *Curr Opin Endocrinol Diabetes*. 2006;13:419-424.
8. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes*. 2011;60(9):2308-2314.
9. Berthoud HR, Jeanrenaud B. Sham feeding-induced cephalic phase insulin release in the rat. *Am J Physiol*. 1982;242(4):E280-E285.
10. Teff KL, Engelman K. Oral sensory stimulation improves glucose tolerance in humans: effects on insulin, C-peptide, and glucagon. *Am J Physiol*. 1996;270(6 Pt 2):R1371-R1379.
11. Teff KL, Levin BE, Engelman K. Oral sensory stimulation in men: effects on insulin, C-peptide, and catecholamines. *Am J Physiol*. 1993;265(6 Pt 2):R1223-R1230.
12. Ahren B, Holst JJ. The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. *Diabetes*. 2001;50(5):1030-1038.
13. Havel PJ, Ahren B. Activation of autonomic nerves and the adrenal medulla contributes to increased glucagon secretion during moderate insulin-induced hypoglycemia in women. *Diabetes*. 1997;46(5):801-807.
14. Teff KL, Townsend RR. Early phase insulin infusion and muscarinic blockade in obese and lean subjects. *Am J Physiol*. 1999;277(1 Pt 2):R198-R208.
15. Hankir MK, Seyfried F, Miras AD, Cowley MA. Brain feeding circuits after roux-en-Y gastric bypass. *Trends Endocrinol Metab*. 2018;29(4):218-237.
16. Konturek SJ, Popiela T, Slowiaczek M, Bielanski W. Gastric acid and pancreatic polypeptide responses to modified sham feeding. Effects of truncal and parietal cell vagotomy. *Gut*. 1987;28(3):280-286.
17. Woods SC, Porte D Jr. Neural control of the endocrine pancreas. *Physiol Rev*. 1974;54(3):596-619.
18. Edwards CM, Todd JF, Mahmoudi M, et al. Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9-39. *Diabetes*. 1999;48(1):86-93.
19. Schirra J, Katschinski M, Weidmann C, et al. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest*. 1996;97(1):92-103.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Salehi M, Gastaldelli A, D'Alessio DA. Role of vagal activation in postprandial glucose metabolism after gastric bypass in individuals with and without hypoglycaemia. *Diabetes Obes Metab*. 2019;21:1513–1517. https://doi.org/10.1111/dom.13676