

Risk Factors for Spontaneously Self-Reported Postprandial Hypoglycemia After Bariatric Surgery

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Context: Postprandial hypoglycemia (PPHG) is a recognized complication of Roux-en-Y gastric bypass (RYGB) surgery. Data on PPHG after laparoscopic sleeve gastrectomy (LSG) are scant.

Objective: The objective of the study was to identify preoperative predictors of PPHG in subjects spontaneously self-reporting PPHG after RYGB or LSG.

Patients, Setting, and Intervention: Nondiabetic patients spontaneously self-reporting symptoms/signs of PPHG (PPHG group, 21 RYGB and 11 LSG) were compared in a case-control design with subjects who never experienced spontaneous or oral glucose tolerance test (OGTT)-induced hypoglycemia over 24 months after surgery (No-PPHG group, 13 RYGB and 40 LSG). Paired pre- and postoperative 3-hour OGTTs were analyzed in all participants.

Main Outcome Measures: Insulin sensitivity was assessed by the oral glucose insulin sensitivity index and β -cell function by mathematical modeling of the C-peptide response to glucose.

Results: Before surgery, the body mass index was lower in PPHG than No-PPHG patients in the RYGB ($P = .002$) and trended similarly in the LSG group ($P = .08$). Fasting glycemia and the glucose-OGTT nadir were lower in the PPHG than the No-PPHG subjects in both surgery groups. Before surgery, insulin sensitivity was higher in PPHG than No-PPHG in the RYGB (393 ± 55 vs 325 ± 44 mL/min⁻¹ · m⁻², $P = .001$) and LSG groups (380 ± 48 vs 339 ± 60 mL/min⁻¹ · m⁻², $P = .05$) and improved to a similar extent in all groups after surgery. Before surgery, β -cell glucose sensitivity was higher in PPHG than No-PPHG in both RYGB (118 ± 67 vs 65 ± 24 pmol/min⁻¹ · m² · mM⁻¹) and LSG patients (114 ± 32 vs 86 ± 33) (both $P = .02$) and improved in all subjects after surgery.

Conclusions: In subjects self-reporting PPHG after surgery, lower presurgery plasma glucose concentrations, higher insulin sensitivity, and better β -cell glucose sensitivity are significant predictors of PPHG after both RYGB and LSG. (*J Clin Endocrinol Metab* 101: 3600–3607, 2016)

Postprandial hypoglycemia (PPHG) is increasingly recognized as a late complication of Roux-en-Y gastric bypass (RYGB) surgery. Although rarely, patients may develop severe hyperinsulinemic hypoglycemia with neuroglycopenia requiring hospitalization (1); 1–3 years after

RYGB, approximately 30% of patients develop mild to moderate PPHG symptoms, resolving with dietary modifications (2). Comparable data for laparoscopic sleeve gastrectomy (LSG) are more scant; a recent study, however, has reported that up to 30% of patients after RYGB

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Abbreviations: BMI, body mass index; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; β -GS, β -cell glucose sensitivity; LSG, laparoscopic sleeve gastrectomy; MCR_I, metabolic clearance rate of insulin; OGIS, oral glucose insulin sensitivity; OGTT, oral glucose tolerance test; PPHG, postprandial hypoglycemia; RYGB, Roux-en-Y gastric bypass.

or LSG have postoperative PPHG based on oral glucose testing (3, 4).

Why some patients develop PPHG whereas others do not is unclear. After bariatric surgery, alterations of gastrointestinal (GI) anatomy and of gastric innervation likely have a profound effect on gastric emptying (5). Thus, meals are more rapidly transferred from the stomach to the small intestine so that the distal intestine is exposed to higher loads of undigested carbohydrates, whereby absorption of glucose into the bloodstream is accelerated. The resulting hyperglycemia stimulates a rapid and excessive secretion of insulin, which can in turn trigger late hypoglycemia. Some authors (5–7) suggested that excessive insulin secretion could be in part consequent on increased incretin hormone release, but the role of these hormones in the development of hypoglycemia remains controversial. An increased secretion of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide has been observed after an oral glucose challenge in patients after gastric resection, esophagectomy, and RYGB (8–11), and these exaggerated responses have been suggested to induce β -cell expansion via an increased expression of islet transcription factors (12, 13). By contrast, in a recent paper, it has been suggested that GLP-1 analogs might provide a new treatment option in patients with late PPHG (14). Furthermore, it has been postulated that, after RYGB, hypoglycemic counterregulation may be dysfunctional due to the lack of inhibition of insulin secretion, subnormal response of the antiinsulin hormones, changes in neuronal/sympathetic activity, and/or low glycogen stores (15, 16).

Severe hypoglycemia can lead to dangerous clinical consequences such as seizure, syncope, and motor vehicle accidents. However, also mild to moderate hypoglycemia (plasma glucose 2.3–3.9 mmol/L) can have a negative health impact both in diabetic and nondiabetic subjects. Thus, in diabetic subjects mild to moderate hypoglycemia can be associated with an increased risk of cardiac arrhythmias (17). Furthermore, hypoglycemia may reduce the amplitude of the blood oxygenation level-dependent responses to simple auditory and visual stimuli in the primary auditory and visual cortex (18). In healthy subjects, clamp-controlled hyperinsulinemic hypoglycemia reduces blood oxygenation level-dependent responses to visual stimulation during moderate hypoglycemia, suggesting regional vulnerability of the brain to hypoglycemia (19). Therefore, recurrent hypoglycemia of any degree can have clinical relevance, and to identify predictive risk factors of this late complication of bariatric surgery becomes important. Recent work (2) has suggested that the presence of preoperative hypoglycemic symptoms may be the strongest indicator of an enhanced risk of PPHG after surgery. Although in this work preoperative hypoglycemia was based on a questionnaire and not on direct measurements,

the suggestion is that patients developing PPHG after RYGB or LSG might have a predisposing phenotype. The aim of the present study was to assess the preoperative clinical and physiological factors that identify patients at highest risk for spontaneous PPHG after bariatric surgery.

Materials and Methods

Subjects

The study included morbidly obese nondiabetic patients on a wait list for laparoscopic RYGB or LSG. Exclusion criteria were as follows: 1) the presence of diabetes mellitus, 2) medical conditions requiring acute hospitalization, 3) blindness, 4) severe medical conditions (liver cirrhosis, end stage renal failure, malignancy, connective tissue diseases, endocrine diseases such as hypo- or hyperthyroidism) or illnesses such as chronic congestive heart failure, recent myocardial infarction or stroke, or unstable angina pectoris, and 5) treatment with pharmacological agents known to affect carbohydrate homeostasis.

Study design

Before surgery, candidate patients are admitted to our hospital ward for a period of 4 days to perform the routine preoperative work-up. As part of this assessment, all patients receive a 75-g, 3-hour oral glucose tolerance test (OGTT). From the cohort of all patients who had undergone surgery between 2013 and 2014 ($n = 216$, 163 RYGB and 53 LSG), we selected those ($n = 32$) who at a follow-up visit at our clinic spontaneously self-reported symptoms/signs of postprandial hypoglycemia (palpitations, finger tremors, diaphoresis, anxiety, cognitive impairment, and behavioral changes) under everyday life conditions 2–3 hours after a meal over the preceding 12–24 months, requiring our attention (Figure 1). On this occasion, the Sigstaad's and Arts' questionnaires (scoring autonomic and/or neuroglycopenic symptoms, including palpitations, sweating, shaking, hunger, profound fatigue, dizzying, and headaches) were administered, and the OGTT was repeated. During this test, all RYGB subjects ($n = 21$) and 5 of the 11 LSG developed similar symptoms of hypoglycemia as those previously self-reported but not symptoms characteristic of an early dumping syndrome. All RYGB ($n = 21$) and LSG ($n = 11$) subjects had a plasma glucose level of 2.7 mmol/L or less at any time during the test (7). Sex- and age-matched subjects who never experienced hypoglycemia either spontaneously after surgery or during the postsurgery OGTT ($n = 53$, 13 after RYGB and 40 after LSG) served as the control group (No-PPHG) for the PPHG group. In the No-PPHG group, the OGTT was repeated on the occasion of the follow-up visit at 24 months.

The type of surgical procedure (laparoscopic RYGB or LSG) was determined as previously described (20). The protocol was approved by the local ethics committee, and all patients signed a consent form before the study.

OGTT protocol

Frequent blood sampling was performed through an indwelling cannula at times –30, 0, 10, 20, 30, 45, 60, 90, 120, 150, and 180 minutes for the measurement of plasma glucose, insulin, and C-peptide.

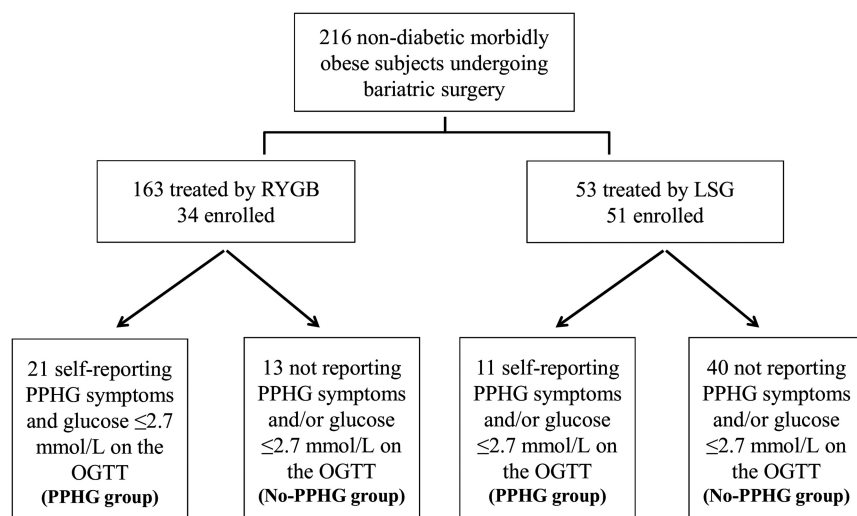


Figure 1. Flow chart of patient enrollment.

Methods

Plasma glucose concentration was measured on a Beckman Glucose Analyzer 2 (Beckman). Plasma insulin and C-peptide were measured on a Cobas e411 (Roche Diagnostics S.p.A.).

Modeling

Insulin sensitivity and β -cell function parameters were derived from mathematical modeling of the plasma glucose, insulin, and C-peptide concentrations measured during the frequently sampled OGTT, as previously described (21, 22). In brief, insulin sensitivity was calculated as the oral glucose insulin sensitivity (OGIS) index, which estimates plasma glucose clearance rate (in milliliters per minute⁻¹ per meter⁻²) at a level of hyperinsulinemia in the range of that achieved during a standard (240 pmol/min⁻¹ · m⁻²) euglycemic hyperinsulinemic clamp, against which this index has been validated in subjects with normal glucose tolerance, impaired glucose tolerance, or overt diabetes (22). The β -cell function model uses the two-exponential model of C-peptide kinetics proposed by Van Cauter et al (23), in which the model parameters are individually adjusted to the subject's anthropometric data to reconstruct insulin secretion rates from plasma C-peptide concentrations. The main output parameter is the mean slope of the dose-response function, representing β -cell glucose sensitivity (β -GS; in picomoles per minute⁻¹ per meter⁻² per millimole⁻¹). The metabolic clearance rate of insulin (MCR_I) was calculated both in the fasting state (as the ratio between fasting insulin secretion rate and fasting insulin concentration) and during the OGTT (as the ratio of total insulin output and mean OGTT plasma insulin concentration).

Statistical analysis

Results are expressed as means \pm SD. Group differences were compared by the χ^2 test for categorical variables, by the Mann-Whitney *U* test for continuous variables, and by the Wilcoxon signed rank test for paired data. Analysis of changes over time (after surgery vs before surgery) was performed by an ANOVA for repeated measures; for this test, parameters with a skewed distribution were log transformed. The output of this ANOVA model is a *P* value for the time factor (ie, overall changes over time), a *P* value for the group (ie, between group differences), and a *P* value for the time \times group interaction (ie, differential changes

between groups over time). A multivariate regression model was used to analyze correlations among variables. A value of *P* < .05 was considered significant.

Results

On the OGTT performed before surgery, two-thirds of the subjects subsequently included in the PPHG group also had plasma glucose values of 2.7 mmol/L or less associated with hypoglycemic symptoms, whereas none of the No-PPHG subjects had plasma glucose values less than 4 mmol/L or symptoms. After surgery, all subjects completed the test. Subjects were kept in the supine position

throughout the test, and plasma glucose concentrations were monitored every 5 minutes. In 26 of 32 PPHG subjects, hypoglycemia resolved spontaneously, whereas six individuals needed iv glucose (which was started at 180 min).

Before surgery, patients undergoing LSG were more obese and older than the RYGB group. Age and sex distribution were similar in groups with (PPHG) or without (No-PPHG) spontaneous PPHG undergoing either surgery.

Roux-en-Y gastric bypass (Table 1)

Before RYGB, PPHG subjects had a lower body mass index (BMI), fasting plasma glucose, and glucose nadir concentrations compared with the No-PPHG subjects, whereas fasting insulin concentrations and insulin secretion rates were similar between the two groups. Insulin sensitivity and β -cell glucose sensitivity were both significantly higher in the PPHG than No-PPHG subjects.

After surgery, BMI decreased in both PPHG and No-PPHG. Likewise, fasting and mean plasma glucose levels decreased in both groups (Figure 2). The time to glucose peak, which averaged 70 minutes before surgery, occurred at significantly earlier times after surgery, similarly for PPHG and No-PPHG. Fasting plasma insulin and insulin secretion decreased to a similar extent in No-PPHG and in PPHG, mean insulin concentrations decreased more in No-PPHG compared with PPHG, and insulin output during the first hour after glucose loading increased more in the PPHG group. Insulin sensitivity and β -cell glucose sensitivity improved after surgery in both groups (Figure 3). Insulin clearance during the OGTT was higher in the No-PPHG than in the PPHG group, independently of surgery. On the contrary, fasting insulin clearance rose more in No-PPHG than in PPHG after surgery.

Table 1. Anthropometrics and Metabolic Parameters of Subjects Undergoing RYGB

	PPHG Before	PPHG After	No-PPHG Before	No-PPHG After	P Value ^a	P Value ^b	P Value ^c	P Value ^d
n	21	21	13	13				
Sex (F/M)	17/4		10/3		ns			
Age, y	42 ± 8		46 ± 10		ns			
BMI, kg/m ²	43.4 ± 5.1	29.2 ± 4.9	49.9 ± 5.6	33.0 ± 5.8	.002	.002	.0001	ns
Fasting glucose, mmol/L	5.1 ± 0.4	4.7 ± 0.4	5.8 ± 0.9	4.9 ± 0.3	.007	.004	.0004	ns
Glucose peak, mmol/L	9.1 ± 1.9	9.7 ± 2.2	9.7 ± 1.6	8.3 ± 1.9	ns	ns	ns	.008
Glucose nadir, mmol/L	5.1 ± 1.3	2.4 ± 0.5	6.2 ± 0.9	4.1 ± 0.3	.01	.0001	.0001	ns
Time of peak glucose, min	64 ± 16	45 ± 15	80 ± 23	47 ± 19	ns	ns	.0001	ns
Fasting insulin, pmol/L	89 ± 59	57 ± 48	122 ± 76	62 ± 51	ns	ns	.007	ns
Fasting ISR, pmol/min ⁻¹ · m ⁻²	113 ± 73	64 ± 37	145 ± 83	61 ± 29	ns	ns	.0001	ns
Total IS, nmol/m ⁻²	59 ± 23	68 ± 40	68 ± 27	55 ± 16	ns	ns	ns	ns
OGIS, mL/min ⁻¹ · m ⁻²	393 ± 55	490 ± 91	325 ± 44	445 ± 50	.001	.003	.0001	ns
Fasting MCR _V , L/min ⁻¹ · m ⁻²	1.3 ± 0.3	1.6 ± 0.5	1.2 ± 0.6	2.1 ± 1.0	ns	ns	.0005	.05
Total MCR _V , L/min ⁻¹ · m ⁻²	0.8 ± 0.2	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	ns	.05	.05	ns
Insulin AUC ₀₋₆₀ , nmol/m ⁻²	29 ± 10	46 ± 3	24 ± 17	34 ± 7	ns	.05	.007	.05
β-GS, pmol/min ⁻¹ · m ² · mM ⁻¹	118 ± 67	128 ± 47	65 ± 24	99 ± 39	.02	.018	.012	ns

Abbreviations: insulin AUC₀₋₆₀, insulin output during the first hour of the OGTT; IS, insulin secretion; ISR, insulin secretion rate; ns, not significant.

^a Before PPHG vs before No-PPHG.

^b PPHG vs No-PPHG group.

^c Before vs after surgery.

^d Surgery × group.

Laparoscopic sleeve gastrectomy (Table 2)

Before LSG, subjects self-reporting PPHG after surgery tended to have a lower BMI ($P = .08$), and their fasting plasma glucose and glucose nadir levels were lower than in

the No-PPHG subjects. Furthermore, mean plasma insulin during the test was higher and insulin sensitivity and β -cell glucose sensitivity were better in PPHG than No-PPHG. After surgery, BMI decreased in both groups in a similar

degree as did fasting plasma glucose and glucose peak levels. The time to glucose peak, which averaged 65 minutes before surgery, occurred at significantly earlier times after surgery, similarly for PPHG and No-PPHG. Reductions in fasting and mean plasma insulin levels and fasting and total insulin secretion were similar in the two groups. However, the area under the insulin secretion rate curve during the first hour after glucose loading increased only in PPHG (Figure 2). Both insulin sensitivity and β -cell glucose sensitivity were markedly improved after surgery to the same extent in the two groups (Figure 3). Insulin clearance during the OGTT was higher in the No-PPHG than in the PPHG group. Insulin clearance increased after RYGB but not LSG.

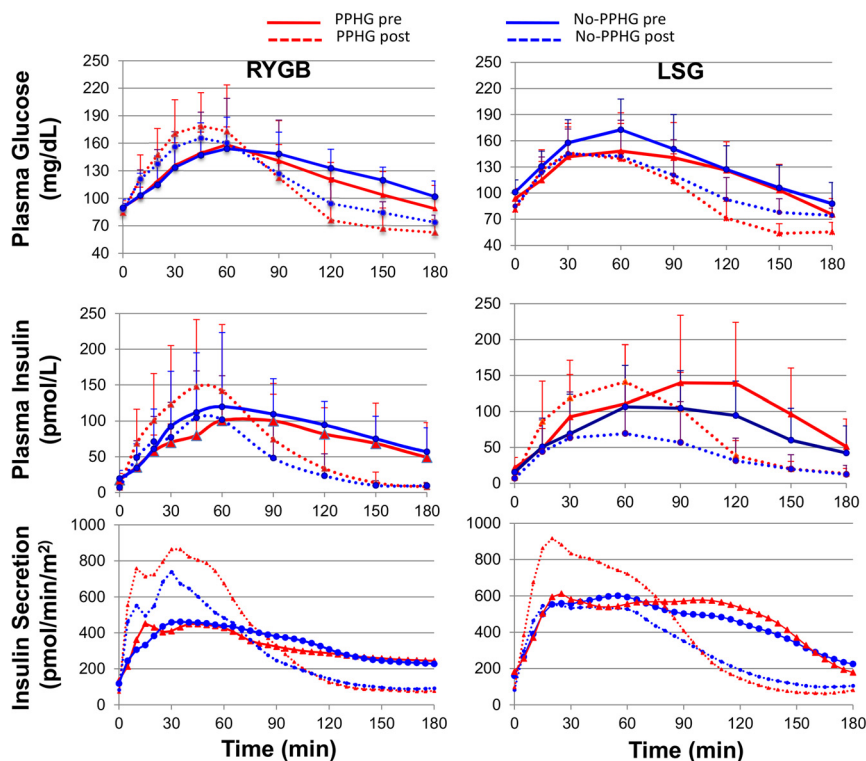


Figure 2. Plasma glucose and insulin concentrations and insulin secretion during the OGTT in RYGB and LSG. Full lines denote presurgery, dotted lines are postsurgery values; subjects with spontaneous self-reported PPHG are in red; and those without PPHG are in blue. Plots are mean ± SEM.

Combined surgery groups

In the pooled data set from all study subjects, surgery-induced changes in

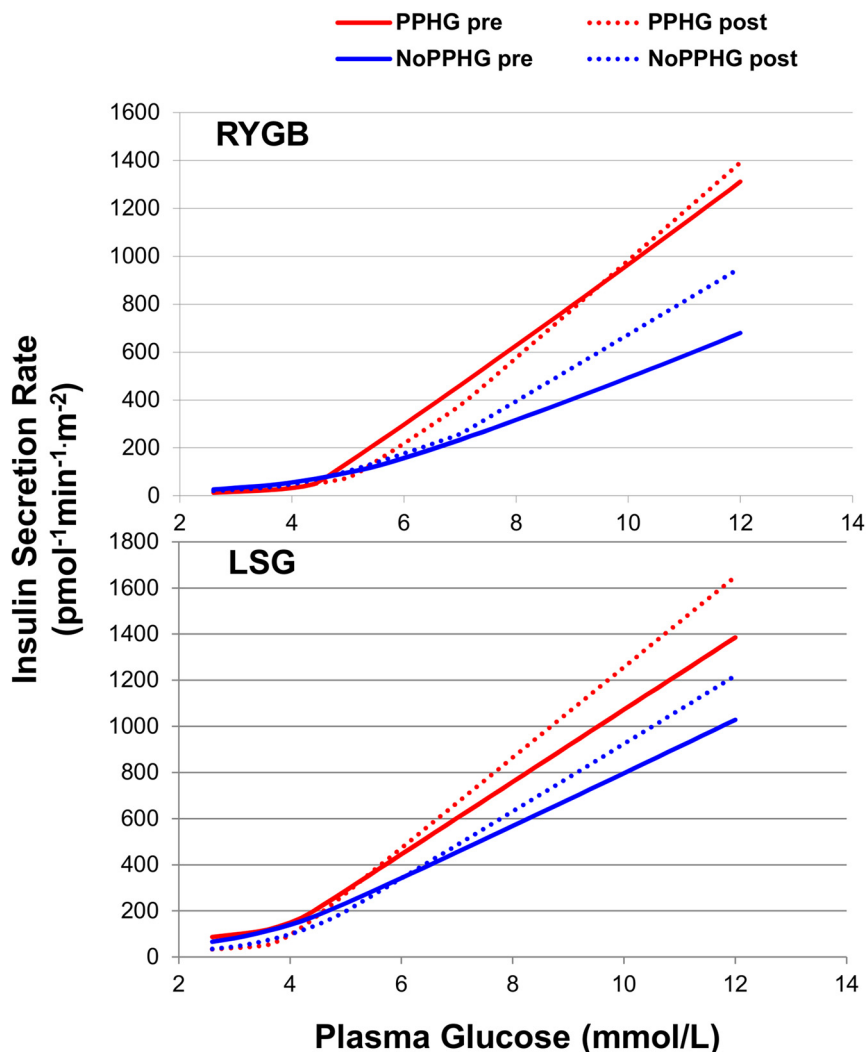


Figure 3. Relationship between insulin secretion rates and concomitant plasma glucose concentrations during the OGTT before and after surgery. The average slope of such regression lines is a measure of β -cell glucose sensitivity.

insulin sensitivity were positively related to the corresponding changes in BMI ($r = 0.67, P < .0001$) and glucose nadir ($r = 0.50, P < .0001$); furthermore, insulin sensitivity was directly correlated with insulin clearance during the OGTT ($r = 0.33, P < .0001$). An inverse correlation was found between β -cell glucose sensitivity and glucose nadir ($r = 0.37, P < .0001$) and BMI ($r = 0.24, P < .001$). The glucose peak was inversely related to insulin clearance ($r = 0.26, P = .001$) and positively with total insulin secretion ($r = 0.27, P = .0006$).

In a logistic regression model, insulin sensitivity ($r = 0.031, P = .002$), insulin clearance ($r = -2.92, P = .029$), and glucose nadir ($r = -0.06, P = .036$) during the pre-surgery OGTT predicted the occurrence of postprandial hypoglycemia after surgery.

Discussion

In the present study, mild to moderate PPHG was identified as spontaneous self-reporting of hypoglycemic symptoms/

signs over 2 years after bariatric surgery, confirmed by low glucose values on an OGTT performed at a follow-up visit. None of the PPHG participants reported severe postprandial hypoglycemia because none required treatment beyond dietary habit changes, and no subjects labeled as No-PPHG had any evidence, clinical or biochemical, of hypoglycemia. Therefore, by design we compared individuals with clinical symptoms and positive on a strong provocative test with individuals who were negative on both accounts to enhance the identification of the factors predictive of postsurgical postprandial hypoglycemia.

The main finding is that higher insulin sensitivity and β -cell glucose sensitivity, and lower plasma glucose nadir and insulin clearance during the presurgery OGTT, are significant predictors of the occurrence of PPHG in nondiabetic subjects undergoing bariatric surgery. In particular, before surgery the study participants (BMI averaging 49 kg/m^2) had an estimated insulin sensitivity of $355 \text{ mL/min}^{-1} \cdot \text{m}^{-2}$, ie, approximately 25% lower than in nondiabetic subjects with a BMI of 25 kg/m^2 or less (24), which improved after surgery in approximate proportion to the fall in BMI, as expected (25). In contrast, their β -cell glucose sensitivity was, on average ($95 \text{ pmol/min}^{-1} \cdot \text{m}^2 \cdot \text{mM}^{-1}$), well within the normal range before the operation and rose significantly after surgery. In the 32 subjects who developed spontaneous self-reported PPHG after either surgery, the baseline BMI was lower (44.6 vs 51.0 kg/m^2), insulin sensitivity was higher (389 vs $336 \text{ mL/min}^{-1} \cdot \text{m}^{-2}$), and β -cell glucose sensitivity was stronger (117 vs $81 \text{ pmol/min}^{-1} \cdot \text{m}^2/\text{mM}^{-1}$, Figure 3) as compared with the subjects without PPHG. As a consequence, the plasma glucose concentrations during the OGTT were lower in PPHG than in No-PPHG (all tables).

The metabolic phenotype included a somewhat lower clearance rate of plasma insulin and higher plasma insulin concentrations during the OGTT. Furthermore, the glucose curve showed an earlier peak with a subsequent more rapid fall toward a lower glucose nadir (Figure 2); correspondingly, the fraction of post-OGTT insulin output occurring during the first hour was larger in PPHG than No-PPHG (45% vs 40%). The latter feature is compatible

Table 2. Anthropometrics and Metabolic Parameters of Subjects Undergoing Sleeve Gastrectomy

	PPHG Before	PPHG After	No-PPHG Before	No-PPHG After	P Value ^a	P Value ^b	P Value ^c	P Value ^d
n	11	11	40	40				
Sex (F/M)	8/3		28/12		ns			
Age, y	45 ± 11		49 ± 10		ns			
BMI, kg/m ²	46.8 ± 7.3	33.9 ± 6.3	51.3 ± 8.2	37.6 ± 6.3	.08	ns	.0001	ns
Fasting glucose, mmol/L	5.1 ± 0.6	4.4 ± 0.2	5.5 ± 0.6	4.7 ± 0.5	.04	ns	ns	ns
Glucose peak, mmol/L	6.8 ± 1.5	5.5 ± 0.8	9.5 ± 1.7	5.9 ± 1.1	ns	ns	.0001	ns
Glucose nadir, mmol/L	4.1 ± 1.2	2.3 ± 0.4	4.6 ± 1.3	3.6 ± 0.6	.05	.0009	.0001	ns
Time of peak glucose, min	68 ± 43	46 ± 21	62 ± 33	43 ± 22	ns	ns	.002	ns
Fasting insulin, pmol/L	113 ± 91	43 ± 30	83 ± 69	35 ± 30	ns	ns	.0001	ns
Fasting ISR, pmol/min ⁻¹ · m ⁻²	159 ± 77	97 ± 29	179 ± 70	94 ± 37	ns	ns	.0001	ns
Total IS, nmol/m ⁻²	89 ± 27	80 ± 14	85 ± 21	65 ± 17	ns	ns	.0001	ns
OGIS, mL/min ⁻¹ · m ⁻²	380 ± 48	461 ± 74	339 ± 60	446 ± 57	.05	ns	.0001	ns
Fasting MCR _I , L/min ⁻¹ · m ⁻²	1.8 ± 0.7	2.1 ± 1.1	2.0 ± 1.1	2.4 ± 1.1	ns	ns	ns	ns
Total MCR _I , L/min ⁻¹ · m ⁻²	1.0 ± 0.3	0.9 ± 0.2	1.1 ± 0.4	1.3 ± 0.5	ns	.014	ns	ns
Insulin AUC ₀₋₆₀ , nmol/m ⁻²	33 ± 13	49 ± 8	30 ± 9	33 ± 10	ns	.006	.0001	.001
β-GS, pmol/min ⁻¹ · m ² · mM ⁻¹	114 ± 32	165 ± 58	86 ± 33	132 ± 69	.02	.014	.0001	ns

Abbreviations: insulin AUC₀₋₆₀, insulin output during the first hour of the OGTT; IS, insulin secretion; ISR, insulin secretion rate; ns, not significant.

^a Before PPHG vs before No-PPHG.

^b PPHG vs No-PPHG group.

^c Before vs after surgery.

^d Surgery × group.

with a more rapid rate of gastric emptying in subjects destined to experience spontaneous PPHG (26). Although GI hormones (eg, GLP-1 and gastric inhibitory peptide) were not measured in the current study, solid evidence links the rate of gastric emptying with the rate of release of GI hormones, in health and type 2 diabetes (27–29) as well as after bariatric surgery (20), which in turn potentiates a glucose-induced insulin response.

After RYGB, the metabolic picture (glucose tolerance, insulin sensitivity, β-cell function) generally improved because the BMI dropped by an average 15 U. In all subjects, RYGB anticipated the time of the OGTT glucose peak and lowered the plasma glucose nadir through more rapid dumping of gastric contents into the small bowel. In the PPHG subjects, however, the features predisposing to PPHG were accentuated as compared with No-PPHG subjects. The relative potency of these factors probably varies among subjects and is difficult to gauge. First, PPHG may be detected beyond the time frame of the current study. Second, in some individuals a lesser weight loss might protect against PPHG despite a high load of predisposing factors; in yet other subjects, GI hormone release or action may be defective or preexisting insulin sensitivity be impaired. Third, gastric emptying may change over time because of long-term adaptations of motility or ensuing autonomic neuropathy (eg, long term and/or uncontrolled diabetes). Finally, the pattern of predisposing factors may differ, depending on whether PPHG manifests itself only once or repeatedly and whether it is mild to moderate or

severe. Our study outlines only the physiological background that constitutes the risk.

The effects of LSG on the measured metabolic changes were generally similar to those of RYGB (all tables). One interesting aspect of our study is the discrepancy between RYGB and LSG in the presence of neuroglycopenic symptoms during OGTT-induced PPHG, with RYGB patients having symptoms and LSG patients not having symptoms in the face of very similar glucose nadirs during testing, although both RYGB and LSG subjects spontaneously self-reported hypoglycemic symptoms in their everyday life after surgery. At present, we have no explanation for this discrepancy, and further studies are needed to elucidate this aspect. Because the postsurgery glucose peak in PPHG was higher with RYGB than LSG, it is possible that the more rapid fall to nadir in the former case triggered a stronger activation of the sympathetic nervous system (30). Nevertheless, even with the relatively small numbers in our series, the fact that no large differences stand out from either the baseline or the postsurgery metabolic results may suggest that the duodenal bypass does not play a major role over and above the size and mode of gastric restriction.

Additional factors that were not measured in our study might have had a part: for example, the following: 1) lack of reduction of β-cell mass, which was constitutively increased during the obese state prior to surgery, 2) gut hormone activation of new β-cell formation due to surgically induced changes in the secretion of insulinotropic incre-

tins or other regulatory peptides, 3) abnormal counter-regulatory hormonal responses, 4) changes in gut microbiota, and 5) changes in bile acid composition.

It should be emphasized that forms of spontaneous PPHG have been described in overweight and obese adults independently of bariatric surgery. Hyperinsulinemic hypoglycemia in adults may be caused by pancreatic β -cell tumors, insulinoma (31, 32), and insulin or insulin receptor autoantibodies (33–35). Cases of spontaneous PPHG have been described to result from mutations in the glucokinase gene (36) and the promoter of monocarboxylate transporter 1 (37). In some of these genetic forms, a reduction in insulin clearance was also described in subjects with spontaneous PPHG. In our study, we did not perform a genetic analysis, but a genetic predisposition may have been present in at least some of these patients after RYGB or LSG.

In summary, after both surgeries the shape of the glucose curve shows an earlier glucose peak followed by a quicker decline in glycemia, an expected consequence of the anatomical changes. This feature alone, however, does not distinguish subjects experiencing spontaneous PPHG from those who do not. In contrast, the occurrence of spontaneous PPHG is consistently predicted by a better metabolic phenotype, including higher insulin sensitivity and β -cell glucose sensitivity before surgery; a lower BMI before the intervention and a higher glucose peak on the OGTT after the operation may make additional contributions. A strong PPHG provocative test such as the OGTT as part of the preoperative assessment may have clinical utility in the prevention of post-bariatric hypoglycemia.

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