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Surgery for Obesity and Related Diseases ■ (2022) 1–6

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Unraveling, contributing factors to the severity of postprandial hypoglycemia after gastric bypass surgery

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Received 24 March 2022; accepted 27 October 2022

Abstract

Background: Despite the increasing prevalence of postbariatric hypoglycemia (PBH), a late metabolic complication of bariatric surgery, our understanding of its diverse manifestations remains incomplete.

Objectives: To contrast parameters of glucose-insulin homeostasis in 2 distinct phenotypes of PBH (mild versus moderate hypoglycemia) based on nadir plasma glucose.

Setting: University Hospital (Bern, Switzerland).

Methods: Twenty-five subjects with PBH following gastric bypass surgery (age, 41 ± 12 years; body mass index, 28.1 ± 6.1kg/m^2) received 75g of glucose with frequent blood sampling for glucose, insulin, C-peptide, and glucagon-like peptide 1 (GLP)-1. Based on nadir plasma glucose (</≥50mg/dL), subjects were grouped into level 1 (L1) and level 2 (L2) PBH groups. Beta-cell function (BCF), GLP-1 exposure (λ), beta-cell sensitivity to GLP-1 (π), potentiation of insulin secretion by GLP-1 (PI), first-pass hepatic insulin extraction (HE), insulin sensitivity (SI), and rate of glucose appearance (Ra) were calculated using an oral model of GLP-1 action coupled with the oral minimal model.

Results: Nadir glucose was 43.3 ± 6.0mg/dL (mean ± standard deviation) and 60.1 ± 9.1mg/dL in L2- and L1-PBH, respectively. Insulin exposure was significantly higher in L2 versus L1 ($P = .004$). Mathematical modeling revealed higher BCF in L2 versus L1 (34.3 versus 18.8 10^{-9}*min^{-1}; $P = .003$). Despite an increased GLP-1 exposure in L2 compared to L1 PBH (50.7 versus 31.9pmol*L^{-1}*min*10^2; $P = .021$), no significant difference in PI was observed ($P = .204$). No significant differences were observed for HE, Ra, and SI.

Conclusions: Our results suggest that higher insulin exposure in PBH patients with lower postprandial nadir glucose values mainly relate to a higher responsiveness to glucose, rather than GLP-1. (Surg Obes Relat Dis 2022; ■:1–6.) © 2022 Published by Elsevier Inc. on behalf of American Society for

Prior Presentation: This work was presented at the 81st Scientific Sessions of the American Diabetes Association; June 25-29, 2021.

Funding: Swiss National Science Foundation (PCEGP3_186978), MIUR (Italian Minister for Education) under the initiative "Departments of Excellence" (Law 232/2016), University of Padova DOR (Project Networking 2019), Diabetes Center Berne.

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https://doi.org/10.1016/j.soard.2022.10.037

Keywords: Bariatric surgery; Hypoglycemia; Insulin regulation; Beta-cell function; GLP-1

Postprandial hypoglycemia is an increasingly recognized late metabolic complication of bariatric surgery also known as post-bariatric hypoglycemia (PBH) [1,2]. The condition affects approximately 30% of patients undergoing Roux-en-Y gastric bypass (RYGB) surgery [3] and is characterized by hypoglycemic episodes occurring ~90–120 minutes after meals. PBH is the result of a dysregulated glucose-insulin homeostasis. Previous work suggested a higher insulin exposure following meal intake with the involvement of several factors such as increased insulin secretion, driven by high incretin levels (another hallmark of PBH) and/or intrinsic β-cell alterations as well as diminished hepatic insulin extraction [4,5]. Differential contribution of these factors may explain why PBH manifests with varying degrees of biochemical severity, ranging from mild transient events to more pronounced episodes requiring self or third party treatment. A better understanding of this clinical heterogeneity has the potential to develop more targeted clinical management strategies and improve safety of affected patients.

The objective of this work is to contrast parameters of glucose-insulin homeostasis in 2 distinct phenotypes of PBH (mild versus moderate hypoglycemia) based on nadir plasma glucose.

Methods

Study design and population

The retrospective analysis included data from studies conducted at the University Hospital Bern (Switzerland). This study involved adults (age ≥18 years) who underwent RYGB >12 months ago. Patients with documented evidence of the Whipple's triad (interstitial or plasma glucose <54mg/dL at time of hypoglycemia symptoms, relieved by correction) were recruited. The respective medical diagnosis was performed on the grounds of objective assessments (supervised diagnostic test or blinded continuous glucose monitoring with symptom tracking during routine care) by a physician outside the team of investigators. Key exclusion criteria were a history of diabetes (glycated hemoglobin ≥6.5% [48mmol/mol]) and medication interfering with glucose-insulin homeostasis (e.g. acarbose). Protocols were approved by the local Ethics Committee and registered on clinicaltrials.gov (NCT03609632 and NCT04330196). All participants provided written informed consent.

Provocative test, blood sampling and laboratory methods

After an overnight fast and 24 hours avoidance of physical activity, alcohol, and caffeine intake, participants underwent an oral glucose tolerance test (75g of glucose in 200ml water ingested within 5 min in an upright position). During the 48 hours before the OGTT (oral glucose tolerance test), participants were instructed to adhere to a weight-maintaining diet (calculated using their estimated REE [resting energy expenditure] multiplied by a physical activity level of 1.3) and refrained from alcohol, caffeine, and physical activity. During this period, participants were fitted with a continuous glucose monitor and were instructed to correct sensor glucose values of less than 54 mg/dL. A peripheral intravenous cannula was inserted for regular blood sampling. Plasma glucose was determined immediately after sampling using the Biosen C-Line glucose analyzer (EKF-diagnostic, Barleben, Germany). Blood samples were kept on ice until centrifugation and plasma was stored at -80°C until analysis. Commercial immunoassays were used to quantify insulin (Elecsys Insulin, Cobas, Roche Diagnostics, Mannheim, Germany), C-peptide (Immulite 2000 C-Peptide analyzer, Siemens, Los Angeles, CA, USA), and Glucagon-like-peptide 1 (glucagon-like peptide 1[GLP-1], GLP-1 7–36 active form, IBL, Hamburg, Germany) concentrations. The cross-reactivity of the enzyme-linked immunosorbent GLP-1 assay with related peptides is as follows: GLP-1 7–36: 100%; GLP-1 (7–37): 100%; GLP-1 1–37: 0.32%; GLP-1 9–36: <0.1%; GLP-2: <0.1%; Glucagon: <0.1%; and GIP: <0.1% (numbers from manufacturer's assay description).

Stratification based on postprandial nadir plasma glucose

Based on plasma glucose nadir during the OGTT, participants were divided into the following 2 groups: level 1 (L1: <70mg/dL and ≥50mg/dL) and level 2 (L2: <50mg/dL) PBH, in line with recently published international consensus guidelines [6].

Calculation of indices of glucose-insulin homeostasis

Insulin exposure was calculated as the area over the baseline insulin concentration curve (iAUC insulin). Indices of glucose-insulin homeostasis were calculated using a modified version of the Oral Minimal Model method [7].

In particular, the oral model of GLP-1 action [8] coupled with the Oral C-peptide Minimal model [9] were used to assess the overall effect of glucose and GLP-1 on β-cell responsivity (Φ), as well as the β-cell responsivity to glucose alone (Φ_{Glu}) and the β-cell sensitivity to GLP-1 (π). GLP-1 exposure (Λ), i.e. the L-cell responsivity to glucose in the gut, was estimated by the area under the above basal GLP-1 concentration. Finally, the overall effect of GLP-1 on

Table 1
Metabolic indices in participants with level 2 versus level 1 hypoglycemia

Metabolic indices	Level 2 PBH Nadir<50mg/dL (n = 11)		Level 1 PBH Nadir ≥50mg/dL (n = 14)		Between group difference Level 2 PBH – level 1 PBH			Physiological correlate
	Median	IQR	Median	IQR	Difference	*95%* CI	*P* value	
iAUC Insulin (pmol/L*min*10^3)	99.9	[52.4; 125.1]	40.3	[31.0; 60.1]	54.4	[10.3; 85.1]	.004	Insulin exposure
HE (%)	26.2*	[18.6; 38.0]	35.5†	[30.1; 43.6]	−10.1	[−19.6; 1.3]	.077	Percentage of first-pass hepatic insulin extraction
Φ (10^{-9}*min^{-1})	34.3*	[24.8; 50.8]	18.8†	[17.1; 26.3]	12	[5.3; 29.1]	.003	Overall beta-cell responsivity to glucose, reflects the combined effect of glucose and GLP-1 on insulin secretion
$\Phi_{(Glu)}$ (10^{-9}*min^{-1})	27.6*	[21.7; 49.3]	13.7†	[10.4; 21.0]	13.3	[2.7; 29.8]	.008	Beta-cell responsivity to glucose alone
λ (pmol/L*min*10^2)	50.7*	[42.2; 75.9]	31.9†	[24.6; 42.1]	19.7	[1.3; 40.8]	.021	GLP-1 exposure, reflects the L-cell sensitvity to glucose in the gut
π (%/[pmol/L])	0	[0.00; 0.50]	0.96†	[0.00; 8.29]	−0.74	[−8.01; 0.33]	.111	Beta-cell sensitivity to GLP-1
PI (%*min*10^2)	0*	[0.0; 26.64]	59.9†	[0.0; 272.6]	−23.1	[−160.6; 2.0]	.204	Potentiation of the insulin secretion in response to glucose by GLP-1, combines GLP-1 sensitivity [π] and GLP-1 exposure [λ]
AUC $Ra_{0\text{-}120}$/D *(%)*	94.0*	[87.4;100.0]	87.3	[82.5; 95.9]	3.8	[−2.5; 12.7]	.186	Percentage of the glucose absorbed in the 120 min following oral intake
SI *(10^{-4}*dL/kg/min per uU/mL)*	7.2*	[6.4; 11.6]	14.0	[5.2; 19.6]	−2.2	[−9.7; 3.5]	.648	Insulin sensitivity

PBH = postbariatric hypoglycaemia; HE = Hepatic insulin extraction; IQR = Interquartile range; CI = confidence interval; iAUC = Area under the above basal concentration curve; SI = Insulin sensitivity; Ra = Rate of oral glucose appearance; D = Oral glucose dose; GLP-1 = glucagon-like peptide 1; CI = Confidence interval.

P values were computed using the Wilcoxon rank sum test. Differences represents the Hodges-Lehman estimator.

* n = 10, One subject was excluded due to poor model fit.

† n = 13, One subject was excluded due to absence of GLP-1 data.

insulin secretion was estimated by the product of β-cell sensitivity to GLP-1 and GLP-1 exposure (PI = π *Λ).

In addition, combining the Oral C-peptide Minimal model [9] with a model of insulin kinetics [7], first-pass hepatic insulin extraction (HE) was estimated, while assuming post-hepatic insulin clearance determined from anthropometric characteristics [10]. C-peptide kinetics (required for the Oral C-peptide Minimal model identification) were estimated by exploiting a recently proposed methodology in this population [9].

To complete the picture of glucose-insulin control, the Oral Glucose-Minimal Model [7] was used to estimate insulin sensitivity (SI) and the rate of gastro-intestinal glucose absorption (Ra) from postprandial glucose and insulin data. Of note, data was right censored following hypoglycemia (i.e. data following hypoglycaemia were not considered to fit the model). An overview of the estimated indices, together with their physiological meaning is provided in Table 1.

Statistical analysis

Indices were compared between the groups using the Wilcoxon rank-sum test. Results are reported as median (interquartile range) unless otherwise specified. *P* values <.05 were considered as statistically significant. Statistical analyses were performed with R (version 4.0.2).

Results

Population

The L2 and L1-PBH groups comprised 11 and 14 participants, respectively. Participants (19 females and 6 males) were aged 44.0 years (32.2; 47.7), had a current body mass index (BMI) of 27.7kg/m^2 (23.4; 32.3), and a presurgery BMI of 41.1 kg/m^2 (39.6; 43.8). Median duration since surgery was 6 years (5; 7). No significant differences in participant characteristics were observed between the 2 groups. Further, sociodemographic and metabolic characteristics are reported in the Supplemental Material. One patient was treated with acarbose at the time of study inclusion (the drug was stopped 5 days before the experimental visit as defined in the study protocol).

Glucose, insulin and C-peptide profiles

Nadir glucose was 42.7mg/dL (36.6; 47.5) and 57.4mg/dL (52.8; 63.4) in the L2- and L1-PBH group, respectively. Peak glucose levels and glucose exposure ($iAUC_{Glucose}$) did

Table 2
Glucose and insulin variables in participants with Level 1 versus Level 2 hypoglycemia

Variables	Level 2 PBH		Level 1 PBH		Between group difference		
	Nadir<50mg/dL (n = 11)		Nadir < 70mg/dL and ≥50mg/dL (n = 14)		Level 2 – level 1 PBH		
	Median	IQR	Median	IQR	Difference	95% CI	*P* value
Glucose							
Fasting (mg/dL)	81.8	[78.6; 84.5]	82.9	[81.5; 88.9]	−2.7	[−8.3; 1.4]	.152
iAUC (mg*min/dL)	4200	[3157; 6310]	4927	[1932; 6298]	−432	[−3645; 2308]	.609
Nadir (mg/dL)	42.7	[36.6; 47.5]	57.4	[52.8; 63.4]	−16.8	[−26.3; −9.7]	<.001
Peak (mg/dL)	182.5	[168.6; 212.2]	187.5	[159.9; 217.2]	−1.3	[−41.4; 27.6]	.979
Time to peak (min)	45	[30; 60]	30	[30; 45]	7.5	[−15; 30]	.317
Time to nadir (min)	120	[110; 135]	128	[113; 176]	−10	[−10; 60]	.346
Insulin							
Fasting (pmol/L)	37.5	[29.8; 46.9]	36.3	[28.1; 46.4]	1.8	[−12.4; 14.5]	.727
iAUC (pmol/L*min*10^3)	99.9	[52.4; 125.1]	40.3	[30.1; 60.1]	54.4	[10.3; 85.1]	.004
Peak (pmol/L)	1656.0	[951.5; 2376.5]	795.0	[628.3; 1038.0]	723.6	[−222.2; 1486.2]	.002
Time to peak (min)	45	[45; 60]	38	[30; 56]	7.5	[−15; 30]	.100

PBH = postbariatric hypoglycemia; iAUC = incremental area under the curve; IQR = interquartile range, CI = Confidence interval.
P values were computed for the difference between the 2 groups using the Wilcoxon rank sum test. Differences represents the Hodges-Lehman estimator.

not significantly differ between the 2 groups, nor did time-to-peak and time-to-nadir glucose. Median insulin exposure ($iAUC_{Insulin}$) was 138% higher in the L2-PBH group versus L1-PBH group ($P < .001$). Similarly, the L2-PBH group showed higher peak insulin levels than the L1-PBH group ($P = .003$) while time-to-peak insulin concentration was not significantly different between the groups (Table 2). Mean time course of plasma glucose, insulin and C-peptide concentrations for the 2 groups are shown in Figure 1.

Indices of glucose-insulin homeostasis

Results of indices of glucose-insulin homeostasis for both groups and between-group differences are provided below. The exact numbers are reported in Table 1.

β-cell function

Both indices of β-cell function (β-cell responsivity to glucose alone [Φ_{Glu}] and β-cell responsivity to glucose potentiated by GLP-1 [Φ]) were higher in the L2-PBH group versus L1-PBH group ($P = .008$ and $P = .003$, respectively).

Effect of GLP-1

GLP-1 exposure [Λ] was higher in L2-PBH compared to L1-PBH ($P = .021$). Differences in β-cell sensitivity to GLP-1 (π) and in the effect of GLP-1 on insulin secretion (PI) were not significantly different between the 2 groups ($P = .111$ and $P = .204$, respectively).

Hepatic insulin extraction and rate of glucose appearance

Median HE was (26.2% [18.6; 38.0] in the L2-PBH versus 35.5% [30.1; 43.6]) in the L1-PBH group (median of the differences was -10.1%, $P = .077$). No significant differences were observed for Ra within the first 2 hours after meal ingestion ($AUC[Ra_{0\text{-}120min}]$/Dose) ($P = .186$) and for SI ($P = .648$).

Discussion

In the present work, we compared indices of glucose-insulin homeostasis between RYGB individuals with mild versus moderate PBH according to nadir plasma glucose following an oral glucose load. Based on the models applied in the present study, the higher insulin exposure in patients with lower glucose nadir appears to be driven by an increased β-cell function [Φ] and is possibly further compounded by a reduced hepatic insulin extraction (although the difference was not statistically significant in the present study). Patients with lower nadir plasma glucose also demonstrated higher GLP-1 exposure [Λ], an observation that is in line with several previous studies [11,12]. Greater GLP-1 exposure is most likely caused by an accelerated nutrient flux and digestion [13,14] and/or alterations in enteroendocrine cells and gut microbiome [15] in more severely affected PBH patients. Despite the higher GLP-1 exposure, we found no evidence for an increased incretin effect ([PI] or the effect of GLP-1 on insulin secretion) using our modeling approach. Lack of the stimulatory effect of GLP-1 must be seen in the context of possible reduced β-cell sensitivity to GLP-1 [π] (albeit lower, no statistical significance was found in the present work). Although the explanation for these findings remains speculative, GLP-1 receptor desensitization in an attempt to prevent hypoglycemia appears to be a possible mechanism and has been previously reported, although in slightly different settings [16].

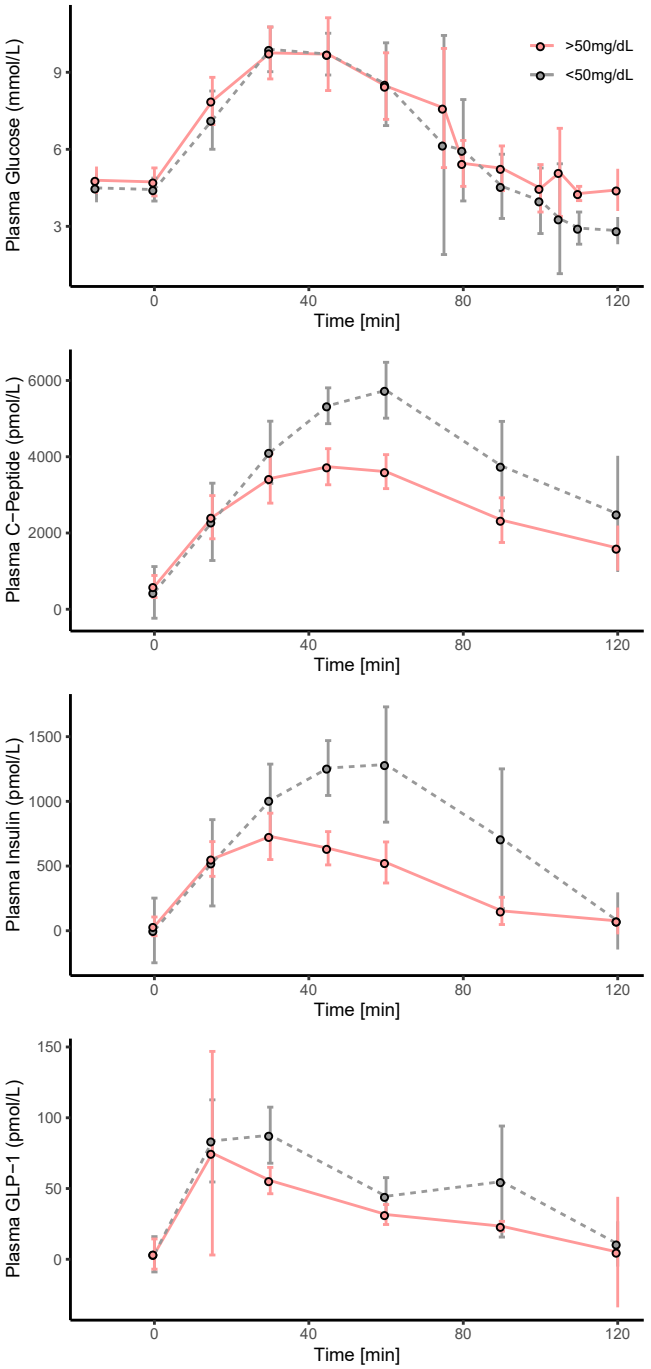

Fig. 1. The mean plasma glucose, insulin, and C-peptide concentrations in response to glucose intake in participants with level 1 (solid line) and level 2 (dotted line) postbariatric hypoglycaemia. Error bars represent standard deviation calculated as described in the work by Moreau [20] to account for the repeated measures design. GLP-1 = glucagon-like peptide 1.

Of note, 2 previous studies explored the effect of GLP-1 on postprandial insulin secretion using GLP-1 receptor blockade with exendin-9-39 (Ex-9) and found conflicting results [5,17]. Following the ingestion of a mixed-meal with clamped hyperglycemic plasma glucose levels, reduction in insulin secretion with Ex-9 versus saline infusion was comparable between PBH and asymptomatic patients following RYGB. Conversely, in a second study which involved Ex-9 in a mixed-meal test setting without a concomitant hyperglycemic clamp, the reduction in postprandial insulin secretion was significantly higher in PBH compared to asymptomatic patients, indicating a role for a heightened GLP-1 effect in the pathogenesis of PBH [5]. Taken together, the heterogeneity in study findings indicates that the role of GLP-1 in the pathogenesis of PBH remains a matter of debate.

In contrast to the responsiveness to GLP-1, responsivity to glucose alone (Φ_{Glu}) was higher in patients with more pronounced PBH. Higher beta-cell responsivity to glucose may reconcile with previously reported post-pancreatectomy findings showing diffuse islet hyperplasia and expansion of beta cell mass in patients with severe PBH [18]. However, subsequent histological examinations were unable to confirm increases in beta-cell mass or formation in pancreatic specimens from PBH [19]. Thus, increased beta-cell responsivity may be rather explained by alterations of beta-cell function (e.g. insulin secretory rate per cell) rather than total cell mass, but more research is needed to make reliable statements regarding intrinsic regulator of beta-cells in PBH.

Finally, our observations do not support the notion that lower nadir glucose plasma is linked with higher insulin sensitivity [SI].

The strengths of the present work lie in the standardized setting on well-characterized individuals (e.g. stratification of participants based on objective criteria). We acknowledge the following limitations: our exploration of underlying mechanisms focused on specific aspects of glucose-insulin homeostasis and other contributors to insulin release (e.g. other peptide hormones or bile acid) were not addressed. We want to emphasize that the selected features are unlikely to cover the entire spectrum of underlying pathophysiological mechanismsor, nor was the study designed to uncover all of these. The applied mathematical representation of the glucose-homeostasis has well-recognized drawbacks such as fixing post-hepatic insulin clearance to population value and utilization of a method to estimate C-peptide kinetics that was only validated in silico [9]. Furthermore, due to the small sample size and the explorative nature of the study, the findings should not be overstated.

Conclusions

In conclusion, our results suggest that PBH patients with lower postprandial nadir glucose values relate to higher insulin exposure mainly caused by a glucose-, rather than GLP-1 stimulated heightened insulin secretion. These findings further deepen our understanding of the mechanisms

behind the heterogeneity of PBH and may inspire future targeted therapeutic approaches.

Data Availability

All datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Acknowledgments

We are grateful to all the study participants for their time and efforts. We thank Nina Omlin (medical student), Sandra Tenisch, and Nicole Truffer (Study Nurses at the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism) for their assistance in patient care and data collection. We thank Laura Goetschi for providing administrative support. GLP-1 concentrations were measured at Medics Laboratory, Berne.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Author Contributions

DH, MS, CDM and LB designed the retrospective analysis. AT, VL, JM and SJ conducted the study visits. LB and TPS conceptualized laboratory analyses. CK performed the sample workup and analytical measurements. DH, MS and CDM analyzed the data and produced the display items. DH, MS, CDM and LB interpreted the results and wrote the manuscript. All authors critically reviewed the manuscript and approved its final version. CDM and LB are the guarantor of this work and take main responsibility for the integrity and accuracy of the data.

Supplementary data

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2022.10.037.

References

1 Ilesanmi I, Tharakan G, Alexiadou K, et al. Roux-en-Y gastric bypass increases Glycemic variability and time in hypoglycemia in patients with obesity and prediabetes or type 2 diabetes: a prospective cohort study. Diabetes Care 2021;44(2):614–7.
2 Bienvenot R, Sirveaux MA, Nguyen-Thi PL, Brunaud L, Quilliot D. Symptomatic hypoglycemia after gastric bypass: Incidence and predictive factors in a cohort of 1,138 consecutive patients. Obesity (Silver Spring) 2021;29:681–8.
3 Capristo E, Panunzi S, De Gaetano A, et al. Incidence of hypoglycemia after gastric bypass vs sleeve gastrectomy: a Randomized trial. J Clin Endocrinol Metab 2018;103(6):2136–46.
4 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):2008–17.
5 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.e2.
6 Scarpellini E, Arts J, Karamanolis G, et al. International consensus on the diagnosis and management of dumping syndrome. Nat Rev Endocrinol 2020;16(8):448–66.
7 Cobelli C, Dalla Man C, Toffolo G, Basu R, Vella A, Rizza R. The oral minimal model method. Diabetes 2014;63(4):1203–13.
8 Dalla Man C, Micheletto F, Sathananthan M, Vella A, Cobelli C. Model-based quantification of glucagon-like peptide-1-induced potentiation of insulin secretion in response to a mixed meal challenge. Diabetes Technol Ther 2016;18(1):39–46.
9 Schiavon M, Herzig D, Hepprich M, Donath M, Bally L, Dalla Man C. Model-based assessment of C-peptide secretion and kinetics in post gastric bypass individuals experiencing postprandial hyperinsulinemic hypoglycemia. Front Endocrinol (Lausanne) 2021;12:611253.
10 Campioni M, Toffolo G, Basu R, Rizza RA, Cobelli C. Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Am J Physiol Endocrinol Metab 2009;297(4):E941–8.
11 Goldfine AB, Mun EC, Devine E, et al. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. J Clin Endocrinol Metab 2007;92(12):4678–85.
12 Patti ME, Li P, Goldfine AB. Insulin response to oral stimuli and glucose effectiveness increased in neuroglycopenia following gastric bypass. Obesity (Silver Spring) 2015;23(4):798–807.
13 Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. Diabetes Care 2013;36(5):1396–405.
14 Chambers AP, Smith EP, Begg DP, et al. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. Am J Physiol Endocrinol Metab 2014;306(4):E424–32.
15 Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. Cell Metab 2015;21(3):369–78.
16 Salehi M, Gastaldelli A, D'Alessio DA. Beta-cell sensitivity to insulinotropic gut hormones is reduced after gastric bypass surgery. Gut 2019;68(10):1838–45.
17 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):2308–14.
18 Patti ME, McMahon G, Mun EC, et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 2005;48(11):2236–40.
19 Meier JJ, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. Diabetes Care 2006;29(7):1554–9.
20 Morey RD. Confidence intervals from normalized data: A correction to cousineau (2005). Tutor Quant Methods Psychol 2008;4(2):61–4.