

Patients with Neuroglycopenia after Gastric Bypass Surgery Have Exaggerated Incretin and Insulin Secretory Responses to a Mixed Meal

A. B. Goldfine, E. C. Mun, E. Devine, R. Bernier, M. Baz-Hecht, D. B. Jones, B. E. Schneider, J. J. Holst, and M. E. Patti

Joslin Diabetes Center (A.B.G., E.D., R.B., M.B.-H., M.E.P.), Boston, Massachusetts 02215; Harvard Medical School (A.B.G., E.C.M., M.B.-H., D.B.J., B.E.S., M.E.P.), Boston, Massachusetts 02115; Brigham and Women's Hospital (A.B.G., E.C.M.), Boston, Massachusetts 02115; Beth Israel Deaconess Medical Center (D.B.J., B.E.S.), Boston, Massachusetts 02215; and Department of Medical Physiology (J.J.H.), The Panum Institute, University of Copenhagen, DK-2200 Copenhagen, Denmark

Context and Objective: Hyperinsulinemic hypoglycemia is newly recognized as a rare but important complication after Roux-en-Y gastric bypass (GB). The etiology of the syndrome and metabolic characteristics remain incompletely understood. Recent studies suggest that levels of incretin hormones are increased after GB and may promote excessive β -cell function and/or growth.

Patients and Methods: We performed a cross-sectional analysis of metabolic variables, in both the fasting state and after a liquid mixed-meal challenge, in four subject groups: 1) with clinically significant hypoglycemia [neuroglycopenia (NG)] after GB surgery, 2) with no symptoms of hypoglycemia at similar duration after GB surgery, 3) without GB similar to preoperative body mass index of the surgical cohorts, and 4) without GB similar to current body mass index of the surgical cohorts.

Results: Insulin and C-peptide after the liquid mixed meal were both higher relative to the glucose level achieved in persons after GB with

NG compared with asymptomatic individuals. Glucagon, glucagon-like peptide 1, and glucose-dependent insulinotropic peptide levels were higher in both post-GB surgical groups compared with both overweight and morbidly obese persons, and glucagon-like peptide 1 was markedly higher in the group with NG. Insulin resistance, assessed by homeostasis model assessment of insulin resistance, the composite insulin sensitivity index, or adiponectin, was similar in both post-GB groups. Dumping score was also higher in both GB groups but did not discriminate between asymptomatic and symptomatic patients. Notably, the frequency of asymptomatic hypoglycemia after a liquid mixed meal was high in post-GB patients.

Conclusion: A robust insulin secretory response was associated with postprandial hypoglycemia in patients after GB presenting with NG. Increased incretin levels may contribute to the increased insulin secretory response. (*J Clin Endocrinol Metab* 92: 4678–4685, 2007)

THE INCREASING PREVALENCE of obesity has led to parallel increases in bariatric surgery, with 13,000 procedures performed in 1998, and over 130,000 in 2005 in the United States alone (1). Sustained weight reductions of up to 50% of excess body weight are achieved in the majority of patients (2), and bariatric surgery is more effective in producing sustained weight loss than nonsurgical approaches (3). Roux-en-Y gastric bypass (GB) may induce weight loss by gastric restriction, leading to distension of the small gastric pouch and early satiety, mild malabsorption, and altered secretion of peptides regulating appetite and satiety, including ghrelin and peptide YY (4–6). Moreover, gastric bypass causes rapid resolution of insulin resistance and improved insulin secretion, perhaps mediated in part by increased

glucagon-like peptide 1 (GLP-1) (7), even before major weight loss has been achieved (8).

Recognized long-term complications of gastric bypass include micronutrient deficiencies, neuropathy, excess skin, and hernia. Anatomical reconfiguration to a small gastric pouch and long enteric limb predisposes to dumping syndrome. A rare complication of GB has recently been recognized, characterized by severe postprandial hypoglycemia and hyperinsulinemia (9–11). In such patients, hypoglycemia is associated with loss of consciousness and/or seizures, and is poorly responsive to nutritional therapy, acarbose, somatostatin analogs, and diazoxide. In the limited number of patients managed with palliative partial pancreatectomy due to hypoglycemia refractory to medical treatment, histopathology has revealed diffuse islet hyperplasia with small and large islets, including areas of sheets of islets, without evidence of insulinoma or neoplastic transformation (9–11). Some islets have been noted to be adjacent to and budding from ducts. Conversely, another study using a large number of autopsy controls for comparison concluded that islet mass was not excessive in post-bypass hypoglycemia patients, but nuclear size was increased, potentially indicating cellular hyperfunction (12). Thus, the complex pathophysiology of this syndrome remains incompletely understood. We as-

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Abbreviations: BMI, Body mass index; CISI, composite insulin sensitivity index; GB, Roux-en Y gastric bypass; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MOB, morbidly obese; NG, neuroglycopenia; OW, overweight.

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sessed basal and provocative metabolic response to a standard mixed meal in patients presenting with clinically significant hypoglycemia in comparison with individuals after gastric bypass without symptoms of hypoglycemia, as well as overweight (OW) and morbidly overweight (MOB) controls.

Subjects and Methods

Subjects

The Joslin Diabetes Center Institutional Review Board approved the study. Written informed consent was obtained from participants. There were 12 subjects recruited from clinical practice who had undergone GB surgery and presented with medically significant hypoglycemia [neuroglycopenia (NG)], defined by documented hypoglycemia associated with altered mental status or level of consciousness, with or without seizure, requiring assistance of others. Nine subjects who had undergone uncomplicated GB procedures 2–4 yr previously and five MOB individuals being evaluated for bariatric surgery were recruited from local clinics, and 10 OW, non-MOB subjects from newspaper advertisement. All subjects were weight stable for 6 months and had no history of diabetes or glucose intolerance.

All subjects were instructed to consume at least 200-g carbohydrate for 3 d before visits. OW and MOB groups underwent 2-h 75-g oral glucose tolerance and were nondiabetic (13). Height and weight were measured using a wall-mounted stadiometer (Holtain Ltd., Crymch, UK) and electronic scale (model 0501; Acme Scale Co., San Leandro, CA), and sitting blood pressure was measured. Fasting blood samples were obtained before a liquid mixed meal (Ensure, 9 g protein, 40 g carbohydrate, 6 g fat, 240 ml; Abbott Laboratories, Abbott Park, IL). Additional blood samples were collected at 10, 20, 30, 60, and 120 min for glucose, insulin, C-peptide, glucagon, GLP-1, and glucose-dependent insulinotropic peptide (GIP).

Assays

Glucose was measured by glucose oxidation, fasting cholesterol and high-density lipoprotein (HDL) by cholesterol esterase assay, triglycerides via hydrolysis to glycerol, and unesterified free fatty acid (Synchron CX3 δ and CX9; Beckman Coulter, Brea, CA), and hemoglobin A1c by HPLC (Tosoh 2.2; Tosoh Bioscience, San Francisco, CA). Immunoassays were performed in duplicate on fasting serum by commercial assay, including RIA for insulin and C-peptide (Diagnostic Systems Laboratories, Webster, TX), RIA for adiponectin and ELISA for leptin (LINCO Research, Inc., St. Charles, MO), and ELISA for visfatin (Phoenix Pharmaceuticals, Belmont, CA).

GIP and GLP-1 were measured from plasma and glucagon from serum after extraction with 70% ethanol (vol/vol, final concentration). For the GIP RIA, C-terminally directed antiserum R65 was used, which cross-reacts fully with human GIP, but not with GIP 8000 (14). The antiserum reacts equally with intact GIP and GIP 3–42, the primary metabolite. Human GIP and 125-I human GIP (70 MBq/nmol) were used for standards and tracer. Plasma GLP-1 concentrations were measured against standards of synthetic GLP-1 7–36 amide using antiserum no. 89390, specific for the amidated C terminus of GLP-1 and, therefore, equally reactive with intact GLP-1 and with GLP-1 3–36 amide, the primary metabolite (15). Because of rapid and intravascular conversion of both GIP and GLP-1 to their primary metabolites, it is essential to determine both intact hormone and the metabolite for estimation of secretion of these hormones. The glucagon RIA was directed against the C terminus of the glucagon molecule (no. 4305) and, therefore, mainly measures glucagon of pancreatic origin (16). Assay sensitivity for GIP, GLP-1, and glucagon was less than 1 pmol/liter, intraassay coefficient of variation less than 6% at 20 pmol/liter, and recovery of standard, added to plasma before extraction, about 100% when corrected for losses inherent in plasma extraction procedures.

Dumping score

Dumping score was calculated using a formula reflecting change in pulse and plasma volume: score = $685 \times (1 - [\text{Hct}_{\text{basal}} (100 - \text{Hct}_{20\text{min}})] /$

$\text{Hct}_{20\text{min}} \times (100 - \text{Hct}_{20\text{min}})] + 100 (\text{Pulse}_{20\text{min}} - \text{Pulse}_{\text{basal}}) / \text{Pulse}_{\text{basal}}$, where Hct is the abbreviation for hematocrit (17).

Insulin sensitivity

Insulin resistance was calculated using homeostatic model assessment as homeostasis model assessment of insulin resistance (HOMA-IR) = $[\text{fasting glucose (mmol/liter)} \times \text{fasting insulin } (\mu\text{U/ml})] / 22.5$ (18) and composite insulin sensitivity index (CISI) as $10,000 / [\text{square root of (fasting glucose} \times \text{fasting insulin)} \times (\text{mean glucose} \times \text{mean insulin during a mixed meal})]$ (19).

Statistical analysis

Results are presented as mean \pm SE. Primary comparisons were performed between post-GB groups with and without NG. ANOVA in multiple-group comparisons and repeated-measures ANOVA for variables measured at several times after a mixed meal were performed using StatView (SAS Institute Inc., Cary, NC). Results were considered significant for two-tailed *P* values less than 0.05.

Results

Characteristics of the 36 subjects are summarized in Table 1. Of the 12 individuals with clinically significant hypoglycemia documented after GB (Table 2), none had diabetes diagnosed preoperatively. Five subjects provided history of symptoms suspicious for hypoglycemia predating GB surgery, although there was no documentation or evaluation preceding surgery. All studies were performed before initiation of specific therapies for hypoglycemia. None had pancreas abnormalities by high-resolution computed tomography or magnetic resonance imaging. Six subjects had abnormal selective arterial calcium stimulation tests indicating pancreatic β -cell hyperfunction. Three subjects underwent 72-h fast; none had hypoglycemia. Two had subsequent subtotal pancreatectomy and pathology suggestive of islet expansion (cases 2 and 3 in Ref. 10).

Persons with gastric bypass and NG (GB + NG) were similar to those who remained asymptomatic (GB) with respect to preoperative body mass index (BMI) (51.1 ± 11.4 vs. 50.2 ± 11.4 kg/m²; *P* = 0.9; GB + NG vs. GB, respectively), duration postoperatively (3.3 ± 1.6 vs. 2.8 ± 1.0 yr; *P* = 0.5), magnitude of weight loss (54.8 ± 23.9 vs. 56.8 ± 32.3 kg; *P* = 0.9), and BMI at the evaluation (30.7 ± 4.9 vs. 29.9 ± 4.5 kg/m²; *P* = 0.7). To control for potential effects related to preoperative obesity magnitude, as well as for current BMI, five MOB subjects matched for preoperative BMI and 10 overweight subjects similar to current BMI (OW) were also studied. Consistent with the positive effects of gastric bypass on metabolic parameters, postoperative subjects had lower BMI, waist circumference, fasting triglyceride, and increased HDL as compared with MOB controls. In addition, post-bypass subjects had lower triglyceride (*P* < 0.02) and higher HDL (*P* < 0.02) than OW. Neither lipids nor blood pressure differed between post-bypass patients with significant hypoglycemia and individuals who remained asymptomatic.

Fasting glucose did not differ between GB + NG and GB groups (86.4 ± 2.3 vs. 83.7 ± 2.3 mg/dl GB + NG vs. GB; *P* = 0.4) (4.80 ± 0.13 vs. 4.64 ± 0.13 mmol/liter) but were lower in both post-GB groups than in either OW (93.9 ± 1.2 mg/dl) (5.21 ± 0.06 mmol/liter) or MOB groups (96.4 ± 4.2 mg/dl) (5.35 ± 0.06 mmol/liter) (all *P* < 0.02) (Fig. 1A). Early glucose levels after a mixed meal were markedly higher in both GB

TABLE 1. Characteristics of the study cohorts

	Gastric bypass with NG	Gastric bypass	OW	MOB
Age (yr)	48 ± 3	48 ± 3	48 ± 3	41 ± 7
Gender (M/F)	2/10	2/7	6/4	0/5
Preop BMI (kg/m ²)	51.1 ± 3.3	50.2 ± 3.8	na	na
BMI (kg/m ²)	30.7 ± 1.4	29.9 ± 1.5	31.5 ± 1.3	52.0 ± 2.9 ^{a,b}
Waist (cm)	96 ± 3	95 ± 6	102 ± 5	143 ± 8 ^{a,b}
HbA1c (%)	5.2 ± 0.1	5.2 ± 0.2	5.6 ± 0.1	5.5 ± 0.2
Chol (mg/dl)	167 ± 9	176 ± 9	188 ± 8	189 ± 16
TG (mg/dl)	78 ± 9	51 ± 4	132 ± 35 ^c	127 ± 32 ^a
HDL (mg/dl)	53 ± 3	71 ± 8	42 ± 3 ^d	39 ± 4 ^e
Systolic BP (mm Hg)	128 ± 8	126 ± 6	120 ± 2	126 ± 6
Diastolic BP (mm Hg)	76 ± 3	73 ± 3	73 ± 2	73 ± 3
HOMA-IR (U)	1.4 ± 0.2	1.7 ± 0.8	3.5 ± 0.8 ^{c,e}	6.8 ± 0.8 ^{a,b,d}
Adiponectin (μg/dl)	26.1 ± 4.7	25.7 ± 3.8	13.2 ± 2.9 ^{c,e}	8.0 ± 1.4 ^{a,d}
Leptin (ng/ml)	15.0 ± 3.2	13.1 ± 1.9	17.2 ± 3.7	70.8 ± 9.9 ^{a,b,d}
Visfatin (ng/ml)	25.2 ± 2.5	30.9 ± 1.7	23.8 ± 1.2	25.3 ± 2.5 ^c
Dumping score (%)	92 ± 18	62 ± 10	-9 ± 10 ^{a,d}	-6 ± 13 ^{a,d}

Characteristics (mean ± SE) of study groups are presented, including after gastric bypass with symptomatic hypoglycemia, after gastric bypass with no symptoms, OW, and MOB. Cholesterol (Chol) (mg/dl) × 0.0259 = (mmol/liter), triglyceride (mg/dl) × 0.0113 = (mmol/liter), and HDL (mg/dl) × 0.0259 = (mmol/liter). BP, Blood pressure; F, female; HbA1c, glycosylated hemoglobin; M, male; na, not applicable; Preop, preoperative; TG, triglyceride.

ANOVA ^c*P* < 0.05 and ^d*P* < 0.009 vs. GB + NG; ^e*P* < 0.05 and ^a*P* < 0.009 vs. GB; and ^b*P* < 0.009 vs. OW.

groups, whereas in the second hour, glucose levels were lower compared with the two nonsurgical groups. The time-to-peak glucose was shorter in GB + NG (18 ± 2.2 vs. 24 ± 2.4 min, GB + NG vs. GB; *P* = 0.02). Glucose levels were significantly lower in GB + NG compared with GB both at 30 min after meal (128 ± 9 vs. 162 ± 13 mg/dl; *P* = 0.01) (7.10 ± 0.50 vs. 8.99 ± 0.72 mmol/liter) and during the first 30 min after meal (repeated measures ANOVA, *P* < 0.03). However, GB + NG demonstrated only marginally lower glucoses over the entire 2 h than GB (repeated-measures ANOVA, *P* = 0.06).

It is important to note that three of the nine asymptomatic individuals after GB surgery developed completely asymptomatic hypoglycemia (<60 mg/dl) (<3.33 mmol/liter) with inappropriately high insulin levels (>4 μU/ml) (27.8 pmol/liter) at 60–120 min after load, and five of nine had glucose levels less than 70 mg/dl (<3.89 mmol/liter) (lower limit of normal) (Table 3). These data demonstrate a high frequency of low blood glucose levels after a mixed meal, even in the absence of symptoms.

Fasting insulin did not differ between GB + NG and GB

(6.4 ± 0.6 vs. 7.9 ± 3.4 μU/ml, GB + NG vs. GB; *P* = 0.7) (44.4 ± 4.2 vs. 54.9 ± 23.6 pmol/liter) but was lower in both GB groups than in OW (15.2 ± 3.2 μU/ml) (105.6 ± 22.2 pmol/liter) and MOB controls (28.1 ± 2.6 μU/ml) (195.1 ± 18.1 pmol/liter) (all *P* < 0.05) (Fig. 1B). The rapid increase in glucose after meal challenge was associated with a rapid increase in insulin in both GB surgical groups within the first 30 min, whereas over the second hour, insulin levels were lower. GB + NG demonstrated only marginally higher dynamic insulin responses than GB (repeated-measures ANOVA, *P* = 0.1). As expected, fasting insulin was higher in the MOB group than OW (*P* = 0.005), as was the insulin response to a mixed meal.

Fasting C-peptide did not differ between those with and without clinically significant hypoglycemia (2.6 ± 0.1 vs. 3.2 ± 0.7 ng/ml, GB + NG vs. GB; *P* = 0.4) (0.87 ± 0.03 vs. 1.07 ± 0.23 nmol/liter) but was lower in GB + NG compared with the two control groups, OW (4.0 ± 0.6 ng/ml; *P* = 0.05) (1.33 ± 0.20 nmol/liter) and MOB (7.3 ± 1.2 ng/ml; *P* < 0.0001) (2.43 ± 0.40 nmol/liter). However, C-peptide was significantly higher at 10 min (12.5 ± 1.4 vs. 8.5 ± 0.9 ng/ml,

TABLE 2. Clinical presentation of NG after gastric bypass surgery

Subject	Time from surgery to first neuroglycopenic event (yr)	Clinical description	Postprandial timing (h)	Glucose level (mg/dl)
A	1.6	Motor vehicle accident	1–1.5	29 (CS)
B	1.8	Loss of consciousness	1	50 (CS)
C	2.4	Presyncope, confusion	3	Low (CS)
D	2.8	Unresponsive	2	58 (CS)
E	0.8	Syncope, blurred vision	1	24 (V) ^a
F	3.3	Confusion, blurred vision	1	47 (CS)
G	1.7	Confusion	1–1.5	25 (V)
H	1.3	Confusion	1.5	39 (V)
I	2.7	Confusion	1	23 (CS)
J	2.0	Presyncope, confusion	3–4	40s (CS)
K	1.3	Syncope	2–3	Low (CS)
L	3.8	Grand mal seizure	1.5	48 (V)

Historical symptoms and laboratory values obtained during first episodes of spontaneous neuroglycopenia. Upon mixed meal tolerance test provocation, venous plasma glucose of patient capillary specimen was 61 mg/dl, and in patient K, 53 mg/dl. CS, Capillary specimen; V, venous specimen. Low, specific glucose value was not documented in medical record, though noted to be low.

^a Concurrent insulin level was 20 μU/ml.

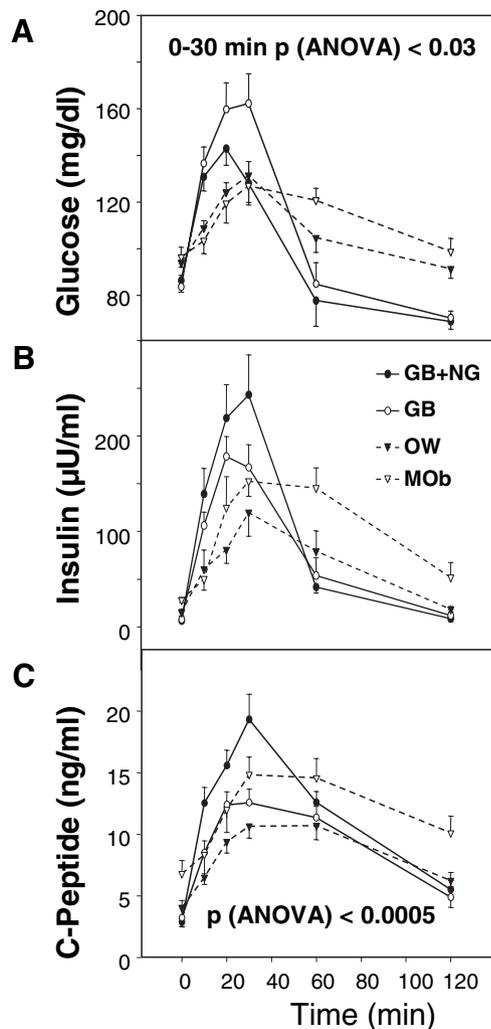


FIG. 1. A, Lower glucose levels after a mixed meal in patients with NG after GB surgery. Glucose excursions are lower in the GB + NG group compared with GB 30 min after a liquid mixed meal (0- to 30-min repeated-measures ANOVA, $P < 0.03$) and tend to be lower over the 2-h interval (0–120 min repeated measures ANOVA, $P = 0.06$). B, Insulin levels are similar after a mixed meal in patients with NG after gastric bypass surgery. Insulin excursions are demonstrated after a liquid mixed meal. C, Higher C-peptide levels after a mixed meal in patients with NG after gastric bypass surgery. C-peptide excursions are highest in the GB + NG group (repeated measures ANOVA, $P < 0.0005$), particularly in the first 30 min after load. Glucose (mg/dl) $\times 0.0555 =$ (mmol/liter). Insulin (μ U/ml) $\times 6.945 =$ (pmol/liter). C-peptide (ng/ml) $\times 0.333 =$ (nmol/liter).

GB + NG vs. GB; $P < 0.02$) (4.16 ± 0.47 vs. 2.83 ± 0.30 nmol/liter), 20 min (15.8 ± 1.3 vs. 12.4 ± 1.1 ng/ml; $P < 0.05$) (5.26 ± 0.43 vs. 4.13 ± 0.34 nmol/liter), and 30 min (19.3 ± 2.0 vs. 12.6 ± 1.1 ng/ml; $P = 0.003$) (6.43 ± 0.67 vs. 4.20 ± 0.37 nmol/liter) after meal stimulus in GB + NG compared with GB (Fig. 1C). GB + NG demonstrated significantly higher C-peptide levels than GB over the entire meal (repeated-measures ANOVA, $P = 0.005$), particularly during the first 30 min. As expected, both fasting ($P < 0.003$) and post-meal C-peptide levels were greater in normoglycemic MOB compared with OW persons.

Next, we assessed the molar ratio of insulin and C-peptide. Both insulin and C-peptide to glucose ratios were higher in GB

TABLE 3. Frequent hypoglycemic response to a mixed meal in asymptomatic patients after gastric bypass surgery

Subject	Fasting	30 min	60 min	120 min
1	79	114	39 ^a	69
2	91	179	91	70
3	83	167	110	82
4	93	155	97	68
5	72	109	47 ^a	66
6	79	226	119	76
7	87	179	83	57 ^a
8	90	196	104	83
9	79	135	74	62

The glucose response to a liquid mixed meal is shown for consecutive persons with no hypoglycemic symptoms after GB surgery. ^a Three of the nine subjects (33%) developed asymptomatic hypoglycemia associated with measurable insulin levels.

+ NG compared with GB (both repeated-measures ANOVA, $P = 0.001$) (Fig. 2, A and B). Similarly, C-peptide levels were higher in GB + NG compared with GB for any glucose level achieved (repeated-measures ANOVA, $P = 0.001$) (Fig. 2C).

We evaluated whether glucagon levels might suggest limited counter-regulatory capacity in GB + NG. Glucagon excursions did not differ in GB + NG compared with GB (Fig. 3A) but were higher after GB than in nonsurgical groups (repeated-measures ANOVA, $P < 0.003$) and in OW compared with MOB (repeated-measures ANOVA, $P = 0.02$).

Fasting GLP-1 levels were significantly higher in GB + NG (24.7 ± 3.6 pmol/liter) compared with GB (13.8 ± 1.7 pmol/liter; $P < 0.02$), tended to be higher than OW (16.6 ± 1.5 pmol/liter; $P = 0.07$), and were similar to MOB (25.4 ± 7.5 pmol/liter; $P = 0.9$) (Fig. 3B, inset). In addition, post-meal GLP-1 levels tended to be higher in GB + NG at 10 and 20 min, and were significantly higher than GB at 30, 60, and 120 min, by 1.4- to 1.7-fold ($P \leq 0.02$) (Fig. 3B). When considering the dynamic GLP-1 response to a mixed meal, GLP-1 levels were significantly higher in GB + NG than in GB (repeated-measures ANOVA, $P = 0.03$). In addition, GLP-1 levels were 5- to 10-fold higher after gastric bypass than in nonsurgical controls (repeated-measures ANOVA, $P < 0.001$).

Levels of the incretin GIP did not differ between groups in the fasting state. Post-meal GIP levels were also higher in both GB groups compared with OW and MOB. However, levels were lower at 10, 20, and 30 min after load in the GB + NG compared with GB (Fig. 3C). Likewise, the overall GIP response after a mixed meal was significantly lower in GB + NG than in GB (repeated-measures ANOVA, $P = 0.0005$).

Consistent with improved insulin sensitivity after surgical weight loss, HOMA-IR was decreased in both post-GB groups (1.4 ± 0.2 vs. 1.7 ± 0.8 , GB + NG vs. GB; $P = 0.6$) compared with OW (3.5 ± 0.8) and MOB (6.8 ± 0.8) (Table 1). Similarly, adiponectin was increased in both post-GB groups (26.1 ± 4.7 vs. 25.7 ± 3.8 μ g/ml, GB + NG vs. GB; $P = 0.9$) compared with OW (13.1 ± 2.9 μ g/ml) and MOB (8.0 ± 1.4 μ g/ml). However, neither measure differed in GB + NG compared with GB. Furthermore, the CISI tended to be lower in GB + NG compared with GB (4.5 ± 0.4 vs. 7.9 ± 3.1 , GB + NG vs. GB; $P = 0.1$). In parallel with weight differences between groups, fasting leptin was higher in MOB compared with all other groups but did not differ in GB + NG compared with GB. Fasting visfatin (pre-B cell colony enhancing factor) was lower in GB + NG

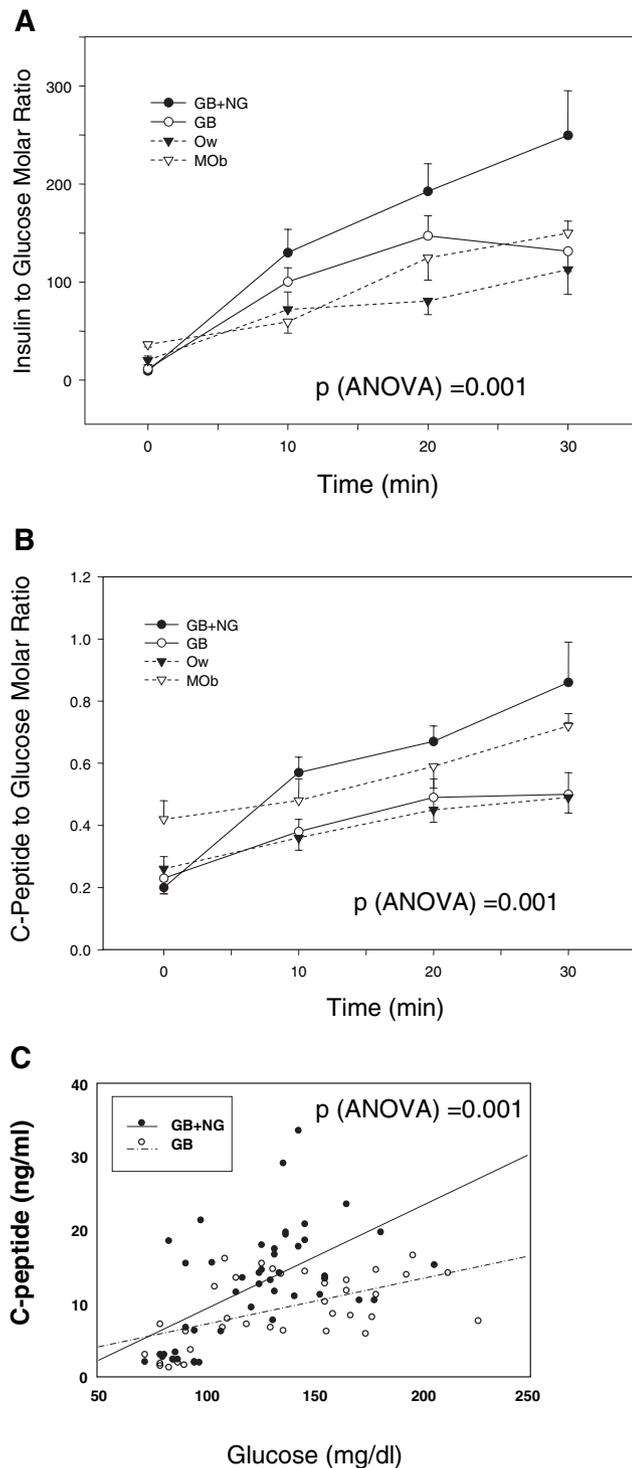


FIG. 2. A, Higher insulin to glucose ratios after a mixed meal in patients with NG after gastric bypass surgery. The molar ratio of insulin to glucose after a mixed meal is higher in the gastric bypass group with NG compared with gastric bypass, and with OW and MOb (repeated-measures ANOVA, $P = 0.001$). B, Higher C-peptide to glucose ratios after a mixed meal in patients with NG after gastric bypass surgery. The molar ratio of C-peptide to glucose is higher after a mixed meal in the GB + NG group compared with GB (repeated-measures ANOVA, $P = 0.001$). C, Higher C-peptide levels for glycemia after a mixed meal in patients with NG after gastric bypass surgery. C-peptide levels are shown for each glucose at times 0–30 min after a liquid mixed meal in GB + NG and GB, and are higher in the GB + NG group compared with GB (repeated measures ANOVA, $P = 0.001$).

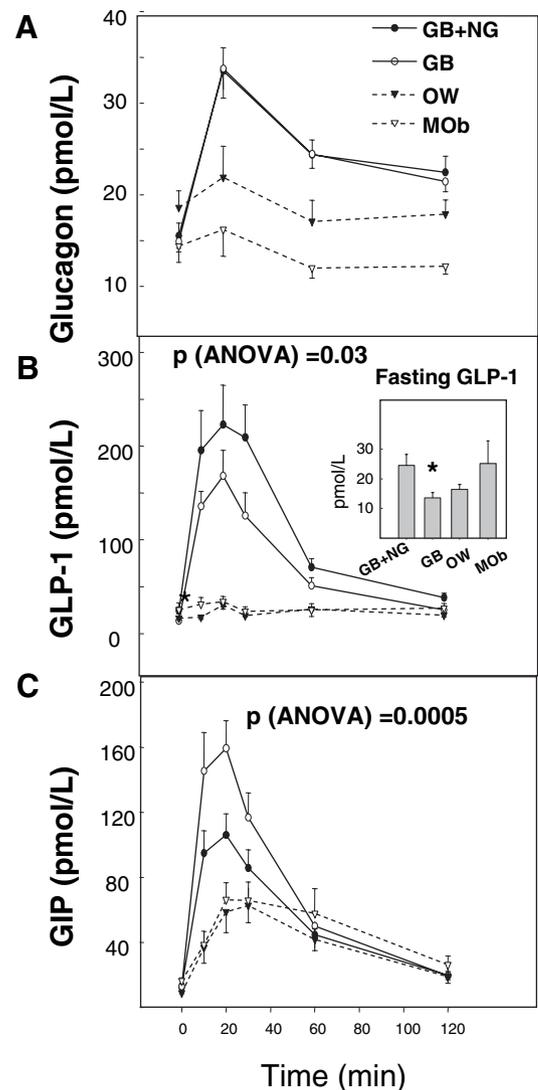


FIG. 3. A, Glucagon levels after a mixed meal are higher after gastric bypass surgery. Glucagon excursions are higher after GB surgery (repeated measures ANOVA, $P < 0.003$) and in OW compared with MOb ($P = 0.02$) but do not differ in the GB + NG compared with GB group. B, Higher GLP-1 after a mixed meal in patients with NG after gastric bypass surgery. GLP-1 excursions are higher after a liquid mixed meal in GB + NG compared with GB (repeated-measures ANOVA, $P = 0.03$). Fasting GLP-1 levels are shown in inset (*, $P < 0.02$ vs. GB + NG, $P = 0.04$ vs. GB). C, GIP levels are higher after a mixed meal in patients with gastric bypass surgery. GIP excursions are higher after a mixed meal in the patients after GB surgery, however, GIP levels are lower in GB + NG group compared with GB (repeated measures ANOVA, $P = 0.0005$).

(21.5 ± 2.5 ng/ml) compared with MOb (30.9 ± 1.7 ng/ml; $P < 0.02$) but did not differ from GB (23.8 ± 1.2 ng/ml; $P = 0.4$) or OW (25.3 ± 2.5 ng/ml; $P = 0.2$). Visfatin levels at 120 min did not differ in any group (data not shown). Finally, there were no differences in fasting or post-meal ghrelin or peptide YY between the two surgical groups (data not shown).

We assessed whether dumping syndrome physiology was playing a role in GB + NG using a previously validated score (17). As expected, both surgical groups had significantly higher dumping scores than either nonsur-

gical group; however, the score did not differ between GB + NG and GB (Table 1).

Discussion

Despite wide implementation and therapeutic success of GB surgery, mechanisms mediating long-term weight loss and improved metabolic homeostasis remain incompletely understood. Severe postprandial hyperinsulinemia with hypoglycemia refractory to dietary and medical management is a recently described complication of GB surgery, which may provide clues to elucidate mechanisms of improved metabolic homeostasis (9–11). The true incidence of this complication is unknown but appears infrequent in proportion to the number of procedures performed. In very severe cases unresponsive to medical and nutritional therapy, pancreatectomy has been performed to ameliorate hypoglycemia; pancreatic pathology has demonstrated diffuse islet hyperplasia or increased nuclear size (12). A similar syndrome occurring in adults without GB, known as noninsulinoma pancreatogenous hyperinsulinemic hypoglycemia, itself is rare (20, 21). Thus, the frequency of hyperinsulinemic hypoglycemia after gastric bypass suggests an association (9). Patterns of high incretin levels and hypoglycemia have been similarly reported after other types of gastric surgery (16, 22, 23). Thus, it is unclear whether the syndrome we are reporting is physiologically distinct. However, it is important due to the large number of bariatric procedures now performed for weight management and the clinical severity of NG in affected individuals. We now report additional cases with clinically significant postprandial hypoglycemia, defined by NG, resistant to medical and nutritional intervention after gastric bypass. We demonstrate robust secretion of insulin, and the incretins GLP-1 and GIP in response to a liquid mixed meal, which together may contribute to severe hypoglycemia.

At present it remains unclear whether patients who develop hyperinsulinemic hypoglycemia after bypass surgery have an unrecognized predisposition to this condition predating bariatric procedures, such as an unrecognized familial hyperinsulinemia syndrome or islet dysfunction. Although in retrospect some patients reported symptoms potentially consistent with hypoglycemia and relieved by food, there was no medical evaluation or documented hypoglycemia predating bariatric surgery. In all subjects, preexisting pathology, if present, may have been partially masked by obesity and insulin resistance before GB.

Alternatively, the syndrome may reflect an altered metabolic milieu after gastric surgery, with potential mechanisms, including: 1) reduced apoptosis of islets after weight loss (in islets previously expanded to compensate for obesity), leading to inappropriately high islet mass relative to current insulin sensitivity; and/or 2) stimulation of islet expansion or hyperfunction by incretins or other metabolic changes induced by gastric bypass surgery. Although two patients with clinically significant hyperinsulinemic hypoglycemia did subsequently demonstrate histopathology consistent with islet expansion (10), it is important to note that we have not assessed islet pathology in the majority of patients in this report because pharmacological approaches to suppress insulin secretion were ongoing, and

surgical therapy was not warranted. However, six subjects had abnormal calcium-stimulated insulin secretion, potentially indicating abnormal function. Furthermore, recent studies demonstrate increased β -cell nuclear diameter, suggestive of increased functional activity (12). In agreement, our studies demonstrate inappropriately robust insulin secretion for the level of glycemia in patients who present with NG after GB.

Several potential mechanisms for functional dysregulation of insulin secretion can be considered. Insulin sensitivity itself may be a determinant of insulin secretion, as recently demonstrated in rodent models of β -cell specific insulin resistance (24). Thus, excessive insulin secretion in humans after GB might be linked to improved insulin sensitivity after weight loss. However, this seems unlikely for several reasons: 1) the discordance in time between rapid improvements in insulin sensitivity after GB and the delay of 1–5 yr after surgery until presentation with NG; and 2) no measurable difference in insulin sensitivity, as assessed by HOMA-IR, CISI, or circulating adiponectin levels. Likewise, we find no evidence for the involvement of other adipocyte-derived cytokines, including leptin or visfatin, which might also regulate systemic metabolism.

The lag time of 1–5 yr until the development of symptomatic hypoglycemia in post-GB patients suggests that islet dysfunction and/or increased mass develops over time after surgery, potentially linked to altered incretin secretion. GLP-1 augments glucose-regulated insulin secretion, promotes islet growth in rodents, and inhibits apoptosis (25). Consistent with short-term trends seen in a previous study (26), fasting levels of GLP-1 were significantly lower in post-GB subjects compared with MOB persons. Fasting and post-meal GLP-1 levels were significantly increased in GB + NG as compared with GB. Increased postprandial levels of GLP-1 in our patients are consistent with other reports demonstrating increased GLP-1 after gastric bypass (26–28) and in patients with postprandial “reactive” hypoglycemia associated with accelerated gastric emptying after gastric surgery (29, 30). In both settings, increased nutrient delivery to intestinal L cells (where GLP-1 is synthesized) may contribute to increased GLP-1 secretion. Such increases can persist for years after surgery, as seen in our cohort. Although GLP-1 can increase insulin secretion, and promote islet hyperplasia, as observed in rodents (25, 31), it is important to note that our studies cannot demonstrate causation. In healthy cynomolgus monkeys, treatment with the GLP-1 analog exenatide for 9 months, at doses more than 400 times those used in humans, caused only minimal to mild islet hypercellularity with no increase in islet size (32).

Incretin levels measured in the peripheral circulation after bariatric surgery were markedly elevated, reaching levels 5- to 10-fold higher than those in OW and MOB groups. Because incretins are rapidly degraded by dipeptidyl peptidase IV enzymes, exposure at the level of the β -cell would be even higher. Although GLP-1 is usually considered to enhance glucose-stimulated insulin secretion, two lines of evidence suggest that these increases in GLP-1 could contribute to overt hypoglycemia. First, in paired studies infusing glucose alone or GLP-1 together with glucose, at a rate adjusted to achieve comparable glycemia in healthy humans, glucose levels decreased further after administration of GLP-1 (29). Second, pathological hypersecretion of GLP-1, as described in a patient with a GLP-1 secreting

tumor, was associated with overt hypoglycemia, which resolved upon tumor resection (33).

GIP, produced by K cells in the duodenum and proximal jejunum, can also promote islet expansion and reduce apoptosis (reviewed in Ref. 34). Anatomical changes associated with GB, which include bypassing this section of small intestine, might be expected to reduce GIP secretion. However, whether bariatric surgery alters GIP secretion remains controversial. Some previous studies demonstrate no change in GIP at 3–12 wk postoperatively in nondiabetic patients and a similar pattern in diabetic subjects (28, 35); others find increases in GIP (36). We also report increased GIP in our post-GB cohorts. It is possible that differences in surgical techniques, such as length of intestinal limb or functional status of the vagus nerve, may contribute to these dissimilarities. In addition, levels of GIP may increase with postoperative duration, either due to persistent alterations in nutrient exposure to intestinal cells, reflux of food into the biliopancreatic limb from the distal anastomosis, or from changes in dietary composition of protein and fat, which may directly regulate secretion and inactivation of incretins (37). The impact of altered patterns of GIP secretion in post-bypass hypoglycemia remains unclear at present.

Postprandial hemodynamic and hormonal changes characteristic of dumping syndrome could also contribute to NG in post-GB patients (38). Dumping syndrome is recognized as a side effect of many types of gastric surgery, caused by rapid emptying of partially digested foods, with mechanical distention, and altered secretion of intestinal hormones, including glucagon (16) and GLP-1 (16, 22, 23, 39). Together, these changes may result in systemic volume contraction, adrenergic stimulation, and late postprandial hypoglycemia (40, 41). Dumping syndrome has developed in 10–15% of gastric bypass patients, usually occurring shortly after surgery, and is often manageable with avoidance of dietary carbohydrates, frequent small meals, and occasionally octreotide (42, 43). Many of our patients describe symptoms consistent with dumping syndrome early in the postoperative period, controlled by dietary modification. However, despite continued avoidance of dietary carbohydrate, these patients developed NG 1–5 yr postoperatively, in the absence of other clinical features of dumping syndrome. Although we observed evidence for asymptomatic dumping, as demonstrated by elevated dumping syndrome scores in all post-GB patients, scores did not differ between those with or without clinically significant hypoglycemia. Moreover, hypoglycemia responded poorly to octreotide therapy in those patients with severe disease ultimately treated with pancreatectomy.

Our data also highlight a surprisingly high rate of completely asymptomatic hypoglycemia in post-GB patients after a liquid mixed meal. This is higher than the 3–4% rate of asymptomatic hyperinsulinemic hypoglycemia after a 75-g glucose load in patients after laparoscopic adjustable gastric banding (44). These data also suggest that repeated asymptomatic bouts of hypoglycemia, with secondary loss of adrenergic symptoms, may be more frequent than recognized in all GB patients, and, thus, may also contribute to the frequency and severity of profound hypoglycemia in the subset of patients with recurrent NG.

We observed no alterations in consciousness in response to a mixed meal stimulus. Potential factors enhancing hypogly-

cemia magnitude in the ambulatory as compared with the research setting include: 1) meal size and composition, 2) increased gastric distention with solid foods, and 3) increased physical activity. Furthermore, altered consciousness in the ambulatory setting may also reflect volume shifts and relative hypotension in the postprandial state. Glucagon levels were not lower in patients with NG; however, additional glucoregulatory factors such as epinephrine, cortisol, or GH, and autonomic or vagal function may also contribute but were not examined.

It is interesting that none of the subjects in the cohort of severe hypoglycemia had a history of diabetes before gastric bypass surgery. This may reflect the fact that patients with diabetes remain a minority of the population of MOB individuals who actually undergo GB, that individuals with diabetes are less susceptible to the incretin effect, or have relatively reduced β -cell mass or function preoperatively. Thus, such individuals may not have sufficient islet mass or may require a longer time interval to develop excess islet mass or function and manifest significant hypoglycemia (45–47). Conversely, these data might also suggest that islet expansion in some MOB patients may be protective for diabetes development, and these same patients are at higher risk for postoperative hypoglycemia. Clearly, additional longitudinal follow-up studies will be required to evaluate preoperative status in individuals who develop this complication compared with those who are protected.

In summary, we demonstrate frequent asymptomatic hypoglycemia and cases of severe symptomatic hypoglycemia occurring several years after GB surgery. Patients with clinically severe hypoglycemia have higher acute insulin secretion and lower glucose levels in response to a mixed meal. Moreover, these patients have markedly increased postprandial incretin secretion that is likely to contribute to the exaggerated insulin secretory response. Thus, targeted interventions to reduce incretin secretion and/or response might be therapeutically beneficial for patients with post-bypass NG. Although the test meal studied did not provoke clinically significant hypoglycemia, in the ambulatory setting, larger meals or carbohydrate load, volume flux, or other metabolic factors, such as those associated with exercise, may contribute to hypoglycemic events associated with altered consciousness. With obesity a national epidemic and the exponential increase in bariatric surgery as an effective treatment, further investigation is crucial to elucidate contributions of genetic, neural, metabolic, and hormonal mechanisms to the complex syndrome of post-bypass hypoglycemia.

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Address all correspondence and requests for reprints to: Allison B. Goldfine, M.D., Joslin Diabetes Center, One Joslin Place, Boston, Massachusetts 02215. E-mail: allison.goldfine@joslin.harvard.edu.

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